Circulation

AHA STATISTICAL UPDATE

Heart Disease and Stroke Statistics—2019 Update

A Report From the American Heart Association

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SUMMARY

Each year, the American Heart Association (AHA), in conjunction with the National Institutes of Health and other government agencies, brings together in a single document the most up-to-date statistics related to heart disease, stroke, and the cardiovascular risk factors in the AHA's My Life Check – Life's Simple 7 (Figure[1]), which include core health behaviors (smoking, physical activity, diet, and weight) and health factors (cholesterol, blood pressure [BP], and glucose control) that contribute to cardiovascular health. The Statistical Update represents a critical resource for the lay public, policy makers, media professionals, clinicians, healthcare administrators, researchers, health advocates, and others seeking the best available data on these factors and conditions. Cardiovascular disease (CVD) produces immense health and economic burdens in the United States and globally. The Statistical Update also presents the latest data on a range of major clinical heart and circulatory disease conditions (including stroke, congenital heart disease, rhythm disorders, subclinical atherosclerosis, coronary heart disease [CHD], heart failure [HF], valvular disease, venous disease, and peripheral arterial disease) and the associated outcomes (including quality of care, procedures, and economic costs). Since 2007, the annual versions of the Statistical Update have been cited >20 000 times in the literature.

Each annual version of the Statistical Update undergoes revisions to include the newest nationally representative data, add additional relevant published scientific findings, remove older information, add new sections or chapters, and increase the number of ways to access and use the assembled information. This year-long process, which begins as soon as the previous Statistical Update is published, is performed by the AHA Statistics Committee faculty volunteers and staff and government agency partners. This year's edition includes data on the monitoring and benefits of cardiovascular health in the population, metrics to assess and monitor healthy diets, a new chapter on sleep, an enhanced focus on social determinants of health, a substantively expanded focus on the global burden of CVD, and further evidence-based approaches to changing behaviors, implementation strategies, and implications of the AHA's 2020 Impact Goals. Below are a few highlights from this year's Statistical Update.

Cardiovascular Health (Chapter 2)

- New data expand the benefits of better cardiovascular health to include lower prevalence of aortic sclerosis and stenosis, improved prognosis after myocardial infarction (MI), lower risk of atrial fibrillation, and greater positive psychological functioning (dispositional optimism).
- Among children, from 1999 to 2000 to 2015 to 2016, prevalence of nonsmoking, ideal total cholesterol, and ideal BP improved. For example, nonsmoking among children aged 12 to 19 years went from 76% to 94%. However, meeting ideal levels for physical activity, body mass index (BMI), and blood glucose did not improve. For example, prevalence of ideal BMI declined from 70% to 60% over the same time period.

Smoking/Tobacco Use (Chapter 3)

- The prevalence of current smoking in the United States in 2016 was 15.5% for adults, and 3.4% of adolescents smoked cigarettes in the past month.

Figure. AHA's My Life Check – Life's Simple 7.
Seven approaches to staying heart healthy: be active, keep a healthy weight, learn about cholesterol, don't smoke or use smokeless tobacco, eat a heart-healthy diet, keep blood pressure healthy, and learn about blood sugar and diabetes mellitus.

Although there has been a consistent decline in tobacco use in the United States, significant disparities persist. Substantially higher tobacco use prevalence rates are observed in American Indian/Alaska Natives and lesbian, gay, bisexual, and transgender populations, as well as among individuals with low socioeconomic status, those with mental illness, individuals with HIV who are receiving medical care, and those who are active-duty military.

- Tobacco use remains a leading cause of preventable death in the United States and globally. It was estimated to account for 7.1 million deaths worldwide in 2016.
- Over the past 6 years, there has been a sharp increase in e-cigarette use among adolescents, and e-cigarettes are now the most commonly used tobacco product in this demographic.
- Policy-level interventions such as Tobacco 21 Laws and MPOWER are being adopted and have been associated with reductions in tobacco use incidence and prevalence.

Physical Inactivity (Chapter 4)

- The trends in the prevalence of self-reported inactivity among adults decreased from 1998 to 2016, with the largest drop occurring in the past decade, from 40.1% to 26.9% between 2007 and 2016, respectively. Despite this decrease in inactivity over recent years, currently, <23% of adults report participating in adequate leisure-time aerobic and muscle-strengthening activity to meet the 2008 federal guidelines for physical activity.
- Converging evidence from epidemiological studies suggests that limiting sedentary time is associated with a lower risk of cardiovascular events and mortality after accounting for other traditional risk factors and physical activity levels.
- A Nielsen report from 2017 suggests that technology use is changing rapidly, with potential implications for influencing sedentary behavior. Although adult television and tablet use has decreased modestly in recent years, adult smartphone use increased from the 2012 to 2014 period to 2017 by >1 hour each day.

Nutrition (Chapter 5)

- In a 2013 to 2014 nationally representative sample of 827 nonpregnant, noninstitutionalized US adults, estimated mean sodium intake by 24-hour urinary excretion was 4205 mg/d for males and 3039 mg/d for females. In a diverse sample of 450 US adults in 3 geographic locations, ≈70% of sodium was added to food outside the home, 13% to 16% was inherent to food, 4% to 9% was added in home food preparation, 3% to 8% was added at the table, and <1% was from dietary supplements and home tap water; amounts varied modestly by race/ethnicity.
- After a 1 peso per liter excise tax on sugar-sweetened beverages (SSBs) was implemented in Mexico in January 2014, SSB purchases were reduced by 5.5% after 1 year and 9.7% after 2 years compared with predicted SSB purchases based on pretax trends. The effect of the SSB tax was greatest among households of the lowest socioeconomic status. A similar 1 cent per ounce excise tax on SSBs was implemented in Berkeley, California, in January 2015, and SSB sales declined by 9.6% after 1 year compared with predicted SSB purchases based on pretax trends.
- The Special Supplemental Nutrition Program for Women, Infants, and Children food package was revised in 2009 to include more fruits, vegetables, whole grains, and lower-fat milk. These food package revisions were associated with a significant improvement in Healthy Eating Index-2010 score (3.7 higher Healthy Eating Index points; 95% CI, 0.6–6.9). By contrast, participation in the Supplemental Nutrition Assistance Program (SNAP), which does not regulate nutritional

quality, was associated with less healthy household purchases (15–20 more calories from SSBs per person per day, 174–195 more milligrams of sodium per person per day, and 0.52 fewer grams of fiber per person per day).

Overweight and Obesity (Chapter 6)

- According to NHANES (National Health and Nutrition Examination Survey) 2015 to 2016, 39.6% of US adults and 18.5% of youths were obese, and 7.7% of adults and 5.6% of youth had severe obesity. The overall prevalence of obesity and severe obesity in youth (aged 2–19 years) did not increase significantly from 2007 to 2008 to 2015 to 2016. However, the age-standardized prevalence of obesity and severe obesity increased significantly in the past decade (from 2007–2008 to 2015–2016) among adults.
- A recent mendelian randomization study of participants from 7 prospective cohorts demonstrated that genetic variants associated with higher BMI were significantly associated with incident atrial fibrillation, which supports a causal relationship between obesity and atrial fibrillation.
- In a study of 189 672 participants from 10 US longitudinal cohort studies, obesity was associated with a shorter total longevity and greater proportion of life lived with CVD. Higher BMI was associated with a significantly higher risk of death attributable to CVD.

High Blood Cholesterol and Other Lipids (Chapter 7)

- Between 1999 and 2016, mean total cholesterol levels declined overall and across all subgroups of race.
- Recent data from the REGARDS study (Reasons for Geographic and Racial Differences in Stroke) indicate that even after accounting for access to medical care, there are disparities in the use of statins in individuals with diabetes mellitus (DM). White males with DM and low-density lipoprotein cholesterol >100 mg/dL were more likely to be prescribed statins (66.0%) than black males (57.8%), white females (55.0%), and black females (53.6%).

High Blood Pressure (Chapter 8)

- In 2011 to 2014, the prevalence of hypertension among US adults was 45.6% (95% CI, 43.6%–47.6%) using the new BP thresholds from the 2017 American College of Cardiology/AHA guidelines versus 31.9% (95% CI, 30.1%–33.7%) using guideline thresholds from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.
- In prospective follow-up of the REGARDS, MESA (Multi-Ethnic Study of Atherosclerosis), and JHS (Jackson Heart Study) cohorts, 63.0% of incident CVD events occurred in participants with systolic BP (SBP) <140 mm Hg and diastolic BP <90 mm Hg.
- US non-Hispanic (NH) blacks (13.2%) are more likely than NH Asians (11.0%), NH whites (8.6%), or Hispanics (7.4%) to use home BP monitoring on a weekly basis.
- In 2015, the worldwide prevalence of SBP ≥140 mm Hg was estimated to be 20 526 per 100 000. This represents an increase from 17 307 per 100 000 in 1990. Also, the prevalence of SBP of 110 to 115 mm Hg or higher increased from 73 119 per 100 000 to 81 373 per 100 000 between 1990 and 2015. There were 3.47 billion adults worldwide with SBP of 110 to 115 mm Hg or higher in 2015.
- Among African Americans in the JHS not taking antihypertensive medication, the prevalence of clinic hypertension (mean SBP ≥140 mm Hg or mean diastolic BP ≥90 mm Hg) was 14.3%, the prevalence of daytime hypertension (mean daytime SBP ≥135 mm Hg or mean daytime diastolic BP ≥85 mm Hg) was 31.8%, and the prevalence of nighttime hypertension (mean nighttime SBP ≥120 mm Hg or mean nighttime diastolic BP ≥70 mm Hg) was 49.4%. Among JHS participants taking antihypertensive medication, the prevalence estimates were 23.1% for clinic hypertension, 43.0% for daytime hypertension, and 61.7% for nighttime hypertension.

Diabetes Mellitus (Chapter 9)

- On the basis of data from NHANES 2013 to 2016, of US adults, an estimated 26 million (9.8%) have diagnosed DM, 9.4 million (3.7%) have undiagnosed DM, and 91.8 million (37.6%) have prediabetes.
- In 2017, the cost of DM was estimated at $327 billion (Table 9-1), up 26% from 2012, accounting for 1 in 4 healthcare dollars. Of these costs, $237 billion were direct medical costs and $90 billion resulted from reduced productivity.
- On the basis of NHANES 2013 to 2016 data for adults with DM, 20.9% had their DM treated and controlled (fasting glucose <126 mg/dL), 45.2% had their DM treated but uncontrolled, 9.2% were aware they had DM but were not treated, and 24.7% were undiagnosed and not treated.

Metabolic Syndrome (Chapter 10)

- The overall prevalence of metabolic syndrome has remained stable at 34.3% across all sex, age, and racial/ethnic groups since 2008 according to data from NHANES 2007 to 2014.
- In a recent meta-analysis of 26 609 young adults (aged 18–30 years) across 34 studies, the prevalence of metabolic syndrome was 4.8% to 7% depending on the definition used.
- In addition to well-established associations with poor CVD outcomes and all-cause mortality, the presence of metabolic syndrome also has been shown to be associated with poorer cancer outcomes, including increased risk of cancer recurrence, cancer-related mortality, and overall mortality.

Kidney Disease (Chapter 11)

- According to the United States Renal Data System, the overall prevalence of chronic kidney disease in the United States among NHANES participants ≥20 years of age was 14.8% (95% CI, 13.6%–16.0%) in 2011 to 2014.
- In 3 community-based cohort studies (JHS, Cardiovascular Health Study, and MESA), absolute incidence rates (per 1000 person-years) for HF, CHD, and stroke for participants with versus without chronic kidney disease were 22 versus 6.2 for HF, 24.5 versus 8.4 for CHD, and 13.4 versus 4.8 for stroke.
- A recent meta-analysis of 43 studies examining associations between socioeconomic indicators (income, education, and occupation) found that lower socioeconomic status, particularly income, was associated with a higher prevalence of chronic kidney disease and faster progression to end-stage renal disease. This association was observed in higher- versus lower- or middle-income countries and was more pronounced in the United States, relative to Europe.

Sleep (Chapter 12)

- Data from the Centers for Disease Control and Prevention indicated that the age-adjusted prevalence of healthy sleep duration (≥7 hours) was 65.2% for all Americans and was lower among Native Hawaiians/Pacific Islanders (53.7%), NH blacks (54.2%), multiracial NH people (53.6%), and American Indians/Alaska Natives (59.6%) compared with NH whites (66.8%), Hispanics (65.5%), and Asians (62.5%).
- A meta-analysis of 43 studies indicated that both short sleep (<7 hours per night; relative risk [RR], 1.13; 95% CI, 1.10–1.17) and long sleep (>8 hours per night; RR, 1.35; 95% CI, 1.29–1.41) were associated with a greater risk of all-cause mortality. In addition, short sleep (<7 hours per night) was associated with total CVD (RR, 1.14; 95% CI, 1.09–1.20) and CHD (RR, 1.22; 95% CI, 1.13–1.31) but not stroke (RR, 1.09; 95% CI, 0.99–1.19). Long sleep duration was associated with total CVD (RR, 1.36; 95% CI, 1.26–1.48), CHD (RR, 1.21; 95% CI, 1.12–1.30), and stroke (RR, 1.45; 95% CI, 1.30–1.62).
- A meta-analysis of 27 cohort studies found that mild obstructive sleep apnea (hazard ratio, 1.19; 95% CI, 0.86–1.65), moderate obstructive sleep apnea (1.28; 95% CI, 0.96–1.69), and severe obstructive sleep apnea (2.13; 95% CI, 1.68–2.68) were associated with all-cause mortality in a dose-response fashion. Only severe obstructive sleep apnea was associated with cardiovascular mortality (hazard ratio, 2.73; 95% CI, 1.94–3.85).

Total Cardiovascular Diseases (Chapter 13)

- On the basis of NHANES 2013 to 2016 data, the prevalence of CVD (comprising CHD, HF, stroke, and hypertension) in adults ≥20 years of age is 48.0% overall (121.5 million in 2016) and increases with advancing age in both males and females. CVD prevalence excluding hypertension (CHD, HF, and stroke only) is 9.0% overall (24.3 million in 2016).
- In 2016, 2 744 248 resident deaths were registered in the United States. Ten leading causes accounted for 74.1% of all registered deaths. The 10 leading causes of death in 2016 were the same as in 2015; these include heart disease (No. 1), cancer (No. 2), unintentional injuries (No. 3), chronic lower respiratory diseases (No. 4), stroke (No. 5), Alzheimer disease (No. 6), DM (No. 7), influenza and pneumonia (No. 8), kidney disease (No. 9), and suicide (No. 10). Seven of the 10 leading causes of death had a decrease in age-adjusted death rates. The age-adjusted death rates decreased 1.8% for heart disease, 1.7% for cancer, 2.4% for chronic lower respiratory diseases, 0.8% for stroke, 1.4% for DM, 11.2% for influenza and pneumonia, and 2.2% for kidney disease. The age-adjusted rate increased 9.7% for unintentional injuries, 3.1% for Alzheimer disease, and 1.5% for suicide.
- In 2016, ≈17.6 million (95% CI, 17.3–18.1 million) deaths were attributed to CVD globally, which amounted to an increase of 14.5% (95% CI, 12.1%–17.1%) from 2006. The age-adjusted death rate per 100 000 population was 277.9 (95% CI, 272.1–284.6), which represents a decrease of 14.5% (95% CI, –16.2% to –12.5%) from 2006.

Stroke (Cerebrovascular Disease) (Chapter 14)

- An estimated 7.0 million Americans ≥20 years of age self-report having had a stroke, and the overall stroke prevalence was an estimated 2.5%.
- In the National (Nationwide) Inpatient Sample, hospitalizations for acute ischemic stroke increased significantly for both males and females and for certain racial/ethnic groups among younger adults aged 18 to 54 years. From 1995 through 2011 to 2012, stroke hospitalization rates almost doubled for males aged 18 to 34 and 35 to 44 years, with a 41.5% increase among males aged 35 to 44 years from 2003 to 2004 through 2011 to 2012.
- In analyses using data from the Global Burden of Disease Study, ≈90% of the stroke risk could be attributed to modifiable risk factors (such as high BP, obesity, hyperglycemia, hyperlipidemia, and renal dysfunction), and 74% could be attributed to behavioral risk factors, such as smoking, sedentary lifestyle, and an unhealthy diet. Globally, 29% of the risk of stroke was attributable to air pollution.
- Although global age-adjusted mortality rates for ischemic and hemorrhagic stroke decreased between 1990 and 2015, the absolute number of people who have strokes annually, as well as related deaths and disability-adjusted life-years lost, increased. The majority of global stroke burden is in low-income and middle-income countries.
- In analyses of 1 165 960 Medicare fee-for-service beneficiaries hospitalized between 2009 and 2013 for ischemic stroke, patients treated at primary stroke centers certified between 2009 and 2013 had lower in-hospital (odds ratio [OR], 0.89; 95% CI, 0.85–0.94), 30-day (hazard ratio, 0.90; 95% CI, 0.89–0.92), and 1-year (hazard ratio, 0.91; 95% CI, 0.90–0.92) mortality than those treated at noncertified hospitals, after adjustment for demographic and clinical factors. Hospitals certified between 2009 and 2013 also had lower in-hospital and 30-day mortality than centers certified before 2009.

Congenital Cardiovascular Defects and Kawasaki Disease (Chapter 15)

- Although estimates of birth prevalence/overall prevalence of congenital cardiovascular defects appear relatively stable, a general trend toward improved outcome/survival continues, which has led to an expanding population of adult congenital heart disease patients.
- Although there remains increased mortality in patients with congenital cardiovascular defects compared with the general population, the standardized mortality ratios after congenital heart disease surgery continue to decrease. In a recent study from the Pediatric Cardiac Care Consortium's US-based multicenter data registry, which examined 35 998 patients with a median follow-up of 18 years, the overall standardized mortality ratio was 8.3% (95% CI, 8.0%–8.7%).

Disorders of Heart Rhythm (Chapter 16)

- The lifetime risk of atrial fibrillation recently has been estimated to be ≈1 in 3 among whites and 1 in 5 among blacks in the United States.
- Individuals with optimal cardiovascular health have a 32% lower risk of atrial fibrillation.
- Approximately 0.7 million (13%) of the ≈5.3 million cases of atrial fibrillation in the United States are undiagnosed.
- Obese individuals have a 51% increased risk of developing atrial fibrillation compared with their nonobese counterparts.
- Patients with atrial fibrillation admitted to rural hospitals had a 17% higher risk of death than those admitted to urban hospitals.

Sudden Cardiac Arrest, Ventricular Arrhythmias, and Inherited Channelopathies (Chapter 17)

- Prevalence of reported current training in cardiopulmonary resuscitation was 18%, and prevalence of having cardiopulmonary resuscitation training at some point was 65% in a survey of 9022 people in the United States in 2015. The prevalence of cardiopulmonary resuscitation training was lower in Hispanic/Latino people, older people, people with less formal education, and the lower-income group.
- Incidence of emergency medical services–assessed out-of-hospital cardiac arrest in people of any age was 110.8 per 100 000 population (95% CI, 108.9–112.6), or 356 461 people (quasi-CI, 350 349–362 252) based on extrapolation from the ROC registry (Resuscitation Outcomes Consortium) of out-of-hospital cardiac arrest to the total population of the United States (325 193 000 as of June 9, 2017).
- Survival of hospitalization after cardiac arrest varied between academic medical centers and was higher in hospitals with higher cardiac arrest volume, higher surgical volume, greater availability of invasive cardiac services, and more affluent catchment areas.

Subclinical Atherosclerosis (Chapter 18)

- Coronary computed tomographic angiography, which includes assessment of the severity of coronary artery stenosis, plaque composition, and coronary segment location, does not offer additional prognostic value for all-cause mortality beyond traditional risk factors and coronary calcium in asymptomatic individuals.

- In contrast to the US population, the majority (≈85%) of middle-aged people living a forager-horticulturalist lifestyle in the Bolivian Amazon remain free of coronary artery calcium, which indicates that coronary atherosclerosis can typically be avoided by maintaining a low lifetime burden of risk factors. Even among those Bolivian Amazon individuals >75 years of age, 65% remained free of coronary artery calcium.

Coronary Heart Disease, Acute Coronary Syndrome, and Angina Pectoris (Chapter 19)

- Data from the BRFSS (Behavioral Risk Factor Surveillance System) 2016 survey indicated that 4.4% of respondents had been told that they had had an MI and 4.1% of respondents had been told that they had angina or CHD.
- From 2006 to 2016, the annual death rate attributable to CHD declined 31.8%. CHD age-adjusted death rates per 100 000 were 132.3 for NH white males, 146.5 for NH black males, and 95.6 for Hispanic males; for NH white females, the rate was 67.9; for NH black females, it was 85.4; and for Hispanic females, it was 54.6 (unpublished National Heart, Lung, and Blood Institute tabulation).
- Compared with nonparticipants, participants in SNAP have twice the risk of CVD mortality, which likely reflects differences in socioeconomic, environmental, and behavioral characteristics.
- In the BRFSS from 2005 to 2015, <40% of patients self-reported participation in cardiac rehabilitation after an acute MI. Between 2011 and 2015, compared with patients who did not participate in cardiac rehabilitation, those who declared such participation were less likely to be female (OR, 0.76; 95% CI, 0.65–0.90; P=0.002) or black (OR, 0.70; 95% CI, 0.53–0.93; P=0.014), were less well educated (high school versus college graduate: OR, 0.69; 95% CI, 0.59–0.81; P<0.001 and less than high school versus college graduate: OR, 0.47; 95% CI, 0.37–0.61; P<0.001), and were more likely to be retired or self-employed (OR, 1.39; 95% CI, 1.24–1.73; P=0.003).

Cardiomyopathy and Heart Failure (Chapter 20)

- The prevalence of HF continues to rise over time with the aging population. In NHANES data, an estimated 6.2 million American adults ≥20 years of age (2.2%) had HF between 2013 and 2016 compared with an estimated 5.7 million between 2009 and 2012.
- Primary prevention of HF can be augmented by greater adherence to the Life's Simple 7 goals; optimal profiles in smoking, BMI, physical activity, diet, cholesterol, BP, and glucose are associated with a lower lifetime risk of HF and more favorable cardiac structure and functional parameters by echocardiography.
- Of incident hospitalized HF events, approximately half are characterized by reduced ejection fraction and the other half by preserved ejection fraction. The prevalence of HF with preserved ejection fraction, compared with prevalence of HF with reduced ejection fraction, appears to be increasing over time along with aging of the population.

Valvular Diseases (Chapter 21)

- Although rheumatic heart disease is uncommon in high-income countries such as the United States, it remains an important cause of morbidity and mortality in low- and middle-income countries. In 2015, 33.4 million people were estimated to be living with rheumatic heart disease around the world, with sub-Saharan Africa, South Asia, and Oceania having the highest concentration of disability-adjusted life-years attributable to rheumatic heart disease.
- Admissions for endocarditis related to injection drug use have risen in recent years in parallel with the opioid drug crisis. The prevalence of documented intravenous drug use among people admitted to a hospital because of endocarditis in the National (Nationwide) Inpatient Sample rose from 4.3% in 2008 to 10% in 2014.

Venous Thromboembolism (Deep Vein Thrombosis and Pulmonary Embolism), Chronic Venous Insufficiency, Pulmonary Hypertension (Chapter 22)

- Traditional atherosclerotic risk factors, including hypertension, hyperlipidemia, and DM, were not associated with risk of venous thromboembolism in a 2017 individual-level meta-analysis of >240 000 participants from 9 cohorts. Cigarette smoking was associated with provoked but not with unprovoked venous thromboembolism events.
- Emerging evidence suggests that autoimmune disease, such as lupus and Sjögren syndrome, could be risk factors for venous thromboembolism.
- African Americans present with higher-severity chronic venous insufficiency and have less improvement with radiofrequency ablation.

Peripheral Artery Disease and Aortic Diseases (Chapter 23)

- A recent Danish trial in men aged 65 to 74 years reported that screening of peripheral artery disease (with ankle-brachial index), abdominal aortic aneurysm (with abdominal ultrasound), and hypertension followed by optimal care resulted in a 7% lower risk of 5-year mortality compared with no screening.
- African Americans have a 37% higher amputation risk than white individuals. In adjusted analyses, lower socioeconomic status was associated with a 12% higher risk for amputation.
- In 2017, the Centers for Medicare & Medicaid Services decided to cover supervised exercise therapy (up to 36 sessions over 12 weeks) for eligible symptomatic peripheral artery disease patients with intermittent claudication.

Quality of Care (Chapter 24)

- Quality and performance measures for MI have been relatively stable in recent years but have improved longitudinally since data collection began.
- Among hospitals that care for Medicare fee-for-service beneficiaries, the implementation of hospital readmission reduction programs was associated with a reduction in 30-day and 1-year hospitalization rates but an increase in 30-day and 1-year mortality.
- According to national Medicare data from July 2015 through June 2016, the median (interquartile range) hospital risk-standardized mortality rate for MI was 13.1% (12.6%, 13.5%), and the median (interquartile range) risk-standardized 30-day readmission rate was 15.8% (15.5%, 16.2%).
- According to national Medicare data from July 2015 through June 2016, the median (interquartile range) hospital risk-standardized mortality rate for HF was 11.6% (10.8%, 12.4%), and the median (interquartile range) risk-standardized 30-day readmission rate was 21.4% (20.8%, 22.1%).

Medical Procedures (Chapter 25)

- Data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database indicate that a total of 159 869 procedures involved isolated coronary artery bypass grafting in 2016.
- In 2017, 3244 heart transplantations were performed in the United States, the most ever.

Economic Cost of Cardiovascular Disease (Chapter 26)

- The average annual direct and indirect cost of CVD and stroke in the United States was an estimated $351.2 billion in 2014 to 2015.
- The estimated direct costs of CVD and stroke increased from $103.5 billion in 1996 to 1997 to $213.8 billion in 2014 to 2015.
- Between 2015 and 2035, the projected total (direct and indirect) costs of total CVD are estimated to remain relatively stable for 18- to 44-year-olds, increase slightly for 45- to 64 year-olds, and increase sharply for 65- to 79-year-olds and adults aged ≥80 years.

Conclusions

The AHA, through its Statistics Committee, continuously monitors and evaluates sources of data on heart disease and stroke in the United States to provide the most current information available in the Statistical Update. The 2019 annual Statistical Update is the product of a full year's worth of effort by dedicated volunteer physicians and scientists, committed government professionals, and AHA staff members, without whom publication of this valuable resource would be impossible. Their contributions are gratefully acknowledged.

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ARTICLE INFORMATION

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Disclosures

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*Modest.

†Significant.

REFERENCE

1. American Heart Association. My Life Check – Life's Simple 7. https://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check--lifes-simple-7. Accessed November 9, 2018.

1. ABOUT THESE STATISTICS

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The AHA works with the NHLBI and other government agencies to derive the annual statistics in this Heart Disease and Stroke Statistics Update. This chapter describes the most important sources and the types of data used from them. For more details, see Chapter 28 of this document, the Glossary.

The surveys used are the following:

- ARIC—CHD and HF incidence rates
- BRFSS—ongoing telephone health survey system
- GCNKSS—stroke incidence rates and outcomes within a biracial population
- HCUP—hospital inpatient discharges and procedures (discharged alive, dead, or status unknown)
- MEPS—data on specific health services that Americans use, how frequently they use them, the cost of these services, and how the costs are paid
- NHANES—disease and risk factor prevalence and nutrition statistics
- NHIS—disease and risk factor prevalence
- NAMCS—physician office visits
- National Home and Hospice Care Survey—staff, services, and patients of home health and hospice agencies
- NHAMCS—hospital outpatient and ED visits
- NIS of the Agency for Healthcare Research and Quality—hospital inpatient discharges, procedures, and charges
- United States Renal Data System—kidney disease prevalence
- WHO—mortality rates by country
- YRBSS—health-risk behaviors in youth and young adults

Abbreviations Used in Chapter 1

AHA	American Heart Association
AP	angina pectoris
ARIC	Atherosclerosis Risk in Communities Study
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CVD	cardiovascular disease
DM	diabetes mellitus
ED	emergency department
FHS	Framingham Heart Study
GCNKSS	Greater Cincinnati/Northern Kentucky Stroke Study
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HF	heart failure
ICD	*International Classification of Diseases*
ICD-9-CM	*International Classification of Diseases, Clinical Modification, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
MEPS	Medical Expenditure Panel Survey
MI	myocardial infarction
NAMCS	National Ambulatory Medical Care Survey
NCHS	National Center for Health Statistics
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NINDS	National Institute of Neurological Disorders and Stroke
NIS	National (Nationwide) Inpatient Sample
PAD	peripheral artery disease
WHO	World Health Organization
YRBSS	Youth Risk Behavior Surveillance System

Disease Prevalence

Prevalence is an estimate of how many people have a condition at a given point or period in time. The NCHS/CDC conducts health examination and health interview surveys that provide estimates of the prevalence of diseases and risk factors. In this Update, the health interview part of the NHANES is used for the prevalence of CVDs. NHANES is used more than the NHIS because in NHANES, AP is based on the Rose Questionnaire; estimates are made regularly for HF; hypertension is based on BP measurements and interviews; and an estimate can be made for total CVD, including MI, AP, HF, stroke, and hypertension.

A major emphasis of this Statistical Update is to present the latest estimates of the number of people in the United States who have specific conditions to provide a realistic estimate of burden. Most estimates based on NHANES prevalence rates are based on data collected from 2013 to 2016. These are applied to census population estimates for 2016. Differences in population estimates cannot be used to evaluate possible trends in prevalence because these estimates are based on extrapolations of rates beyond the data collection period by use of more recent census population estimates. Trends can only be evaluated by comparing prevalence rates estimated from surveys conducted in different years.

A major enhancement in the 2019 Statistical Update is the addition of a new chapter, Sleep (Chapter 12). Also this year, there is an emphasis on social determinants of health that are built across the various chapters, and global estimates are provided where available.

Risk Factor Prevalence

The NHANES 2013 to 2016 data are used in this Update to present estimates of the percentage of people with high lipid values, DM, overweight, and obesity. The NHIS 2015 data are used for the prevalence of cigarette smoking and physical inactivity.

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Data for students in grades 9 through 12 are obtained from the YRBSS.

Incidence and Recurrent Attacks

An incidence rate refers to the number of new cases of a disease that develop in a population per unit of time. The unit of time for incidence is not necessarily 1 year, although incidence is often discussed in terms of 1 year. For some statistics, new and recurrent attacks or cases are combined. Our national incidence estimates for the various types of CVD are extrapolations to the US population from the FHS, the ARIC study, and the CHS, all conducted by the NHLBI, as well as the GCNKSS, which is funded by the NINDS. The rates change only when new data are available; they are not computed annually. Do not compare the incidence or the rates with those in past editions of the Heart Disease and Stroke Statistics Update (also known as the Heart and Stroke Statistical Update for editions before 2005). Doing so can lead to serious misinterpretation of time trends.

Mortality

Mortality data are generally presented according to the underlying cause of death. "Any-mention" mortality means that the condition was nominally selected as the underlying cause or was otherwise mentioned on the death certificate. For many deaths classified as attributable to CVD, selection of the single most likely underlying cause can be difficult when several major comorbidities are present, as is often the case in the elderly population. It is useful, therefore, to know the extent of mortality attributable to a given cause regardless of whether it is the underlying cause or a contributing cause (ie, the "any-mention" status). The number of deaths in 2016 with any mention of specific causes of death was tabulated by the NHLBI from the NCHS public-use electronic files on mortality.

The first set of statistics for each disease in this Update includes the number of deaths for which the disease is the underlying cause. Two exceptions are Chapter 8 (High Blood Pressure) and Chapter 20 (Cardiomyopathy and Heart Failure). High BP, or hypertension, increases the mortality risks of CVD and other diseases, and HF should be selected as an underlying cause only when the true underlying cause is not known. In this Update, hypertension and HF death rates are presented in 2 ways: (1) As nominally classified as the underlying cause and (2) as any-mention mortality.

National and state mortality data presented according to the underlying cause of death were computed from the mortality tables of the NCHS/CDC website or the CDC compressed mortality file. Any-mention numbers of deaths were tabulated from the electronic mortality files of the NCHS/CDC website.

Population Estimates

In this publication, we have used national population estimates from the US Census Bureau for 2016[1] in the computation of morbidity data. NCHS/CDC population estimates[2] for 2016 were used in the computation of death rate data. The Census Bureau website contains these data, as well as information on the file layout.

Hospital Discharges and Ambulatory Care Visits

Estimates of the numbers of hospital discharges and numbers of procedures performed are for inpatients discharged from short-stay hospitals. Discharges include those discharged alive, dead, or with unknown status. Unless otherwise specified, discharges are listed according to the first-listed (primary) diagnosis, and procedures are listed according to all listed procedures (primary plus secondary). These estimates are from the HCUP 2014. Ambulatory care visit data include patient visits to primary providers' offices and hospital outpatient departments and EDs. Ambulatory care visit data reflect the first-listed (primary) diagnosis. These estimates are from the NAMCS and NHAMCS of the NCHS/CDC. Data for community health centers, which were included in estimates in previous years, were not available for 2015 NAMCS estimates included in this Update.

International Classification of Diseases

Morbidity (illness) and mortality (death) data in the United States have a standard classification system: the *ICD*. Approximately every 10 to 20 years, the *ICD* codes are revised to reflect changes over time in medical technology, diagnosis, or terminology. If necessary for comparability of mortality trends across the 9th and 10th *ICD* revisions, comparability ratios computed by the NCHS/CDC are applied as noted.[3] Effective with mortality data for 1999, we are using the 10th revision (*ICD-10*).[4] It will be a few more years before the 10th revision is systematically used for hospital discharge data and ambulatory care visit data, which are based on *ICD-9-CM*.[5]

Age Adjustment

Prevalence and mortality estimates for the United States or individual states comparing demographic groups or estimates over time are either age specific or age adjusted to the year 2000 standard population by the direct method.[6] International mortality data are age adjusted to the European standard.[7] Unless otherwise stated, all death rates in this publication are age adjusted and are deaths per 100 000 population.

Data Years for National Estimates

In this Update, we estimate the annual number of new (incidence) and recurrent cases of a disease in the United States by extrapolating to the US population in 2014 from rates reported in a community- or hospital-based study or multiple studies. Age-adjusted incidence rates by sex and race are also given in this report as observed in the study or studies. For US mortality, most numbers and rates are for 2016. For disease and risk factor prevalence, most rates in this report are calculated from the 2013 to 2016 NHANES. Because NHANES is conducted only in the noninstitutionalized population, we extrapolated the rates to the total US resident population on July 1, 2016, recognizing that this probably underestimates the total prevalence, given the relatively high prevalence in the institutionalized population. The numbers and rates of hospital inpatient discharges for the United States are for 2014. Numbers of visits to primary providers' offices and hospital EDs are for 2015, whereas hospital outpatient department visits are for 2011. Except as noted, economic cost estimates are for 2014 to 2015.

Cardiovascular Disease

For data on hospitalizations, primary provider office visits, and mortality, CVD is defined according to *ICD* codes given in Chapter 13 of the present document. This definition includes all diseases of the circulatory system, as well as congenital CVD. Unless otherwise specified, an estimate for total CVD does not include congenital CVD. Prevalence of CVD only includes people with hypertension, HD, stroke, PAD, and diseases of the veins.

Race/Ethnicity

Data published by governmental agencies for some racial groups are considered unreliable because of the small sample size in the studies. Because we try to provide data for as many racial and ethnic groups as possible, we show these data for informational and comparative purposes.

Contacts

If you have questions about statistics or any points made in this Update, please contact the AHA National Center, Office of Science & Medicine. Direct all media inquiries to News Media Relations at http://newsroom.heart.org/connect or 214-706-1173.

The AHA works diligently to ensure that this Update is error free. If we discover errors after publication, we will provide corrections at http://www.heart.org/statistics and in the journal *Circulation*.

REFERENCES

1. US Census Bureau population estimates: historical data: 2000s. US Census Bureau website. http://www.census.gov/popest/. Accessed August 4, 2016.
2. Centers for Disease Control and Prevention. U.S. Census Populations With Bridged Race Categories. http://www.cdc.gov/nchs/nvss/bridged_race.htm Accessed July 23, 2017.
3. National Center for Health Statistics. *Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities*. Hyattsville, MD: National Center for Health Statistics; 2015. http://www.cdc.gov/nchs/data/hus/hus15.pdf. Accessed June 15, 2016.
4. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision.* 2008 ed. Geneva, Switzerland: World Health Organization; 2009.
5. National Center for Health Statistics, Centers for Medicare and Medicaid Services. ICD-9-CM Official Guidelines for Coding and Reporting, 2011. http://www.cdc.gov/nchs/data/icd/icd9cm_guidelines_2011.pdf. Accessed October 29, 2012.
6. Anderson RN, Rosenberg HM. Age standardization of death rates: implementation of the year 2000 standard. *Natl Vital Stat Rep*. 1998;47:1–16, 20.
7. World Health Organization. *World Health Statistics Annual*. Geneva, Switzerland: World Health Organization; 1998.

2. CARDIOVASCULAR HEALTH

See Tables 2-1 through 2-6 and Charts 2-1 through 2-12

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In 2011, the AHA created a new set of central Strategic Impact Goals to drive organizational priorities for the current decade:

> *By 2020, to improve the cardiovascular health of all Americans by 20%, while reducing deaths from CVDs and stroke by 20%.*[1]

These goals introduced a new concept of cardiovascular health, characterized by 7 metrics (Life's Simple 7),[2] including health behaviors (diet quality, PA, smoking, BMI) and health factors (blood cholesterol, BP, blood glucose). Ideal cardiovascular health is defined by the absence of clinically manifest CVD together with the simultaneous presence of optimal levels of all 7 metrics, including not smoking and having a healthy diet pattern, sufficient PA, normal body weight, and normal levels of TC, BP, and fasting blood glucose, in the absence of drug treatment (Table 2-1). Because a spectrum of cardiovascular health is possible and the ideal cardiovascular health profile is known to be rare in the US population, a broader spectrum of cardiovascular health can also be represented as being *ideal*, *intermediate*, or *poor* for each of the health behaviors and health factors.[1] Table 2-1 provides the specific definitions for ideal, intermediate, and poor cardiovascular health for each of the 7 metrics, both for adults and for children.

This concept of cardiovascular health represented a new focus for the AHA, with 3 central and novel emphases:

- An expanded focus on CVD prevention and promotion of positive "cardiovascular health," in addition to the treatment of established CVD.
- Efforts to promote both healthy behaviors (healthy diet pattern, appropriate energy intake, PA, and nonsmoking) and healthy biomarker levels (optimal blood lipids, BP, glucose levels) throughout the lifespan.
- Population-level health promotion strategies to shift the majority of the public toward greater cardiovascular health, in addition to targeting those individuals at greatest CVD risk, because healthy lifestyles in all domains are uncommon throughout the US population.

Beginning in 2011, and recognizing the time lag in the nationally representative US data sets, this chapter in the annual Statistical Update has evaluated and published metrics and information to provide insights into both progress toward meeting the 2020 AHA goals and areas that require greater attention to meet these goals. The AHA has advocated for raising the visibility of patient-reported cardiovascular health status, which includes symptom burden, functional status, and health-related quality of life, as an indicator of cardiovascular health in future organizational goal setting.[3]

Abbreviations Used in Chapter 2

AF	atrial fibrillation
AHA	American Heart Association
BMI	body mass index
BP	blood pressure
CAC	coronary artery calcification
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
DM	diabetes mellitus
F&V	fruits and vegetables
FPG	fasting plasma glucose
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HBP	high blood pressure
HF	heart failure
HR	hazard ratio
IHD	ischemic heart disease
IMT	intima-media thickness
MI	myocardial infarction
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
PA	physical activity
PE	pulmonary embolism
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SBP	systolic blood pressure
SFat	saturated fat
SSB	sugar-sweetened beverage
TC	total cholesterol
VTE	venous thromboembolism

Relevance of Ideal Cardiovascular Health

- Since the AHA announced its 2020 Impact Goals, multiple independent investigations (summaries below) have confirmed the importance of these metrics and the concept of cardiovascular health. Findings include strong inverse, stepwise associations in the United States of the metrics and cardiovascular health with all-cause mortality, CVD mortality, and HF; with preclinical measures of atherosclerosis such as carotid IMT, arterial stiffness, and coronary artery calcium (CAC) prevalence and progression; with physical functional impairment and frailty[4]; and with cognitive decline and depression.[4,5] Similar relationships have also been seen in non-US populations.[4–9]
- A recent study in a large Hispanic/Latino cohort study in the United States found that associations of CVD and cardiovascular health metrics compared favorably with existing national estimates;

however, some of the associations varied by sex and heritage.[10]

- A recent study in blacks found that risk of incident HF was 61% lower among those with ≥4 ideal cardiovascular health metrics than among those with 0 to 2 ideal metrics.[11]
- Ideal health behaviors and ideal health factors are each independently associated with lower CVD risk in a stepwise fashion (Chart 2-1). In other words, across any level of health behaviors, health factors are associated with incident CVD; conversely, across any level of health factors, health behaviors are still associated with incident CVD.[12]
- Analyses from the US Burden of Disease Collaborators demonstrated that poor levels of each of the 7 health factors and behaviors resulted in substantial mortality and morbidity in the United States in 2010. The top risk factor related to overall disease burden was suboptimal diet, followed by tobacco smoking, high BMI, raised BP, high fasting plasma glucose, and physical inactivity.[13]
- A stepwise association was present between the number of ideal cardiovascular health metrics and risk of death based on NHANES 1988 to 2006 data.[14] The HRs for people with 6 or 7 ideal health metrics compared with 0 ideal health metrics were 0.49 (95% CI, 0.33–0.74) for all-cause mortality, 0.24 (95% CI, 0.13–0.47) for CVD mortality, and 0.30 (95% CI, 0.13–0.68) for IHD mortality.[14]
- A recent meta-analysis of 9 prospective cohort studies involving 12 878 participants reported that achieving the most ideal cardiovascular health metrics was associated with a lower risk of all-cause mortality (RR, 0.55; 95% CI, 0.37–0.80), cardiovascular mortality (RR, 0.25; 95% CI, 0.10–0.63), CVD (RR, 0.20; 95% CI, 0.11–0.37), and stroke (RR, 0.31; 95% CI, 0.25–0.38).[15]
- The adjusted population attributable fractions for CVD mortality were as follows[14]:
  - — 40.6% (95% CI, 24.5%–54.6%) for HBP
  - — 13.7% (95% CI, 4.8%–22.3%) for smoking
  - — 13.2% (95% CI, 3.5%–29.2%) for poor diet
  - — 11.9% (95% CI, 1.3%–22.3%) for insufficient PA
  - — 8.8% (95% CI, 2.1%–15.4%) for abnormal glucose levels
- The adjusted population attributable fractions for IHD mortality were as follows[14]:
  - — 34.7% (95% CI, 6.6%–57.7%) for HBP
  - — 16.7% (95% CI, 6.4%–26.6%) for smoking
  - — 20.6% (95% CI, 1.2%–38.6%) for poor diet
  - — 7.8% (95% CI, 0%–22.2%) for insufficient PA
  - — 7.5% (95% CI, 3.0%–14.7%) for abnormal glucose levels
- Data from the REGARDS cohort also demonstrated a stepwise association between cardiovascular health metrics and incident stroke. Using a cardiovascular health score scale ranging from 0 to 14, every unit increase in cardiovascular health was associated with an 8% lower risk of incident stroke (HR, 0.92; 95% CI, 0.88–0.95), with a similar effect size for white (HR, 0.91; 95% CI, 0.86–0.96) and black (HR, 0.93; 95% CI, 0.87–0.98) participants.[16]
- The Cardiovascular Lifetime Risk Pooling Project showed that adults with all-optimal risk factor levels (similar to having ideal cardiovascular health factor levels of cholesterol, blood sugar, and BP, as well as not smoking) have substantially longer overall and CVD-free survival than those who have poor levels of ≥1 of these cardiovascular health factor metrics. For example, at an index age of 45 years, males with optimal risk factor profiles lived on average 14 years longer free of all CVD events, and 12 years longer overall, than people with ≥2 risk factors.[17]
- Better cardiovascular health is associated with less incident HF,[18] less subclinical vascular disease,[19,20] better global cognitive performance and cognitive function,[21,22] lower prevalence[23] and incidence[24] of depressive symptoms, lower loss of physical functional status,[25] longer leukocyte telomere length,[26] less end-stage renal disease,[27] and less pneumonia, chronic obstructive pulmonary disease,[28] VTE/PE,[29] lower prevalence of aortic sclerosis and stenosis,[30] better prognosis after MI,[31] and lower risk of AF.[32] In addition, a recent study among a sample of Hispanics/Latinos residing in the United States reported that a measure of greater positive psychological functioning (dispositional optimism) was associated with higher cardiovascular health scores as defined by the AHA.[33]
- On the basis of NHANES 1999 to 2006 data, several social risk factors (low family income, low education level, minority race, and single-living status) were related to lower likelihood of attaining better cardiovascular health as measured by Life's Simple 7 scores.[34]
- Cardiovascular health metrics are also associated with lower healthcare costs. A recent report from a large, ethnically diverse insured population[35] found that people with 6 or 7 and those with 3 to 5 of the cardiovascular health metrics in the ideal category had a $2021 and $940 lower annual mean healthcare expenditure, respectively, than those with 0 to 2 ideal health metrics.

Cardiovascular Health: Current Prevalence (See Table 2-2 and Charts 2-2 through 2-9)

- The most up-to-date data on national prevalence of ideal, intermediate, and poor levels of each of the 7 cardiovascular health metrics are shown for adolescents and teens (Chart 2-2) and for adults (Chart 2-3).
- For most metrics, the prevalence of ideal levels of health behaviors and health factors is higher in US children than in US adults. The main exceptions are diet and PA, for which the prevalence of ideal levels in children is worse than in adults.
- Among US children aged 12 to 19 years (Chart 2-2), the prevalence (unadjusted) of ideal levels of cardiovascular health behaviors and factors currently varies from <1% for the healthy diet pattern (ie, <1 in 100 US children meets at least 4 of the 5 dietary components or a corresponding AHA diet score of at least 80) to >85% for the smoking, BP, and fasting glucose metrics (unpublished AHA tabulation).
- Among US adults (Chart 2-3), the age-standardized prevalence of ideal levels of cardiovascular health behaviors and factors currently varies from <1% for having a healthy diet pattern to up to 78% for never having smoked or being a former smoker who has quit for >12 months. In 2015 to 2016, only about half (49%) of all adults had ideal levels of TC (<200 mg/dL).
- Age-standardized and age-specific prevalence estimates for ideal cardiovascular health and for ideal levels of each of its components are shown for 2013 to 2014 and 2015 to 2016 in Table 2-2. NHANES 2013 to 2014 data were used for some of the statistics that required nutritional data and for DM. The prevalence of ideal levels across 7 health factors and health behaviors generally was lower with increasing age. The exception was diet, for which prevalence of ideal levels was highest in older adults but still very low (<1%).
- Chart 2-4 displays the prevalence estimates for the population of US children (12–19 years of age) meeting different numbers of criteria for ideal cardiovascular health (of 7 possible) in 2013 to 2014.
  - — Few US children 12 to 19 years of age (≈4%) meet <2 criteria for ideal cardiovascular health.
  - — Approximately half of US children (48%) meet 3 or 4 criteria for ideal cardiovascular health, and ≈47% meet 5 or 6 criteria.
  - — <1% of children meet all 7 criteria for ideal cardiovascular health.
- Charts 2-5 and 2-6 display the age-standardized prevalence estimates of US adults meeting different numbers of criteria for ideal cardiovascular health in 2013 to 2014, overall and stratified by age, sex, and race.
  - — Approximately 2% of US adults meet 0 of the 7 criteria at ideal levels, and another 15% meet only 1 of 7 criteria. Having ≤1 ideal metric is much more common among adults (17%) than among children (12–19 years of age), for whom having ≤1 ideal metric is very rare (<1%).
  - — Most US adults (≈62%) have 3 or fewer cardiovascular metrics in the ideal cardiovascular health range.
  - — Approximately 13% of US adults meet ideal levels in 5 categories, 5% have 6 ideal metrics, and virtually 0% meet all 7 criteria at ideal levels.
  - — Presence of ideal cardiovascular health by age and sex is shown in Chart 2-5. Younger adults are more likely to meet greater numbers of ideal metrics than are older adults. More than 60% of Americans >60 years of age have ≤2 metrics at ideal levels. At any age, females tend to have more metrics at ideal levels than do males.
  - — Presence of ideal cardiovascular health also varies by race (Chart 2-6). Blacks and Hispanics tend to have fewer metrics at ideal levels than whites or other races. Having ≥4 ideal metrics is most common among Asians (48%), followed by whites (38%), Hispanics (34%), blacks (30%), and others (24%).
- Chart 2-7 displays the age-standardized percentages of US adults and the percentages of children who have ≥5 of the metrics (of 7 possible) at ideal levels in 2007 to 2008 and 2013 to 2014.
  - — Currently, nearly half (47%) of US children 12 to 19 years of age have ≥5 metrics at ideal levels, with similar prevalence in boys (49%) and girls (46%).
  - — In comparison, only 18% of US adults have ≥5 metrics at ideal levels, with lower prevalence in males (15%) than in females (22%).
  - — All populations showed improvement compared with baseline year 2007 to 2008.
- Chart 2-8 displays the age-standardized percentages of US adults and percentages of children by race/ethnicity who have ≥5 of the metrics (of 7 possible) at ideal levels.
  - — In adults, NH Asians tend to have a higher prevalence of having ≥5 metrics at ideal levels

than other racial/ethnic groups. In children, the prevalence of ≥5 metrics at ideal levels is highest for NH whites (53%), followed by NH Asians (48%), Hispanics (40%), and NH blacks (36%).

- Chart 2-9 displays the age-standardized percentages of US adults meeting different numbers of criteria for both poor and ideal cardiovascular health in 2013 to 2014. Meeting the AHA 2020 Strategic Impact Goals is predicated on reducing the relative percentage of those with poor levels while increasing the relative percentage of those with ideal levels for each of the 7 metrics.
  - Approximately 92% of US adults have ≥1 metric at poor levels.
  - Approximately 36% of US adults have ≥3 metrics at poor levels.
  - Few US adults (3%) have ≥5 metrics at poor levels.
  - More US adults have 4 to 6 ideal metrics than 4 to 6 poor metrics.

Cardiovascular Health: Trends Over Time (See Charts 2-10 and 2-11)

- The trends over the past decade in each of the 7 cardiovascular health metrics (for diet, trends from 1999–2000 through 2015–2016) are shown in Chart 2-10 (for children 12–19 years of age) and Chart 2-11 (for adults ≥20 years of age).
  - Among children, from 1999 to 2000 to 2015 to 2016, the prevalence of nonsmoking, ideal TC, and ideal BP improved. For example, the prevalence of nonsmoking among children aged 12 to 19 years increased from 76% to 94%, and for ideal TC, the prevalence increased from 72% to 78%. However, there were no improvements in meeting ideal levels for PA, BMI, and blood glucose. For example, the prevalence of ideal BMI declined from 70% in 1999 to 2000 to 60% in 2015 to 2016.
  - Among adults, the prevalence of nonsmoking and ideal TC, BP, and PA improved. For example, nonsmoking increased from 73% of the adult population in 1999 to 2000 to 79% in 2015 to 2016. For TC, the prevalence of ideal levels increased from 45% of the adult population in 1999 to 2000 to 49% of the adult population in 2015 to 2016.
- On the basis of NHANES data from 1988 to 2008, if current trends continue, estimated cardiovascular health is projected to improve by 6% between 2010 and 2020, short of the AHA's goal of 20% improvement.[36] On the basis of current trends among individual metrics, anticipated declines in prevalence of smoking, high cholesterol, and HBP (in males) would be offset by substantial increases in the prevalence of obesity and DM and smaller changes in ideal dietary patterns or PA.[36]
- On the basis of these projections for cardiovascular health factors and behaviors, CHD deaths are projected to decrease by 30% between 2010 and 2020 because of projected improvements in TC, SBP, smoking, and PA (≈167 000 fewer deaths), offset by increases in DM and BMI (≈24 000 more deaths).[37]

Achieving the 2020 Impact Goals[1] (See Tables 2-3 through 2-6 and Chart 2-12)

To achieve the AHA's 2020 Impact Goals of reducing deaths attributable to CVD and stroke by 20%, continued emphasis is needed on the treatment of acute CVD events and secondary prevention through treatment and control of health behaviors and risk factors.

- Taken together, the data continue to demonstrate both the tremendous relevance of the AHA 2020 Impact Goals for cardiovascular health and the progress that will be needed to achieve these goals by the year 2020 (Chart 2-12).
- For each cardiovascular health metric, modest shifts in the population distribution toward improved health would produce appreciable increases in the proportion of Americans in both ideal and intermediate categories. For example, on the basis of NHANES 2015 to 2016, the current prevalence of ideal levels of BP among US adults is 41%. To achieve the 2020 goals, a 20% relative improvement would require an increase in this proportion to 49.2% by 2020 (41% × 1.20). On the basis of NHANES data, a reduction in population mean BP of just 5 mm Hg would result in 52% of US adults having ideal levels of BP, which represents a 27% relative improvement in this metric (Table 2-3). Larger population reductions in BP would lead to even greater numbers of people with ideal levels of BP. Such small reductions in population BP could result from small health behavior changes at a population level, such as increased PA, increased fruit and vegetable consumption, decreased sodium intake, decreased adiposity, or some combination of these and other lifestyle changes, with

resulting substantial projected decreases in CVD rates in US adults.[38]

- A range of complementary strategies and approaches can lead to improvements in cardiovascular health.[37] These include the following:
  - — Individual-focused approaches that target lifestyle and treatments at the individual level (Table 2-4).
  - — Healthcare systems approaches that encourage, facilitate, and reward efforts by providers to improve health behaviors and health factors (Table 2-5).
  - — Population approaches that target lifestyle and treatments in schools or workplaces, local communities, and states, as well as throughout the nation (Table 2-6).
- Such approaches can focus on both (1) improving cardiovascular health among those who currently have less than optimal levels and (2) preserving cardiovascular health among those who currently have ideal levels (in particular, children, adolescents, and young adults) as they age.
- The metrics with the greatest potential for improvement in the United States are health behaviors, including diet quality, PA, and body weight. However, each of the 7 cardiovascular health metrics can be improved and deserves major focus.

Table 2-1. Definitions of Poor, Intermediate, and Ideal Cardiovascular Health for Each Metric in the AHA 2020 Goals

	Level of Cardiovascular Health for Each Metric		
	Poor	Intermediate	Ideal
Current smoking			
Adults ≥20 y of age	Yes	Former ≥12 mo	Never or quit >12 mo
Children 12–19 y of age*	Tried during the prior 30 d	…	Never tried; never smoked whole cigarette
BMI†			
Adults ≥20 y of age	≥30 kg/m²	25–29.9 kg/m²	<25 kg/m²
Children 2–19 y of age	>95th percentile	85th–95th percentile	<85th percentile
Physical activity			
Adults ≥20 y of age	None	1–149 min/wk moderate or 1–74 min/wk vigorous or 1–149 min/wk moderate + 2× vigorous	≥150 min/wk moderate or ≥75 min/wk vigorous or ≥150 min/wk moderate + 2× vigorous
Children 12–19 y of age	None	>0 and <60 min of moderate or vigorous every day	≥60 min of moderate or vigorous every day
Healthy diet pattern, No. of components (AHA diet score)‡			
Adults ≥20 y of age	<2 (0–39)	2–3 (40–79)	4–5 (80–100)
Children 5–19 y of age	<2 (0–39)	2–3 (40–79)	4–5 (80–100)
Total cholesterol, mg/dL			
Adults ≥20 y of age	≥240	200–239 or treated to goal	<200
Children 6–19 y of age	≥200	170–199	<170
Blood pressure			
Adults ≥20 y of age	SBP ≥140 mm Hg or DBP ≥90 mm Hg	SBP 120–139 mm Hg or DBP 80–89 mm Hg or treated to goal	<120 mm Hg/<80 mm Hg
Children 8–19 y of age	>95th percentile	90th–95th percentile or SBP ≥120 mm Hg or DBP ≥80 mm Hg	<90th percentile
Fasting plasma glucose, mg/dL			
Adults ≥20 y of age	≥126	100–125 or treated to goal	<100
Children 12–19 y of age	≥126	100–125	<100

AHA indicates American Heart Association; BMI, body mass index; DBP, diastolic blood pressure; ellipses (…), data not available; and SBP, systolic blood pressure.
*Age ranges in children for each metric depend on guidelines and data availability.
†Represents appropriate energy balance, that is, appropriate dietary quantity and physical activity to maintain normal body weight.
‡In the context of a healthy dietary pattern that is consistent with a Dietary Approaches to Stop Hypertension (DASH)–type eating pattern, to consume ≥4.5 cups/d of fruits and vegetables, ≥2 servings/wk of fish, and ≥3 servings/d of whole grains and no more than 36 oz/wk of sugar-sweetened beverages and 1500 mg/d of sodium. The consistency of one's diet with these dietary targets can be described using a continuous AHA diet score, scaled from 0 to 100 (see chapter on Nutrition).
Modified from Lloyd-Jones et al.[1]

Table 2-2. Prevalence of Ideal Cardiovascular Health and Its Components in the US Population in Selected Age Strata: NHANES 2013 to 2014 and 2015 to 2016

	NHANES Cycle	Age 12–19 y	Age ≥20 y*	Age 20–39 y	Age 40–59 y	Age ≥60 y
Ideal cardiovascular health profile (7/7)	2013–2014	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
≥6 Ideal	2013–2014	9.4 (1.3)	5.1 (0.4)	9.0 (0.9)	4.2 (0.6)	0.6 (0.3)
≥5 Ideal	2013–2014	47.2 (2.0)	18.1 (1.0)	30.8 (1.8)	13.3 (1.5)	5.0 (0.9)
Ideal health factors (4/4)	2013–2014	57.7 (2.1)	18.4 (0.9)	32.6 (2.1)	13.1 (1.2)	2.9 (0.5)
Total cholesterol <200 mg/dL	2015–2016	77.7 (1.3)	49.4 (1.1)	72.9 (1.4)	39.0 (1.7)	25.2 (1.2)
SBP <120/DBP <80 mm Hg	2015–2016	85.2 (1.0)	41.0 (1.2)	61.7 (1.7)	34.1 (2.0)	15.6 (2.1)
Nonsmoker	2015–2016	93.6 (0.9)	78.8 (1.0)	75.0 (1.4)	77.0 (1.5)	86.5 (1.4)
FPG <100 mg/dL and HbA_{1c} <5.7%	2013–2014	87.6 (1.0)	60.8 (1.1)	78.5 (1.3)	57.7 (1.8)	35.4 (1.7)
Ideal health behaviors (4/4)	2013–2014	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
PA at goal	2013–2014	27.7 (1.2)	36.7 (1.1)	45.0 (2.0)	34.2 (1.6)	26.7 (1.5)
Nonsmoker	2015–2016	91.4 (1.4)	77.1 (1.2)	72.6 (1.4)	74.7 (2.1)	87.7 (1.2)
BMI <25 kg/m²	2013–2014	63.1 (2.4)	29.6 (0.8)	36.3 (1.5)	25.4 (1.4)	25.6 (1.1)
4–5 Diet goals met†	2013–2014	0.0 (0.0)	0.2 (0.1)	0.0 (0.0)	0.2 (0.1)	0.4 (0.2)
F&V ≥4.5 C/d	2013–2014	6.5 (1.4)	10.3 (0.7)	8.5 (1.0)	9.7 (1.2)	13.8 (1.7)
Fish ≥2 svg/wk	2013–2014	8.5 (1.4)	20.1 (1.6)	16.4 (1.7)	21.8 (2.1)	23.1 (2.2)
Sodium <1500 mg/d	2013–2014	0.5 (0.5)	0.6 (0.2)	0.9 (0.3)	0.6 (0.4)	0.2 (0.1)
SSB <36 oz/wk	2013–2014	37.0 (2.3)	51.2 (1.9)	41.8 (1.9)	53.0 (3.3)	64.5 (2.8)
Whole grains ≥3 1-oz/d	2013–2014	3.4 (1.1)	7.1 (0.4)	5.3 (0.8)	6.6 (0.6)	10.4 (1.1)
Secondary diet metrics						
Nuts/legumes/seeds ≥4 svg/wk	2013–2014	31.7 (1.9)	49.7 (1.3)	46.8 (2.1)	51.0 (2.3)	53.5 (2.4)
Processed meats ≤2 svg/wk	2013–2014	44.4 (3.2)	45.0 (1.3)	44.7 (1.5)	47.3 (2.4)	41.4 (2.3)
SFat <7% total kcal	2013–2014	8.9 (1.3)	9.2 (0.4)	9.7 (0.9)	9.4 (0.9)	8.4 (1.2)

Values are % (standard error). BMI indicates body mass index; DBP, diastolic blood pressure; F&V, fruits and vegetables; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c} (glycosylated hemoglobin); NHANES, National Health and Nutrition Examination Survey; PA, physical activity; SBP, systolic blood pressure; SFat, saturated fat; SSB, sugar-sweetened beverages; and svg, servings.

*Standardized to the age distribution of the 2000 US standard population.

†Scaled to 2000 kcal/d and in the context of appropriate energy balance and a DASH (Dietary Approaches to Stop Hypertension)–type eating pattern.

Table 2-3. Reduction in BP Required to Increase Prevalence of Ideal BP Among Adults ≥20 Years Old: NHANES 2015 to 2016

	%
Percent BP ideal among adults, 2015–2016	41.0
20% Relative increase	49.2
Percent whose BP would be ideal if population mean BP were lowered by*:	
2 mm Hg	44.6
3 mm Hg	47.2
4 mm Hg	49.0
5 mm Hg	52.0

Standardized to the age distribution of the 2000 US standard population. BP indicates blood pressure; and NHANES, National Health and Nutrition Examination Survey.

*Reduction in BP = (observed average systolic BP – X mm Hg) and (observed average diastolic BP – X mm Hg).

Table 2-4. Evidence-Based Individual Approaches for Improving Health Behaviors and Health Factors in the Clinic Setting

Set specific, shared, proximal goals (*Class I; Level of Evidence A*): Set specific, proximal goals with the patient, including a personalized plan to achieve the goals (eg, over the next 3 mo, increase fruits by 1 serving/d, reduce smoking by half a pack/d, or walk 30 min 3 times/wk).
Establish self-monitoring (*Class I; Level of Evidence A*): Develop a strategy for self-monitoring, such as a dietary or physical activity diary or web-based or mobile applications.
Schedule regular follow-up (*Class I; Level of Evidence A*): Schedule regular follow-up (in person, telephone, written, and electronic), with clear frequency and duration of contacts, to assess success, reinforce progress, and set new goals as necessary.
Provide feedback (*Class I; Level of Evidence A*): Provide feedback on progress toward goals, including using in-person, telephone, and/or electronic feedback.
Increase self-efficacy (*Class I; Level of Evidence A*): Increase the patient's perception that they can successfully change their behavior.*
Use motivational interviewing† (*Class I; Level of Evidence A*): Use motivational interviewing when patients are resistant or ambivalent about behavior change.
Provide long-term support (*Class I; Level of Evidence B*): Arrange long-term support from family, friends, or peers for behavior change, such as in other workplace, school, or community-based programs.
Use a multicomponent approach (*Class I; Level of Evidence A*): Combine ≥2 of the above strategies into the behavior change efforts.

*Examples of approaches include mastery experiences (set a reasonable, proximal goal that the person can successfully achieve); vicarious experiences (have the person see someone with similar capabilities performing the behavior, such as walking on a treadmill or preparing a healthy meal); physiological feedback (explain to the patient when a change in their symptoms is related to worse or improved behaviors); and verbal persuasion (persuade the person that you believe in their capability to perform the behavior).

†Motivational interviewing represents use of individual counseling to explore and resolve ambivalence toward changing behavior. Major principles include fostering the person's own awareness and resolution of their ambivalence, as well as their own self-motivation to change, in a partnership with the counselor or provider.

Modified from Artinian et al.[40] Copyright © 2010, American Heart Association, Inc.

Table 2-5. Evidence-Based Healthcare Systems Approaches to Support and Facilitate Improvements in Health Behaviors and Health Factors[41–43]

Electronic systems for scheduling and tracking initial visits and regular follow-up contacts for behavior change and treatments
Electronic medical records systems to help assess, track, and report on specific health behaviors (diet, PA, tobacco, body weight) and health factors (BP, cholesterol, glucose), as well as to provide feedback and the latest guidelines to providers
Practical paper or electronic toolkits for assessment of key health behaviors and health factors, including during, before, and after provider visits
Electronic systems to facilitate provision of feedback to patients on their progress during behavior change and other treatment efforts
Education and ongoing training for providers on evidence-based behavior change strategies, as well as the most relevant behavioral targets, including training on relevant ethnic and cultural issues
Integrated systems to provide coordinated care by multidisciplinary teams of providers, including physicians, nurse practitioners, dietitians, PA specialists, and social workers
Reimbursement guidelines and incentives that reward efforts to change health behaviors and health factors. Restructuring of practice goals and quality benchmarks to incorporate health behavior (diet, PA, tobacco, body weight) and health factor (BP, cholesterol, glucose) interventions and targets for both primary and secondary prevention

BP indicates blood pressure; and PA, physical activity.

Table 2-6. Summary of Evidence-Based Population Approaches for Improving Diet, Increasing Physical Activity, and Reducing Tobacco Use*

Diet	
Media and education	Sustained, focused media and educational campaigns, using multiple modes, for increasing consumption of specific healthful foods or reducing consumption of specific less healthful foods or beverages, either alone (*Class IIa; Level of Evidence B*) or as part of multicomponent strategies (*Class I; Level of Evidence B*)†‡§
	On-site supermarket and grocery store educational programs to support the purchase of healthier foods (*Class IIa; Level of Evidence B*)†
Labeling and information	Mandated nutrition facts panels or front-of-pack labels/icons as a means to influence industry behavior and product formulations (*Class IIa; Level of Evidence B*)†
Economic incentives	Subsidy strategies to lower prices of more healthful foods and beverages (*Class I; Level of Evidence A*)†
	Tax strategies to increase prices of less healthful foods and beverages (*Class IIa; Level of Evidence B*)†
	Changes in both agricultural subsidies and other related policies to create an infrastructure that facilitates production, transportation, and marketing of healthier foods, sustained over several decades (*Class IIa; Level of Evidence B*)†
Schools	Multicomponent interventions focused on improving both diet and physical activity, including specialized educational curricula, trained teachers, supportive school policies, a formal physical education program, healthy food and beverage options, and a parental/family component (*Class I; Level of Evidence A*)†
	School garden programs, including nutrition and gardening education and hands-on gardening experiences (*Class IIa; Level of Evidence A*)†
	Fresh fruit and vegetable programs that provide free fruits and vegetables to students during the school day (*Class IIa; Level of Evidence A*)†
Workplaces	Comprehensive worksite wellness programs with nutrition, physical activity, and tobacco cessation/prevention components (*Class IIa; Level of Evidence A*)†
	Increased availability of healthier food/beverage options and/or strong nutrition standards for foods and beverages served, in combination with vending machine prompts, labels, or icons to make healthier choices (*Class IIa; Level of Evidence B*)†
Local environment	Increased availability of supermarkets near homes (*Class IIa; Level of Evidence B*)†‡‖
Restrictions and mandates	Restrictions on television advertisements for less healthful foods or beverages advertised to children (*Class I; Level of Evidence B*)†
	Restrictions on advertising and marketing of less healthful foods or beverages near schools and public places frequented by youths (*Class IIa; Level of Evidence B*)†
	General nutrition standards for foods and beverages marketed and advertised to children in any fashion, including on-package promotion (*Class IIa; Level of Evidence B*)†
	Regulatory policies to reduce specific nutrients in foods (eg, *trans* fats, salt, certain fats) (*Class I; Level of Evidence B*)†§
Physical activity	
Labeling and information	Point-of-decision prompts to encourage use of stairs (*Class IIa; Level of Evidence A*)†
Economic incentives	Increased gasoline taxes to increase active transport/commuting (*Class IIa; Level of Evidence B*)†
Schools	Multicomponent interventions focused on improving both diet and physical activity, including specialized educational curricula, trained teachers, supportive school policies, a formal physical education program, serving of healthy food and beverage options, and a parental/family component (*Class IIa; Level of Evidence A*)†
	Increased availability and types of school playground spaces and equipment (*Class I; Level of Evidence B*)†
	Increased number of physical education classes, revised physical education curricula to increase time in at least moderate activity, and trained physical education teachers at schools (*Class IIa; Level of Evidence A/Class IIb; Level of Evidence A*¶)†
	Regular classroom physical activity breaks during academic lessons (*Class IIa; Level of Evidence A*)†§

(Continued)

Table 2-6. Continued

Workplaces	Comprehensive worksite wellness programs with nutrition, physical activity, and tobacco cessation/prevention components (*Class IIa; Level of Evidence A*)†
	Structured worksite programs that encourage activity and also provide a set time for physical activity during work hours (*Class IIa; Level of Evidence B*)†
	Improving stairway access and appeal, potentially in combination with "skip-stop" elevators that skip some floors (*Class IIa; Level of Evidence B*)†
	Adding new or updating worksite fitness centers (*Class IIa; Level of Evidence B*)†
Physical activity Continued	
Local environment	Improved accessibility of recreation and exercise spaces and facilities (eg, building of parks and playgrounds, increasing operating hours, use of school facilities during nonschool hours) (*Class IIa; Level of Evidence B*)†
	Improved land-use design (eg, integration and interrelationships of residential, school, work, retail, and public spaces) (*Class IIa; Level of Evidence B*)†
	Improved sidewalk and street design to increase active commuting (walking or bicycling) to school by children (*Class IIa; Level of Evidence B*)†
	Improved traffic safety (*Class IIa; Level of Evidence B*)†
	Improved neighborhood aesthetics (to increase activity in adults) (*Class IIa; Level of Evidence B*)†
	Improved walkability, a composite indicator that incorporates aspects of land-use mix, street connectivity, pedestrian infrastructure, aesthetics, traffic safety, and crime safety (*Class IIa; Level of Evidence B*)†
Smoking	
Media and education	Sustained, focused media and educational campaigns to reduce smoking, either alone (*Class IIa; Level of Evidence B*) or as part of larger multicomponent population-level strategies (*Class I; Level of Evidence A*)†
Labeling and information	Cigarette package warnings, especially those that are graphic and health related (*Class I; Level of Evidence B*)†‡§
Economic incentives	Higher taxes on tobacco products to reduce use and fund tobacco control programs (*Class I; Level of Evidence A*)†‡§
Schools and workplaces	Comprehensive worksite wellness programs with nutrition, physical activity, and tobacco cessation/prevention components (*Class IIa; Level of Evidence A*)†
Local environment	Reduced density of retail tobacco outlets around homes and schools (*Class I; Level of Evidence B*)†
	Development of community telephone lines for cessation counseling and support services (*Class I; Level of Evidence A*)†
Restrictions and mandates	Community (city, state, or federal) restrictions on smoking in public places (*Class I; Level of Evidence A*)†
	Local workplace-specific restrictions on smoking (*Class I; Level of Evidence A*)†‡§
	Stronger enforcement of local school-specific restrictions on smoking (*Class IIa; Level of Evidence B*)†
	Local residence-specific restrictions on smoking (*Class IIa; Level of Evidence B*)†§
	Partial or complete restrictions on advertising and promotion of tobacco products (*Class I; Level of Evidence B*)†

*The specific population interventions listed here are either a Class I or IIa recommendation with a Level of Evidence grade of either A or B.

†At least some evidence from studies conducted in high-income Western regions and countries (eg, North America, Europe, Australia, New Zealand).

‡At least some evidence from studies conducted in high-income non-Western regions and countries (eg, Japan, Hong Kong, South Korea, Singapore).

§At least some evidence from studies conducted in low- or middle-income regions and countries (eg, Africa, China, Pakistan, India).

‖Based on cross-sectional studies only; only 2 longitudinal studies have been performed, with no significant relations seen.

¶*Class IIa; Level of Evidence A* for improving physical activity; *Class IIb; Level of Evidence B* for reducing adiposity.

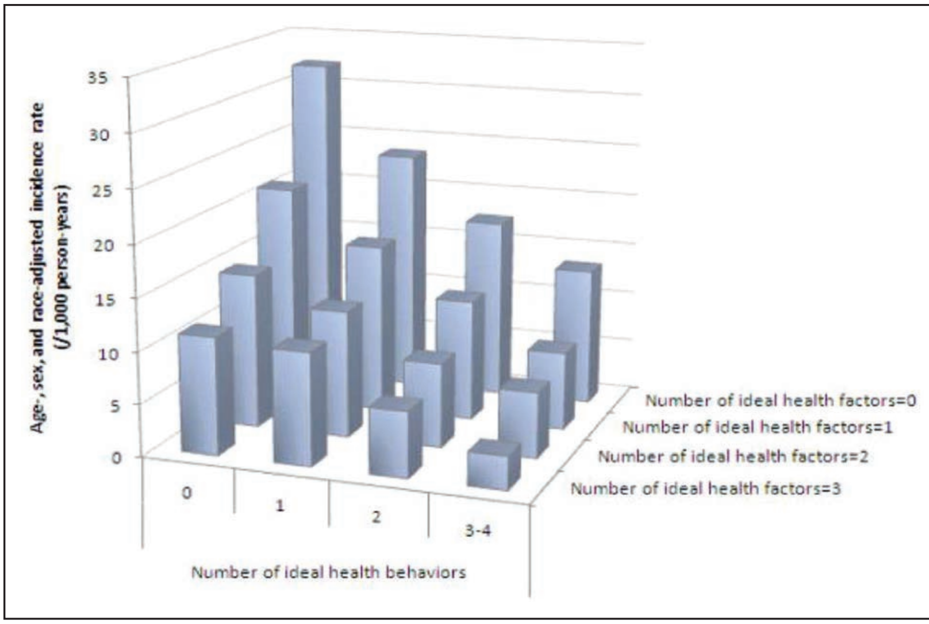

Chart 2-1. **Incidence of cardiovascular disease according to the number of ideal health behaviors and health factors.**
Reprinted from Folsom et al[12] with permission from the American College of Cardiology Foundation. Copyright © 2011, the American College of Cardiology Foundation.

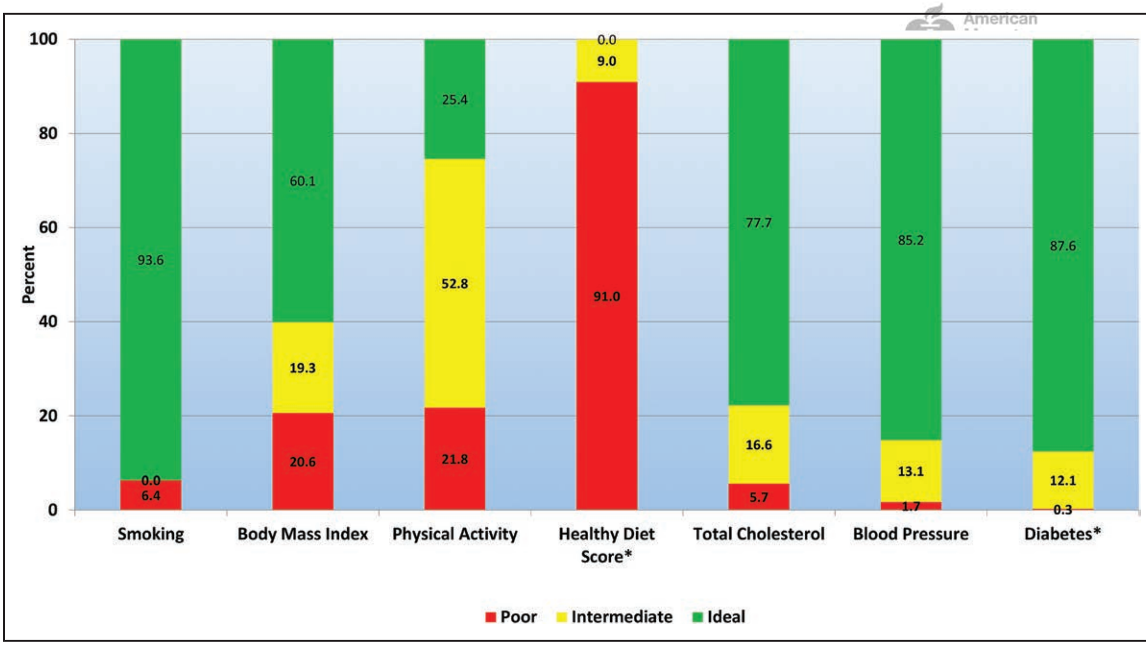

Chart 2-2. **Prevalence (unadjusted) estimates of poor, intermediate, and ideal cardiovascular health for each of the 7 metrics of cardiovascular health in the AHA 2020 goals, among US children aged 12 to 19 years.**
AHA indicates American Heart Association.
*Healthy Diet Score reflects 2013 to 2014 NHANES (National Health and Nutrition Examination Survey).
Source: National Center for Health Statistics, NHANES, 2015 to 2016.

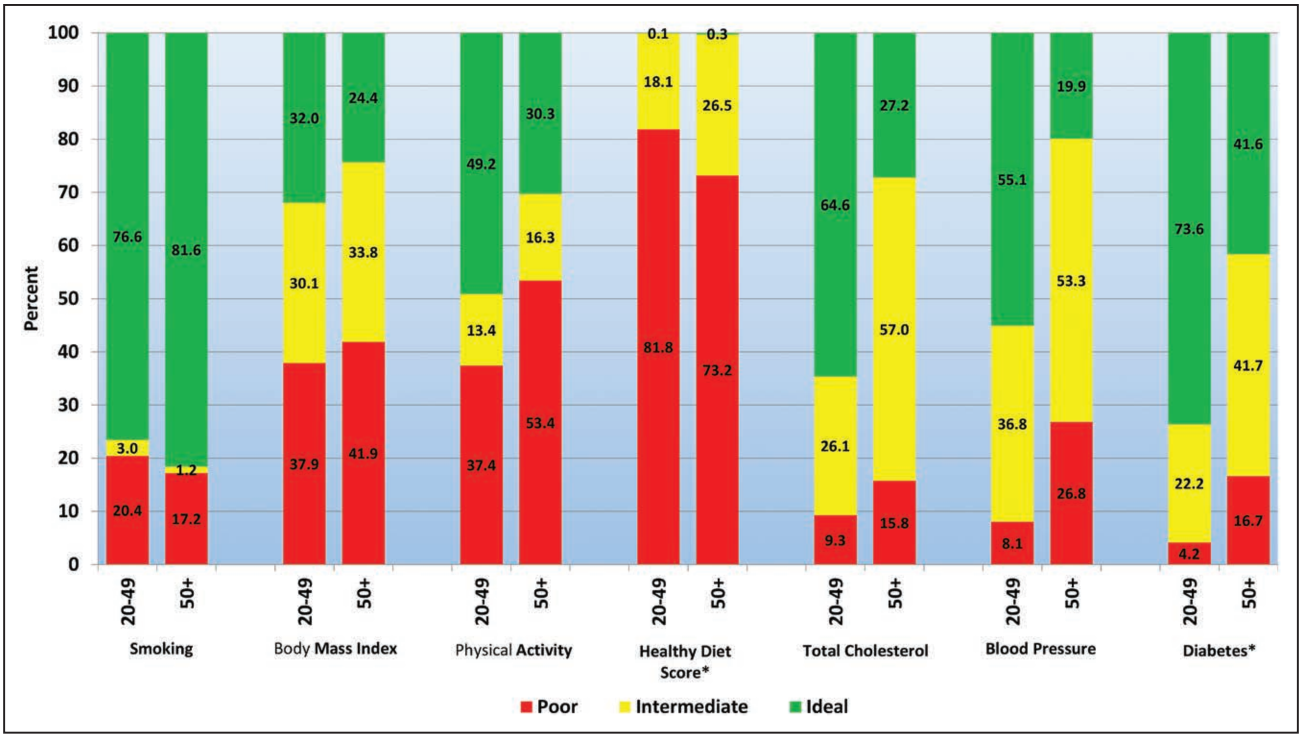

Chart 2-3. **Prevalence (unadjusted) estimates of poor, intermediate, and ideal cardiovascular health for each of the 7 metrics of cardiovascular health in the AHA 2020 goals among US adults aged 20 to 49 and ≥50 years.**
AHA indicates American Heart Association.
*Healthy Diet Score reflects 2013 to 2014 NHANES (National Health and Nutrition Examination Survey).
Source: National Center for Health Statistics, NHANES, 2015 to 2016.

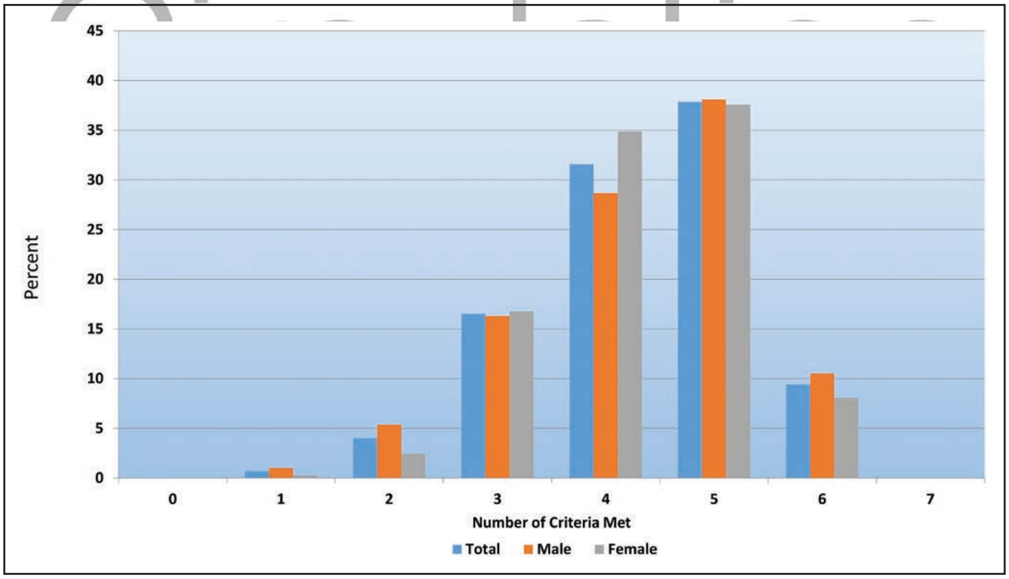

Chart 2-4. **Proportion (unadjusted) of US children aged 12 to 19 years meeting different numbers of criteria for ideal cardiovascular health, overall and by sex.**
Source: National Center for Health Statistics, National Health and Nutrition Examination Survey, 2013 to 2014.

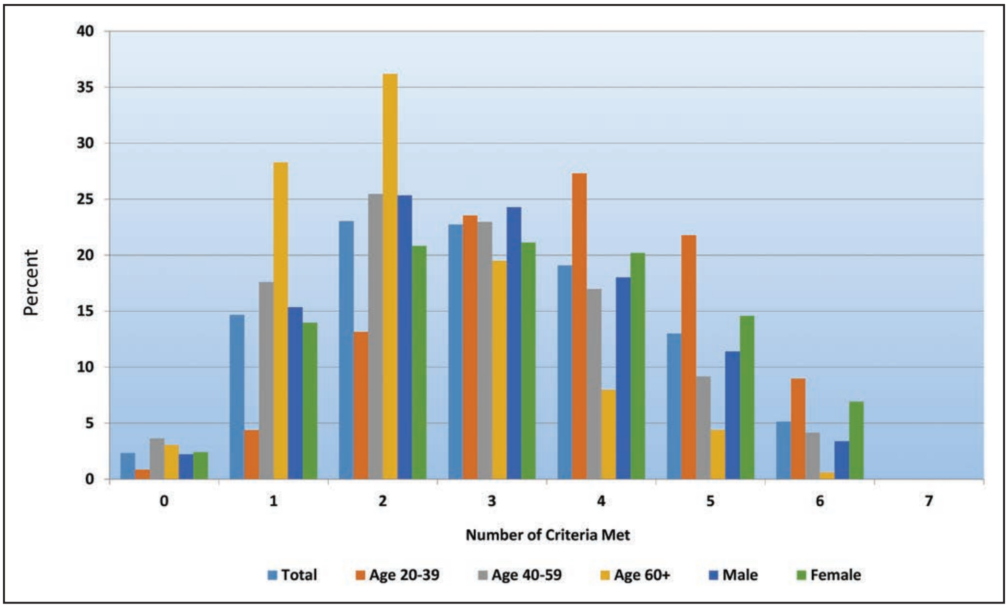

Chart 2-5. Age-standardized prevalence estimates of US adults aged ≥20 years meeting different numbers of criteria for ideal cardiovascular health, overall and by age and sex subgroups.
Source: National Center for Health Statistics, National Health and Nutrition Examination Survey, 2013 to 2014.

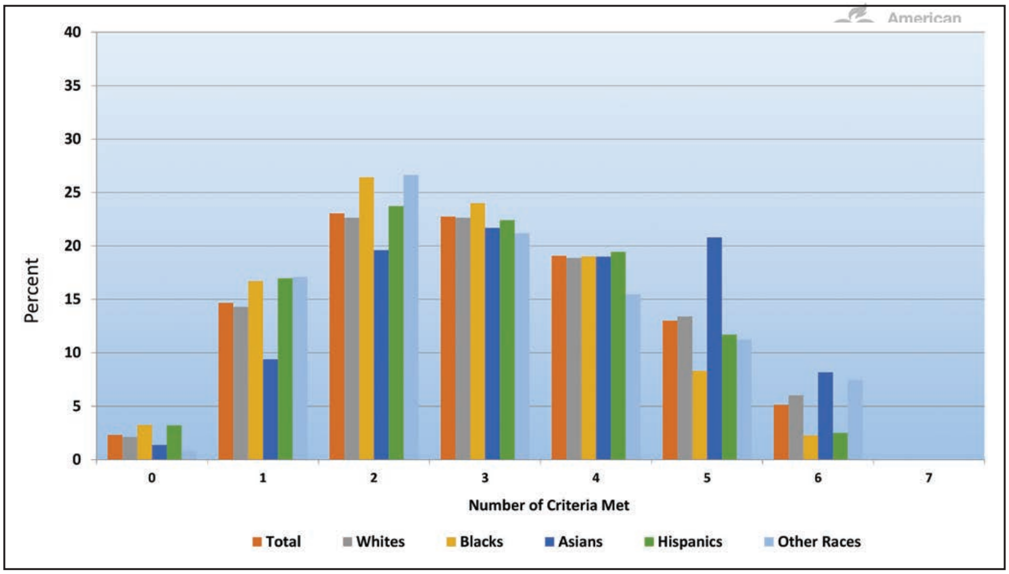

Chart 2-6. Age-standardized prevalence estimates of US adults aged ≥20 years meeting different numbers of criteria for ideal cardiovascular health, overall and in selected race subgroups.
Source: National Center for Health Statistics, National Health and Nutrition Examination Survey 2013 to 2014.

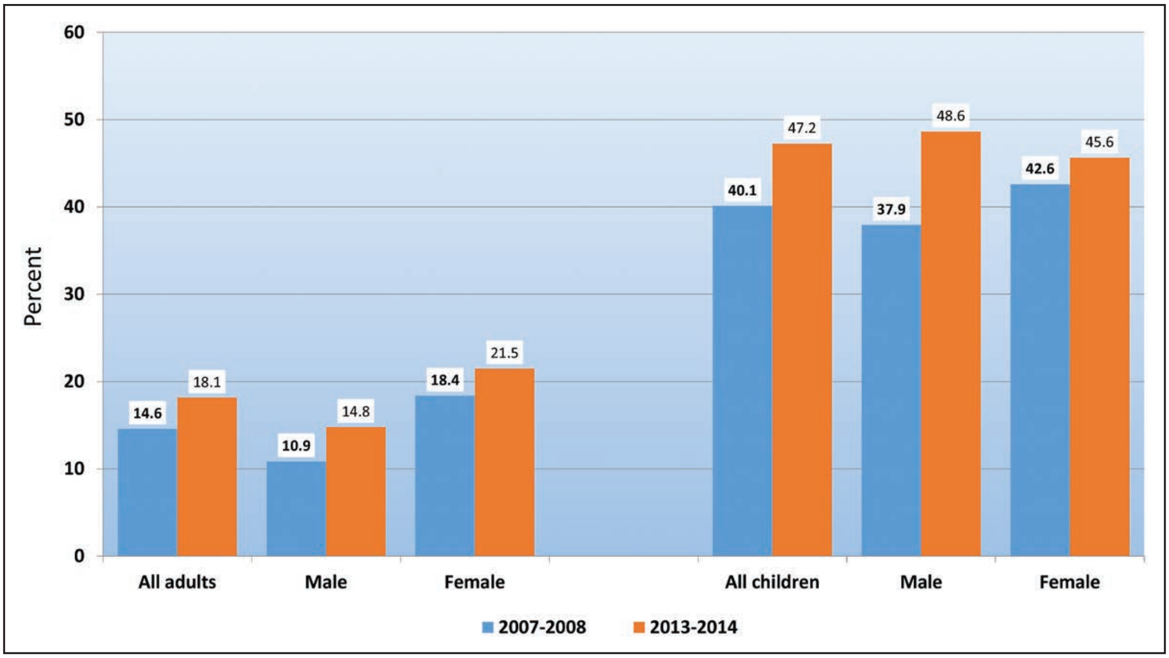

Chart 2-7. Prevalence of meeting ≥5 criteria for ideal cardiovascular health among US adults aged ≥20 years (age standardized) and US children aged 12 to 19 years, overall and by sex.

Source: National Center for Health Statistics, National Health and Nutrition Examination Survey, 2007 to 2008 and 2013 to 2014.

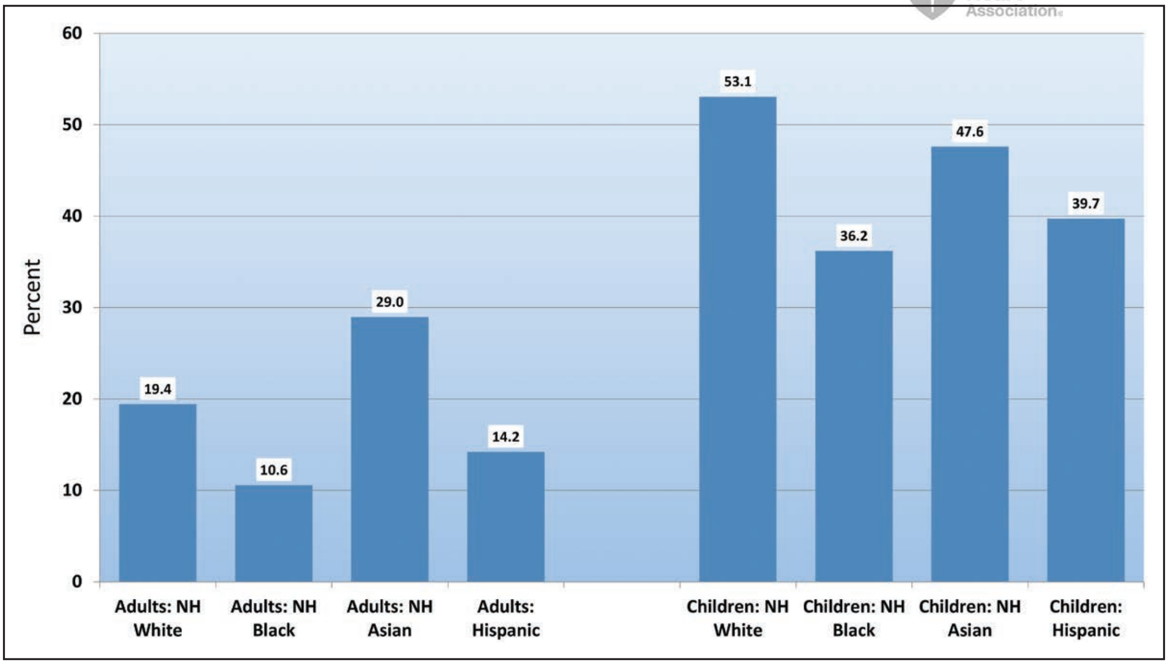

Chart 2-8. Prevalence of meeting ≥5 criteria for ideal cardiovascular health among US adults aged ≥20 years (age standardized) and US children aged 12 to 19 years, by race/ethnicity.

NH indicates non-Hispanic.

Source: National Center for Health Statistics, National Health and Nutrition Examination Survey, 2013 to 2014.

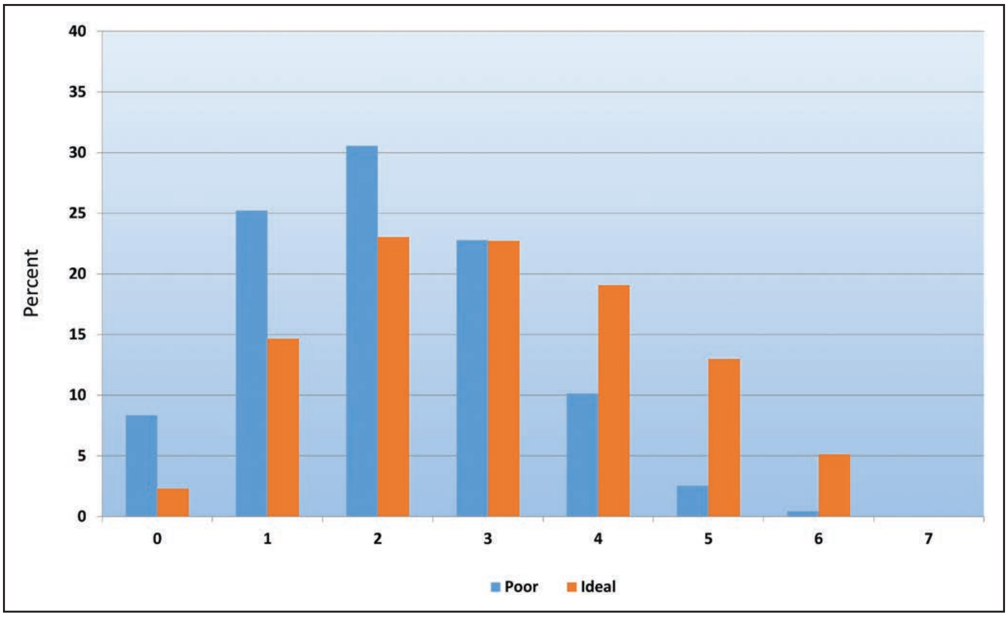

Chart 2-9. Age-standardized prevalence estimates of US adults meeting different numbers of criteria for ideal and poor cardiovascular health for each of the 7 metrics of cardiovascular health in the AHA 2020 goals among US adults aged ≥20 years.
AHA indicates American Heart Association.
Source: National Center for Health Statistics, National Health and Nutrition Examination Survey, 2013 to 2014.

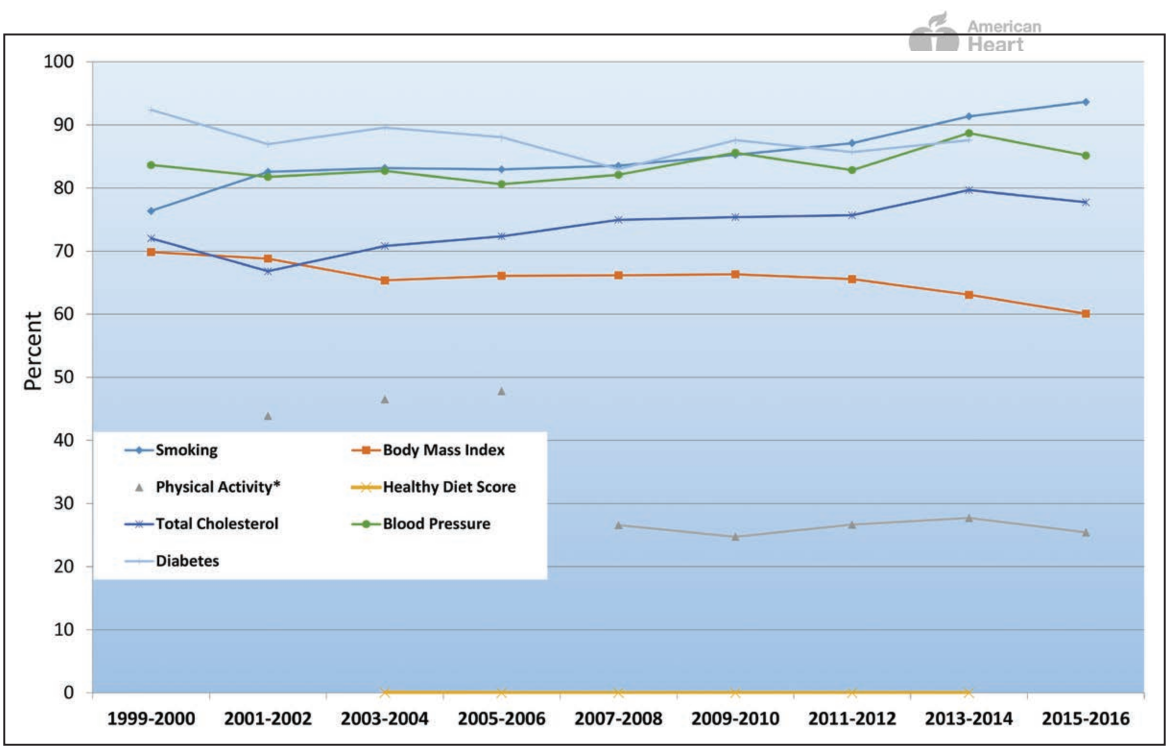

Chart 2-10. Trends in prevalence (unadjusted) of meeting criteria for ideal cardiovascular health for each of the 7 metrics among US children aged 12 to 19 years.
Data for the Healthy Diet Score, based on a 2-day average intake, were only available for the 2003 to 2004, 2005 to 2006, 2007 to 2008, 2009 to 2010, and 2011 to 2012 NHANES cycles at the time of this analysis.
NHANES indicates National Health and Nutrition Examination Survey.
*Because of changes in the physical activity questionnaire between different cycles of NHANES, trends over time for this indicator should be interpreted with caution, and statistical comparisons should not be attempted.
Source: National Center for Health Statistics, NHANES, 1999 to 2000 through 2015 to 2016.

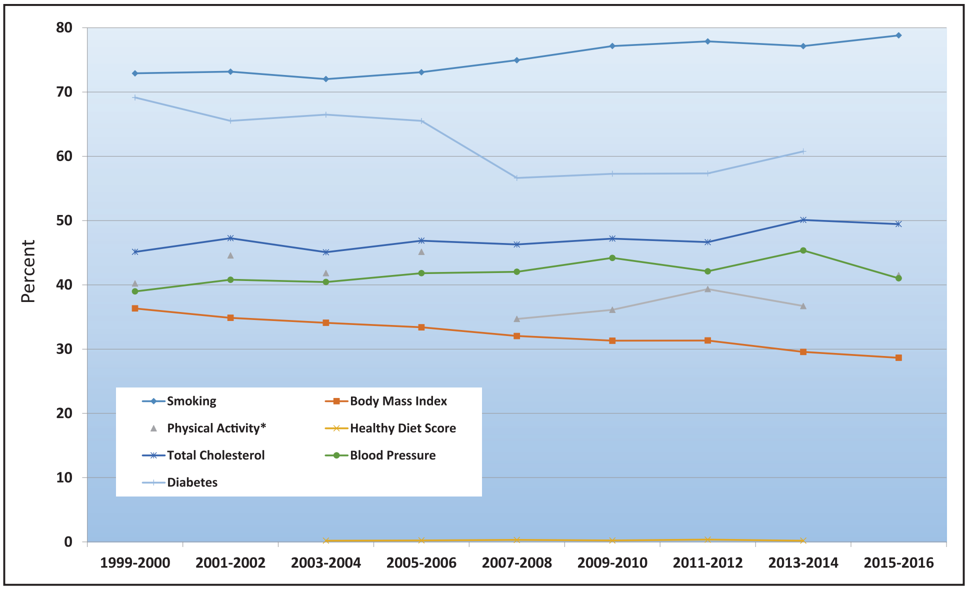

Chart 2-11. Age-standardized trends in prevalence of meeting criteria for ideal cardiovascular health for each of the 7 metrics among US adults aged ≥20 years.

Data for the Healthy Diet Score, based on a 2-day average intake, were only available for the 2003 to 2004, 2005 to 2006, 2007 to 2008, 2009 to 2010, and 2011 to 2012 NHANES cycles at the time of this analysis.

NHANES indicates National Health and Nutrition Examination Survey.

*Because of changes in the physical activity questionnaire between different cycles of NHANES, trends over time for this indicator should be interpreted with caution, and statistical comparisons should not be attempted.

Source: National Center for Health Statistics, NHANES, 1999 to 2000 through 2015 to 2016.

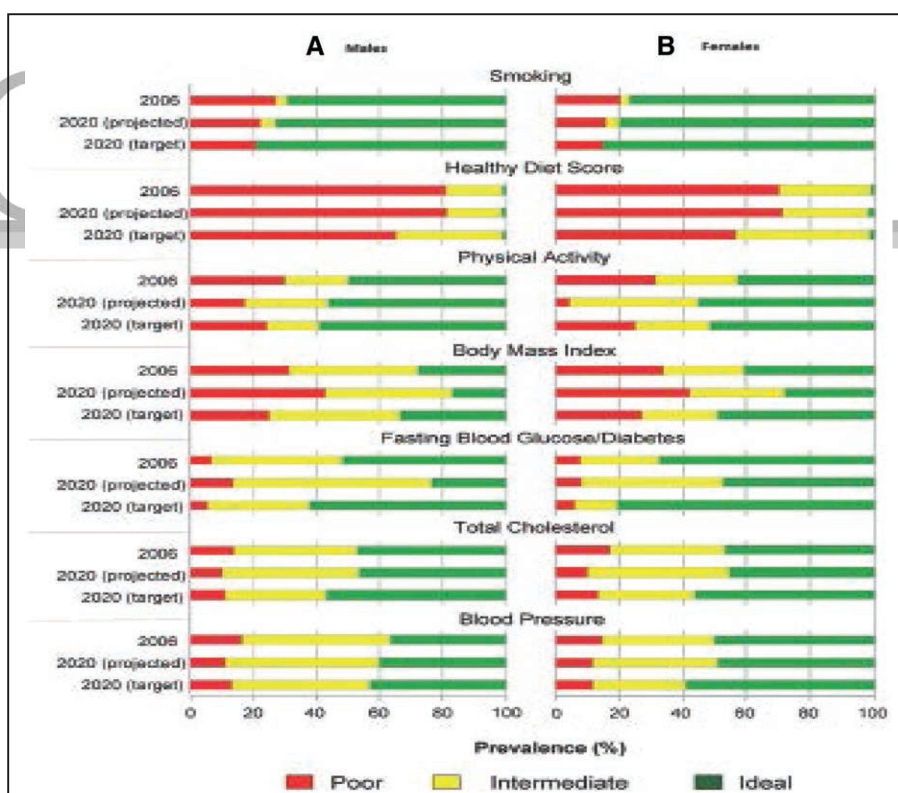

Chart 2-12. Prevalence of ideal, intermediate, and poor cardiovascular health metrics in 2006 (AHA 2020 Strategic Impact Goals baseline year) and 2020 projections assuming current trends continue.

The 2020 targets for each cardiovascular health metric assume a 20% relative increase in ideal cardiovascular health prevalence metrics and a 20% relative decrease in poor cardiovascular health prevalence metrics for males and females.

AHA indicates American Heart Association.

REFERENCES

1. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
2. American Heart Association. My Life Check – Life's Simple 7. https://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check--lifes-simple-7. Accessed November 9, 2018.
3. Rumsfeld JS, Alexander KP, Goff DC Jr, Graham MM, Ho PM, Masoudi FA, Moser DK, Roger VL, Slaughter MS, Smolderen KG, Spertus JA, Sullivan MD, Treat-Jacobson D, Zerwic JJ; on behalf of the American Heart Association Council on Quality of Care and Outcomes Research, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Stroke Council. Cardiovascular health: the importance of measuring patient-reported health status: a scientific statement from the American Heart Association. *Circulation*. 2013;127:2233–2249. doi: 10.1161/CIR.0b013e3182949a2e
4. Shay CM, Gooding HS, Murillo R, Foraker R. Understanding and improving cardiovascular health: an update on the American Heart Association's concept of cardiovascular health. *Prog Cardiovasc Dis*. 2015;58:41–49. doi: 10.1016/j.pcad.2015.05.003
5. Chang Y, Guo X, Chen Y, Guo L, Li Z, Yu S, Yang H, Sun G, Sun Y. Prevalence and metrics distribution of ideal cardiovascular health: a population-based, cross-sectional study in rural China. *Heart Lung Circ*. 2016;25:982–992. doi: 10.1016/j.hlc.2016.02.007
6. Laitinen T. *Cardiovascular Health From Childhood to Adulthood–With Special Reference to Early Vascular Changes: The Cardiovascular Risk in Young Finns Study* [master's thesis]. Helsinki, Finland; University of Turku; 2015.
7. Laitinen TT, Pahkala K, Magnussen CG, Oikonen M, Viikari JS, Sabin MA, Daniels SR, Heinonen OJ, Taittonen L, Hartiala O, Mikkilä V, Hutri-Kähönen N, Laitinen T, Kähönen M, Raitakari OT, Juonala M. Lifetime measures of ideal cardiovascular health and their association with subclinical atherosclerosis: The Cardiovascular Risk in Young Finns Study. *Int J Cardiol*. 2015;185:186–191. doi: 10.1016/j.ijcard.2015.03.051
8. Younus A, Aneni EC, Spatz ES, Osondu CU, Roberson L, Ogunmoroti O, Malik R, Ali SS, Aziz M, Feldman T, Virani SS, Maziak W, Agatston AS, Veledar E, Nasir K. A systematic review of the prevalence and outcomes of ideal cardiovascular health in US and non-US populations. *Mayo Clin Proc*. 2016;91:649–670. doi: 10.1016/j.mayocp.2016.01.019
9. Zhou L, Zhao L, Wu Y, Wu Y, Gao X, Li Y, Mai J, Nie Z, Ou Y, Guo M, Liu X. Ideal cardiovascular health metrics and its association with 20-year cardiovascular morbidity and mortality in a Chinese population. *J Epidemiol Community Health*. 2018;72:752–758. doi: 10.1136/jech-2017-210396
10. González HM, Tarraf W, Rodríguez CJ, Gallo LC, Sacco RL, Talavera GA, Heiss G, Kizer JR, Hernandez R, Davis S, Schneiderman N, Daviglus ML, Kaplan RC. Cardiovascular health among diverse Hispanics/Latinos: Hispanic Community Health Study/Study of Latinos (HCHS/SOL) results. *Am Heart J*. 2016;176:134–144. doi: 10.1016/j.ahj.2016.02.008
11. Spahillari A, Talegawkar S, Correa A, Carr JJ, Terry JG, Lima J, Freedman JE, Das S, Kociol R, de Ferranti S, Mohebali D, Mwasongwe S, Tucker KL, Murthy VL, Shah RV. Ideal cardiovascular health, cardiovascular remodeling, and heart failure in blacks: the Jackson Heart Study. *Circ Heart Fail*. 2017;10:e003682. doi: 10.1161/CIRCHEARTFAILURE.116.003682
12. Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, Rosamond WD; ARIC Study Investigators. Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence. *J Am Coll Cardiol*. 2011;57:1690–1696. doi: 10.1016/j.jacc.2010.11.041
13. US Burden of Disease Collaborators. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. *JAMA*. 2013;310:591–606. doi: 10.1001/jama.2013.13805
14. Yang Q, Cogswell ME, Flanders WD, Hong Y, Zhang Z, Loustalot F, Gillespie C, Merritt R, Hu FB. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. *JAMA*. 2012;307:1273–1283. doi: 10.1001/jama.2012.339
15. Fang N, Jiang M, Fan Y. Ideal cardiovascular health metrics and risk of cardiovascular disease or mortality: a meta-analysis. *Int J Cardiol*. 2016;214:279–283. doi: 10.1016/j.ijcard.2016.03.210
16. Kulshreshtha A, Vaccarino V, Judd SE, Howard VJ, McClellan WM, Muntner P, Hong Y, Safford MM, Goyal A, Cushman M. Life's Simple 7 and risk of incident stroke: the Reasons for Geographic and Racial Differences in Stroke study. *Stroke*. 2013;44:1909–1914. doi: 10.1161/STROKEAHA.111.000352
17. Wilkins JT, Ning H, Berry J, Zhao L, Dyer AR, Lloyd-Jones DM. Lifetime risk and years lived free of total cardiovascular disease. *JAMA*. 2012;308:1795–1801. doi: 10.1001/jama.2012.14312
18. Folsom AR, Shah AM, Lutsey PL, Roetker NS, Alonso A, Avery CL, Miedema MD, Konety S, Chang PP, Solomon SD. American Heart Association's Life's Simple 7: avoiding heart failure and preserving cardiac structure and function. *Am J Med*. 2015;128:970–976.e2. doi: 10.1016/j.amjmed.2015.03.027
19. Robbins JM, Petrone AB, Carr JJ, Pankow JS, Hunt SC, Heiss G, Arnett DK, Ellison RC, Gaziano JM, Djoussé L. Association of ideal cardiovascular health and calcified atherosclerotic plaque in the coronary arteries: the National Heart, Lung, and Blood Institute Family Heart Study. *Am Heart J*. 2015;169:371–378.e1. doi: 10.1016/j.ahj.2014.12.017
20. Saleem Y, DeFina LF, Radford NB, Willis BL, Barlow CE, Gibbons LW, Khera A. Association of a favorable cardiovascular health profile with the presence of coronary artery calcification. *Circ Cardiovasc Imaging*. 2015;8:e001851. doi: 10.1161/CIRCIMAGING.114.001851
21. Crichton GE, Elias MF, Davey A, Alkerwi A. Cardiovascular health and cognitive function: the Maine-Syracuse Longitudinal Study. *PLoS One*. 2014;9:e89317. doi: 10.1371/journal.pone.0089317
22. Thacker EL, Gillett SR, Wadley VG, Unverzagt FW, Judd SE, McClure LA, Howard VJ, Cushman M. The American Heart Association Life's Simple 7 and incident cognitive impairment: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *J Am Heart Assoc*. 2014;3:e000635. doi: 10.1161/JAHA.113.000635
23. Kronish IM, Carson AP, Davidson KW, Muntner P, Safford MM. Depressive symptoms and cardiovascular health by the American Heart Association's definition in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *PLoS One*. 2012;7:e52771. doi: 10.1371/journal.pone.0052771
24. España-Romero V, Artero EG, Lee DC, Sui X, Baruth M, Ruiz JR, Pate RR, Blair SN. A prospective study of ideal cardiovascular health and depressive symptoms. *Psychosomatics*. 2013;54:525–535. doi: 10.1016/j.psym.2013.06.016
25. Dhamoon MS, Dong C, Elkind MS, Sacco RL. Ideal cardiovascular health predicts functional status independently of vascular events: the Northern Manhattan Study. *J Am Heart Assoc*. 2015;4:e001322. doi: 10.1161/JAHA.114.001322
26. Gebreab SY, Manna ZG, Khan RJ, Riestra P, Xu R, Davis SK. Less than ideal cardiovascular health is associated with shorter leukocyte telomere length: the National Health and Nutrition Examination Surveys, 1999–2002. *J Am Heart Assoc*. 2017;6:e004105. doi: 10.1161/JAHA.116.004105
27. Han QL, Wu SL, Liu XX, An SS, Wu YT, Gao JS, Chen SH, Liu XK, Zhang Q, Mao RY, Shang XM, Jonas JB. Ideal cardiovascular health score and incident end-stage renal disease in a community-based longitudinal cohort study: the Kailuan Study. *BMJ Open*. 2016;6:e012486. doi: 10.1136/bmjopen-2016-012486
28. Fan W, Lee H, Lee A, Kieu C, Wong ND. Association of lung function and chronic obstructive pulmonary disease with American Heart Association's Life's Simple 7 cardiovascular health metrics. *Respir Med*. 2017;131:85–93. doi: 10.1016/j.rmed.2017.08.001
29. Olson NC, Cushman M, Judd SE, McClure LA, Lakoski SG, Folsom AR, Safford MM, Zakai NA. American Heart Association's Life's Simple 7 and risk of venous thromboembolism: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *J Am Heart Assoc*. 2015;4:e001494. doi: 10.1161/JAHA.114.001494
30. Sengeløv M, Cheng S, Biering-Sørensen T, Matsushita K, Konety S, Solomon SD, Folsom AR, Shah AM. Ideal cardiovascular health and the prevalence and severity of aortic stenosis in elderly patients. *J Am Heart Assoc*. 2018;7:e007234. doi: 10.1161/JAHA.117.007234
31. Mok Y, Sang Y, Ballew SH, Rebholz CM, Rosamond WD, Heiss G, Folsom AR, Coresh J, Matsushita K. American Heart Association's Life's Simple 7 at middle age and prognosis after myocardial infarction in later life. *J Am Heart Assoc*. 2018;7:e007658. doi: 10.1161/JAHA.117.007658
32. Garg PK, O'Neal WT, Chen LY, Loehr LR, Sotoodehnia N, Soliman EZ, Alonso A. American Heart Association's Life Simple 7 and risk of atrial fibrillation in a population without known cardiovascular disease: the ARIC (Atherosclerosis Risk in Communities) Study. *J Am Heart Assoc*. 2018;7:e008424. doi: 10.1161/JAHA.117.008424

33. Hernandez R, González HM, Tarraf W, Moskowitz JT, Carnethon MR, Gallo LC, Penedo FJ, Isasi CR, Ruiz JM, Arguelles W, Buelna C, Davis S, Gonzalez F, McCurley JL, Wu D, Daviglus ML. Association of dispositional optimism with Life's Simple 7's Cardiovascular Health Index: results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Sociocultural Ancillary Study (SCAS). *BMJ Open*. 2018;8:e019434. doi: 10.1136/bmjopen-2017-019434
34. Caleyachetty R, Echouffo-Tcheugui JB, Muennig P, Zhu W, Muntner P, Shimbo D. Association between cumulative social risk and ideal cardiovascular health in US adults: NHANES 1999-2006. *Int J Cardiol*. 2015;191:296–300. doi: 10.1016/j.ijcard.2015.05.007
35. Osondu CU, Aneni EC, Valero-Elizondo J, Salami JA, Rouseff M, Das S, Guzman H, Younus A, Ogunmoroti O, Feldman T, Agatston AS, Veledar E, Katzen B, Calitz C, Sanchez E, Lloyd-Jones DM, Nasir K. Favorable cardiovascular health is associated with lower health care expenditures and resource utilization in a large US employee population: the Baptist Health South Florida Employee Study. *Mayo Clin Proc*. 2017;92:512–524. doi: 10.1016/j.mayocp.2016.12.026
36. Huffman MD, Capewell S, Ning H, Shay CM, Ford ES, Lloyd-Jones DM. Cardiovascular health behavior and health factor changes (1988-2008) and projections to 2020: results from the National Health and Nutrition Examination Surveys. *Circulation*. 2012;125:2595–2602. doi: 10.1161/CIRCULATIONAHA.111.070722
37. Huffman MD, Lloyd-Jones DM, Ning H, Labarthe DR, Guzman Castillo M, O'Flaherty M, Ford ES, Capewell S. Quantifying options for reducing coronary heart disease mortality by 2020. *Circulation*. 2013;127:2477–2484. doi: 10.1161/CIRCULATIONAHA.112.000769
38. Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, Goldman L. Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med*. 2010;362:590–599. doi: 10.1056/NEJMoa0907355
39. Fang J, Yang Q, Hong Y, Loustalot F. Status of cardiovascular health among adult Americans in the 50 States and the District of Columbia, 2009. *J Am Heart Assoc*. 2012;1:e005371. doi: 10.1161/JAHA.112.005371.
40. Artinian NT, Fletcher GF, Mozaffarian D, Kris-Etherton P, Van Horn L, Lichtenstein AH, Kumanyika S, Kraus WE, Fleg JL, Redeker NS, Meininger JC, Banks J, Stuart-Shor EM, Fletcher BJ, Miller TD, Hughes S, Braun LT, Kopin LA, Berra K, Hayman LL, Ewing LJ, Ades PA, Durstine JL, Houston-Miller N, Burke LE; on behalf of the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122:406–441. doi: 10.1161/CIR.0b013e3181e8edf1
41. Mozaffarian D, Afshin A, Benowitz NL, Bittner V, Daniels SR, Franch HA, Jacobs DR Jr, Kraus WE, Kris-Etherton PM, Krummel DA, Popkin BM, Whitsel LP, Zakai NA; on behalf of the American Heart Association Council on Epidemiology and Prevention, Council on Nutrition, Physical Activity and Metabolism, Council on Clinical Cardiology, Council on Cardiovascular Disease in the Young, Council on the Kidney in Cardiovascular Disease. Population approaches to improve diet, physical activity, and smoking habits: a scientific statement from the American Heart Association. *Circulation*. 2012;126:1514–1563. doi: 10.1161/CIR.0b013e318260a20b
42. Bodenheimer T. Helping patients improve their health-related behaviors: what system changes do we need? *Dis Manag*. 2005;8:319–330. doi: 10.1089/dis.2005.8.319
43. Simpson LA, Cooper J. Paying for obesity: a changing landscape. *Pediatrics*. 2009;123(suppl 5):S301–S307. doi: 10.1542/peds.2008-2780I

3. SMOKING/TOBACCO USE

See Table 3-1 and Charts 3-1 through 3-6

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Tobacco use is one of the leading preventable causes of death in the United States and globally.[1] Tobacco smoking, the most common form of tobacco use, is a major risk factor for CVD and stroke.[2] The AHA has identified never having tried smoking or never having smoked a whole cigarette (for children) and never having smoked or having quit >12 months ago (for adults) as 1 of the 7 components of ideal cardiovascular health in Life's Simple 7.[3] Unless otherwise stated, throughout the rest of the chapter we will report tobacco use and smoking estimates from the NSDUH[4] for adolescents (12–17 years of age) and from the NHIS[5] for adults (≥18 years of age), because these data sources have more recent data.

Other forms of tobacco use are becoming increasingly common. Electronic cigarette (e-cigarette) use, which involves inhalation of a vaporized liquid that includes nicotine, solvents, and flavoring ("vaping"), has risen dramatically, particularly among young people. The variety of e-cigarette–related products has increased exponentially, giving rise to the more general term *electronic nicotine delivery systems*.[6] Use of cigars, cigarillos, filtered cigars, and hookah also has become increasingly common in recent years. Thus, each section below will address the most recent statistical estimates for combustible cigarettes, electronic nicotine delivery systems, and other forms of tobacco use if such estimates are available.

Abbreviations Used in Chapter 3

ACS	acute coronary syndrome
AHA	American Heart Association
AIAN	American Indian or Alaska Native
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
DALY	disability-adjusted life-year
DM	diabetes mellitus
EAGLES	Study Evaluating the Safety and Efficacy of Varenicline and Bupropion for Smoking Cessation in Subjects With and Without a History of Psychiatric Disorders
EVITA	Evaluation of Varenicline in Smoking Cessation for Patients Post-Acute Coronary Syndrome
GBD	Global Burden of Disease
HD	heart disease
HIV	human immunodeficiency virus
HR	hazard ratio
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NNT	number needed to treat
NSDUH	National Survey on Drug Use and Health
OR	odds ratio
PAF	population attributable fraction
PAR	population attributable risk
PATH	Population Assessment of Tobacco and Health
RCT	randomized controlled trial
RR	relative risk
SAH	subarachnoid hemorrhage
SBP	systolic blood pressure
SHS	Strong Heart Study
UI	uncertainty interval
WHO	World Health Organization

Prevalence (See Charts 3-1 through 3-4)

Youth

- Prevalence of cigarette use in the past month for adolescents aged 12 to 17 years by sex and race/ethnicity in 2014 and 2015 is shown in Chart 3-1.
- According to the NSDUH 2016 data, for adolescents aged 12 to 17 years[4]:
  - — 5.3% (1 319 541) used tobacco products, and 3.4% (846 498) smoked cigarettes in the past month.
  - — 1.4% (348 558) used smokeless tobacco in the past month.
  - — Of adolescents who smoked, 15% (126 975) smoked cigarettes daily.
  - — 1.8% (448 146) were current cigar smokers, and 0.5% (124 485) were current pipe tobacco smokers.
- In 2015, tobacco use within the past month for youth 12 to 17 years of age varied slightly by region: 6.2% in the Northeast, 7.0% in the Midwest, 6.0% in the South, and 4.9% in the West.[4]
- In 2015, 21.6% of adults aged 18 to 20 years were current cigarette smokers compared with 8.7% of adolescents aged 16 to 17 years.[4]
- The PATH study assessed the use of different types of tobacco products, including cigarettes, e-cigarettes, cigars, cigarillos, filtered cigars, pipe tobacco, hookah, snus pouches, smokeless tobacco, dissolvable tobacco, bidis, and kreteks. This study estimated that in 2013 to 2014, 8.9% of youth aged 12 to 18 years used some form of tobacco in the past 30 days, and 1.6% were daily users.[7]
- Data from the National Youth Tobacco Survey indicate that the percentage of high school students who used e-cigarettes (11.3%) exceeded the proportion using cigarettes (8.0%) in 2016 (Chart 3-2).[8]

Adults

- According to the NHIS 2016 data, among adults ≥18 years of age[6]:

<zjs;AHA Statistical Update> • <zjss;10163> • <zdoi;10.1161/CIR.0000000000000659>

- 15.5% of adults (37.8 million) are current smokers.
- 17.5% of males and 13.5% of females are current smokers.
- 13.1% of those 18 to 24 years of age, 17.6% of those 25 to 44 years of age, 18.0% of those 45 to 64 years of age, and 8.8% of those ≥65 years old are current smokers.
- 31.8% of American Indians or Alaska Natives, 16.5% of blacks, 9% of Asians, 10.7% of Hispanics, and 16.6% of whites are current smokers.
- 25.3% of people below the poverty level based on family income and family size are current smokers.

- 20.5% of lesbian/gay/bisexual individuals are current smokers.
- By region, the prevalence of current cigarette smokers was highest in the Midwest (18.5%) and lowest in the West (12.3%).[7]
- In 2009, 42.4% of adults with HIV receiving medical care were current smokers.[9]
- Using data from BRFSS 2016, the state with the highest age-adjusted percentage of current cigarette smokers was West Virginia (26.2%). The state with the lowest age-adjusted percentage of current cigarette smokers was Utah (8.7%) (Chart 3-3).[9a]
- In 2016, smoking prevalence was higher among adults ≥18 years of age who reported having a disability or activity limitation (21.2%) than among those reporting no disability or limitation (14.4%).[7]
- 9.3% of males and 33.6% of females with mental illness were current smokers.[10]
- Among females who gave birth in 2016, 7.2% smoked cigarettes during pregnancy. Smoking prevalence during pregnancy was greatest for females aged 20 to 24 years (10.7%), followed by females aged 15 to 19 years (8.5%) and 25 to 29 years (8.2%).[11] Rates were highest among NH American Indian or Alaska Native females (16.7%) and lowest in NH Asian females (0.6%). With respect to differences by education, cigarette smoking prevalence was highest among females who completed high school (12.2%), followed by females with less than high school education (11.7%).
- The PATH study assessed the use of different types of tobacco products, including cigarettes, e-cigarettes, cigars, cigarillos, filtered cigars, pipe tobacco, hookah, snus pouches, smokeless tobacco, dissolvable tobacco, bidis, and kreteks. This study estimated that in 2013 to 2014, 34.8% of adult males and 20.8% of adult females were current users of some form of tobacco.[7]
- E-cigarette prevalence in 2016 is shown in Chart 3-4.

Incidence

- According to the 2015 NSDUH, approximately 1.96 million people ≥12 years of age had smoked cigarettes for the first time within the past 12 months, a decrease from 2.3 million in 2012.[4] The 2015 estimate averages out to ≈5390 new cigarette smokers every day. Of new smokers in 2015, 823 000 (42.1%) were 12 to 17 years old, 762 000 (39%) were 18 to 20 years old, and 287 000 (14.7%) were 21 to 25 years old; only 84 000 (4.3%) were ≥26 years when they first smoked cigarettes.
- The number of new smokers 12 to 17 years of age (823 000) decreased from 2002 (1.3 million); however, new smokers 18 to 25 years of age increased from ≈600 000 in 2002 to 1.05 million in 2015.
- According to the NHIS, in 2015, the average age for initiation of cigarette use was 17.9 years.[5]
- According to data from PATH, in youth 12 to 17 years of age, use of an e-cigarette was independently associated with combustible cigarette use 1 year later (OR, 1.87; 95% CI, 1.15–3.05). For youth who tried hookah, noncigarette combustible tobacco, or smokeless tobacco, a similar strength of association for tobacco use at 1 year was observed.[12]

Lifetime Risk and Cumulative Incidence in Youth (12 to 17 Years Old) in 2015

- Per NSDUH data for individuals aged 12 to 17 years, overall, the lifetime use of tobacco products declined from 18.5% to 17.3%, with lifetime cigarette use declining from 14.2% to 13.2% during the same time period ($P<0.05$ for both).[4]
- The lifetime use of tobacco products among adolescents 12 to 17 years old varied by the following[4]:
  - Sex: Lifetime use was higher among boys (19.1%) than girls (15.3%).
  - Race/ethnicity: Lifetime use was highest among whites (19.9%), followed by American Indians or Alaska Natives (19.6%), Hispanics or Latinos (14.5%), African Americans (13.8%), and Asians (7.7%).
  - Geographic division: The highest lifetime use was observed in the South (East South Central 22.8%), and the lowest was observed in the Pacific West (13.0%).

Adults

- According to NSDUH data, the lifetime use of tobacco products in individuals aged ≥18 years declined significantly (*P*<0.01) between 2014 and 2015, from 71.1% to 68.7%, with cigarette use declining in the same interval from 65.9% to 63.1% (both *P*<0.01).[4] Similar to the patterns in youth, lifetime risk of tobacco products varied by demographic factors:
  - Sex: Lifetime use was higher in males (78.1%) than females (60.0%).
  - Race/ethnicity: Lifetime use was highest in American Indians or Alaska Natives (75.9%) and whites (75.9%), followed by blacks (58.4%), Native Hawaiian or Other Pacific Islander (56.8%), Hispanics or Latinos (56.7%), and Asians (37.9%).
- In 2015, the lifetime use of smokeless tobacco for adults ≥18 years of age was 17.4%.
- Lifetime tobacco use for people with psychiatric diagnoses was 56.1%, 55.6%, and 70.1% in patients with mood disorders, anxiety disorders, and schizophrenia, respectively.[13]

Mortality

- Of risk factors evaluated by the US Burden of Disease Collaborators, tobacco use was the second-leading risk factor for death in the United States and the leading cause of DALYs, accounting for 11% of DALYs, in 2016.[14]
- Overall mortality among US smokers is 3 times higher than that for never-smokers.[15]
- On average, male smokers die 12 years earlier than male never-smokers, and female smokers die 11 years earlier than female never-smokers.[9a,16]
- Increased CVD mortality risks persist for older (≥60 years old) smokers as well. A meta-analysis comparing CVD risks in 503 905 cohort participants ≥60 years of age reported an HR for cardiovascular mortality of 2.07 (95% CI, 1.82–2.36) compared with never-smokers and 1.37 (95% CI, 1.25–1.49) compared with former smokers.[18]
- In a sample of Native Americans (SHS), among whom the prevalence of tobacco use is highest in the United States, the PAR for total mortality was 18.4% for males and 10.9% for females.[19]
- Since the first report on the dangers of smoking was issued by the US Surgeon General in 1964, tobacco control efforts have contributed to a reduction of 8 million premature smoking-attributable deaths.[20]
- If current smoking trends continue, 5.6 million US children will die of smoking prematurely during adulthood.[21]

Secular Trends (See Charts 3-2 and 3-5)

Youth

The percentage of adolescents (12–17 years old) who reported smoking in the past month declined from 13% in 2002 to 3.4% in 2016 (Chart 3-5).[22] The percentages for daily cigarette use among past-month cigarette-smoking adolescents were 31.8% in 2002 and 15% in 2016. Among high school students between 2011 and 2016, past-month cigarette smoking declined from 15.8% to 8.0% (Chart 3-2).[8]

Adults

Since the US Surgeon General's first report on the health dangers of smoking, age-adjusted rates of smoking among adults have declined, from 51% of males smoking in 1965 to 16.7% in 2015 and from 34% of females in 1965 to 13.6% in 2015, according to NHIS data.[10,12] The decline in smoking, along with other factors (including improved treatment and reductions in the prevalence of risk factors such as uncontrolled hypertension and high cholesterol), is a contributing factor to secular declines in the HD death rate.[16]

- On the basis of weighted NHIS data, the current smoking status among 18- to 24-year-old men declined 46.5%, from 28.0% in 2005 to 15.0% in 2015; for 18- to 24-year-old females, smoking declined 47.0%, from 20.7% to 11.0%, over the same time period.[10] On the basis of age-adjusted estimates in 2015, among people ≥65 years of age, 9.7% of males and 8.3% of females were current smokers.
- From 2005 to 2015, adjusted prevalence rates for tobacco use in individuals with serious psychological distress (according to the Kessler Scale) went from 41.9% to 40.6%, which represents a nonsignificant decline; however, rates for people without serious psychological stress declined significantly, from 20.3% to 14.0%.[10]

Cardiovascular Health Impact

- A 2010 report of the US Surgeon General on how tobacco causes disease summarized an extensive body of literature on smoking and CVD and the mechanisms through which smoking is thought to cause CVD.[21] There is a sharp increase in CVD risk with low levels of exposure to cigarette smoke, including secondhand smoke, and a less rapid further increase in risk as the number of cigarettes per day increases. Similar health risks for CHD events are reported with regular cigar smoking as well.[23]
- Smoking is an independent risk factor for CHD and appears to have a multiplicative effect with the other major risk factors for CHD: high serum levels of lipids, untreated hypertension, and DM.[21]

- Cigarette smoking and other traditional CHD risk factors might have a synergistic interaction in HIV-positive individuals.[24]
- A meta-analysis of 75 cohort studies (≈2.4 million individuals) demonstrated a 25% greater risk for CHD in female smokers than in male smokers (RR, 1.25; 95% CI, 1.12–1.39).[25]
- Cigarette smoking is an independent risk factor for both ischemic stroke and SAH and has a synergistic effect on other stroke risk factors such as SBP[26] and oral contraceptive use.[27,28]
- A meta-analysis comparing pooled data of ≈3.8 million smokers and nonsmokers found a similar risk of stroke associated with current smoking in females and males.[26]
- Current smokers have a 2- to 4-times increased risk of stroke compared with nonsmokers or those who have quit for >10 years.[29,30]
- Short-term exposure to water pipe smoking is associated with a significant increase in SBP and heart rate compared with nonsmoking control subjects,[31] but long-term effects remain unclear. Current use of smokeless tobacco is associated with an increased risk of CVD events in cigarette nonsmokers.[32]
- The CVD risks associated with e-cigarette use are not known.[33,34]

Healthcare Utilization: Hospital Discharges/Ambulatory Care Visits

Cost

- Each year from 2005 to 2009, US smoking-attributable economic costs were between $289 billion and $333 billion, including $133 billion to $176 billion for direct medical care of adults and $151 billion for lost productivity related to premature death.[16]
- In the United States, cigarette smoking was associated with 8.7% of annual aggregated healthcare spending from 2006 to 2010.[35]
- In 2016, $9.5 billion was spent on marketing cigarettes and smokeless tobacco in the United States.[36]
- 249 billion cigarettes were sold in the United States in 2017, which is a 3.5% decrease from the number sold in 2016.[36]
- Cigarette prices in the United States increased steeply between the early 1980s and 2016, in large part because of excise taxes on tobacco products.[36]

Smoking Prevention

Tobacco 21 laws increase the minimum age of sale for tobacco products from 18 to 21 years.

- Such legislation would likely reduce the rates of smoking during adolescence, a time during which the majority of smokers start smoking, by limiting access, because most people who buy cigarettes for adolescents are <21 years of age.[37]
- In several towns where Tobacco 21 laws have been enacted, 47% reductions in smoking prevalence among high school students have been reported.[36]
- Furthermore, the National Academy of Medicine estimates that a nationwide Tobacco 21 law would result in 249 000 fewer premature deaths, 45 000 fewer lung cancer deaths, and 4.2 million fewer lost life-years among Americans born between 2010 and 2019.[38]
- As of March 30, 2018, 5 states (California, New Jersey, Oregon, Hawaii, and Maine) and at least 300 localities, including New York City, Chicago, San Antonio, Boston, Cleveland, and both Kansas Cities, have set the minimum age for the purchase of tobacco to 21 years.[39]

Awareness, Treatment, and Control

Smoking Cessation

- According to NHIS 2015 data, 59.1% of adult ever-smokers had stopped smoking.[40]
  - — The majority (68.0%) of adult smokers wanted to quit smoking; 55.4% had tried in the past year, 7.4% had stopped recently, and 57.2% had received healthcare provider advice to quit.
  - — Receiving advice to quit smoking was lower in uninsured smokers and varied by race, with a lower prevalence in Asian (34.2%), American Indian/Alaska Native (38.1%), and Hispanic (42.2%) smokers than in white smokers (60.2%).
  - — The period from 2000 to 2015 revealed significant increases in the prevalence of smokers who had tried to quit in the past year, had stopped recently, had a health professional recommend quitting, or had used cessation counseling or medication.
  - — In 2015, less than one-third of smokers attempting to quit used evidence-based therapies: 4.7% used both counseling and medication, 6.8% used counseling, and 29.0% used medication (16.6% nicotine patch, 12.5% gum/lozenges, 2.4% nicotine spray/inhaler, 2.7% bupropion, and 7.9% varenicline).
- Smoking cessation reduces the risk of cardiovascular morbidity and mortality for smokers with and without CHD.
  - — There is no convincing evidence to date that smoking fewer cigarettes per day reduces the risk of CVD, although in several studies, a dose-response relationship has been seen among

current smokers between the number of cigarettes smoked per day and CVD incidence.[15]
- — Quitting smoking at any age significantly lowers mortality from smoking-related diseases, and the risk declines more the longer the time since quitting smoking.[2] Cessation appears to have both short-term (weeks to months) and long-term (years) benefits for lowering CVD risk. Overall, CVD risk appears to approach that of nonsmokers after ≈10 years of cessation.
- — Smokers who quit smoking at 25 to 34 years of age gained 10 years of life compared with those who continued to smoke. Those aged 35 to 44 years gained 9 years and those aged 45 to 54 years gained 6 years of life, on average, compared with those who continued to smoke.[15]

- Cessation medications (including sustained-release bupropion, varenicline, and nicotine gum, lozenge, nasal spray, and patch) are effective for helping smokers quit.[41]
- EVITA was an RCT that examined the efficacy of varenicline versus placebo for smoking cessation among smokers who were hospitalized for ACS. At 24 weeks, rates of smoking abstinence and reduction were significantly higher among patients randomized to varenicline. Point-prevalence abstinence rates were 47.3% in the varenicline group and 32.5% in the placebo group (*P*=0.012; NNT=6.8). Continuous abstinence rates and reduction rates (≥50% of daily cigarette consumption) were also higher in the varenicline group.[42]
- The EAGLES trial[43] demonstrated the efficacy and safety of 12 weeks of varenicline, bupropion, or nicotine patch in motivated-to-quit smoking patients with major depressive disorder, bipolar disorder, anxiety disorders, posttraumatic stress disorder, obsessive-compulsive disorder, social phobia, psychotic disorders including schizophrenia and schizoaffective disorders, and borderline personality disorder. Of note, these participants were all clinically stable from a psychiatric perspective and were believed not to be at high risk for self-injury.[43]
- Extended use of a nicotine patch (24 weeks compared with 8 weeks) has been demonstrated to be safe and efficacious in recent randomized clinical trials.[44]
- An RCT demonstrated the effectiveness of individual- and group-oriented financial incentives for tobacco abstinence through at least 12 months of follow-up.[45]
- In addition to medications, smoke-free policies, increases in tobacco prices, cessation advice from healthcare professionals, and quit-lines and other counseling have contributed to smoking cessation.[40,46]
- Mass media antismoking campaigns, such as the CDC's Tips campaign (Tips From Former Smokers), have been shown to reduce smoking-attributable morbidity and mortality and are cost-effective.[47]
- Despite states having collected $25.6 billion in 2012 from the 1998 Tobacco Master Settlement Agreement and tobacco taxes, <2% of those funds are spent on tobacco prevention and cessation programs.[48]

Electronic Cigarettes (See Charts 3-2 and 3-5)

- Electronic nicotine delivery systems, more commonly called electronic cigarettes or e-cigarettes, are battery-operated devices that deliver nicotine, flavors, and other chemicals to the user in an aerosol. Although e-cigarettes were introduced less than a decade ago, there are currently >450 e-cigarette brands on the market, and sales in the United States were projected to be $2 billion in 2014.
- Current e-cigarette user prevalence for 2016 is shown in Chart 3-4.
- According to the National Youth Tobacco Survey, in 2016, e-cigarettes were the most commonly used tobacco products in youth: in the prior 30 days, 4.3% of middle school and 11.3% of high school students endorsed use (Chart 3-2).[8] Despite a general trend of increased use between 2011 and 2016, the prevalence of e-cigarette use decreased between 2015 and 2016, from 5.3% to 4.3% in middle school students and from 16.0% to 11.3% in high school students. Among high school students, rates of use were most pronounced in males (13.1%) and NH whites (13.7%). In middle school students, higher rates were observed in males (5.1%) than females (3.4%) and in Hispanics (5.6%) than in other racial/ethnic groups (3.7% in NH white students and 4.0% in NH black students)
- In 2014, 18.3 million US middle and high school students (68.9%) were exposed to e-cigarette advertising.[4,49]
- Among US adults, awareness and use of e-cigarettes has increased considerably.[50] In 2014, 12.6% of all adults and nearly half (49%) of current daily cigarette smokers had tried an e-cigarette.[51]
- According to NHIS 2014 data, among US working adults, 3.8% (≈5.5 million) currently used e-cigarettes. The use of e-cigarettes was significantly higher among current smokers (16.2%) than among past smokers (4.3%) or never-smokers (0.5%). Similarly, prevalence was significantly

higher among males (4.5%), NH whites (4.5%), younger adults (18–24 years; 5.1%), individuals without health insurance (5.9%), individuals with incomes <$35 000, and those residing in the Midwest (4.5%).[52]

- Effective August 8, 2016, the US Food and Drug Administration's Deeming Rule prohibited sale of e-cigarettes to individuals <18 years of age.[53]

Secondhand Smoke

- Data from the US Surgeon General on the consequences of secondhand smoke indicate the following:
  - — Nonsmokers who are exposed to secondhand smoke at home or at work increase their risk of developing CHD by 25% to 30%.[21]
  - — Exposure to secondhand smoke increases the risk of stroke by 20% to 30%, and it is associated with increased mortality (adjusted mortality rate ratio, 2.11) after a stroke.[51]
- A meta-analysis of 23 prospective and 17 case-control studies of cardiovascular risks associated with secondhand smoke exposure demonstrated 18%, 23%, 23%, and 29% increased risks for total mortality, total CVD, CHD, and stroke, respectively, in those exposed to secondhand smoke.[52]
- A meta-analysis of 24 studies demonstrated that secondhand smoke can increase risks for preterm birth by 20%.[53]
- As of April 1, 2018, 11 states (California, Connecticut, Delaware, Hawaii, Maine, New Jersey, New York, North Dakota, Oregon, Utah, and Vermont), the District of Columbia, and Puerto Rico have passed comprehensive smoke-free indoor air laws that include e-cigarettes. These laws prohibit smoking and the use of e-cigarettes in indoor areas of private work sites, restaurants, and bars.[39]
- Pooled data from 17 studies in North America, Europe, and Australia suggest that smoke-free legislation can reduce the incidence of acute coronary events by 10%.[54]
- The percentage of the US nonsmoking population with serum cotinine ≥0.05 ng/mL (which indicates exposure to secondhand smoke) declined from 52.5% in 1999 to 2000 to 25.3% in 2011 to 2012, with declines occurring for both children and adults. During 2011 to 2012, the percentage of nonsmokers with detectable serum cotinine was 40.6% for those 3 to 11 years of age, 33.8% for those 12 to 19 years of age, and 21.3% for those ≥20 years of age. The percentage was higher for NH blacks (46.8%) than for NH whites (21.8%) and Mexican Americans (23.9%). People living below the poverty level (43.2%) and those living in rental housing (36.8%) had higher rates of secondhand smoke exposure than their counterparts (21.1% of those living above the poverty level and 19.0% of those who owned their homes; NHANES).[55]

Family History and Genetics

- Genetic factors might contribute to smoking behavior; several loci have been identified that are associated with smoking initiation, number of cigarettes smoked per day, and smoking cessation.[55]
- Genetics might also modify adverse cardiovascular health outcomes among smokers, with variation in *ADAMTS7* associated with loss of cardioprotection in smokers.[56]

Global Burden of Tobacco Use (See Table 3-1 and Chart 3-6)

- Although tobacco use in the United States has been declining, the absolute number of tobacco users worldwide has climbed steeply.[42]
- On the basis of the GBD synthesis of >2800 data sources, the age-standardized global prevalence of daily smoking in 2016 was 25.1% (95% UI, 22.7%–28.7%) in males and 7.9% (95% UI, 6.5%–10.6%) in females. The investigators estimate that since 1990, smoking rates have declined globally by 29.6% in males and 28.6% in females.[1]
- The GBD 2016 study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories. Eastern and Central Europe, East Asia, Southeast Asia, and southern sub-Saharan Africa have the highest mortality rates attributable to tobacco (Chart 3-6).[57]
- The number of smokers was estimated to have grown from 721 million in 1980 to 967 million in 2012.[58]
- Worldwide, ≈80% of smokers live in low- and middle-income countries.[59]
- Tobacco smoking (including secondhand smoke) caused an estimated 7.1 million deaths in 2016. Among the leading risk factors for death, smoking ranked fourth in DALYs globally.[14]
- The WHO estimated that the economic cost of smoking-attributable diseases accounted for US $422 billion, which represented ≈5.7% of global health expenditures.[60] The total economic costs, including both health expenditures and lost productivity, amounted to approximately US $1436 billion, which was roughly equal to 1.8% of the

world's annual gross domestic product. The WHO further estimated that 40% of the expenditures were in developing countries.

- To help combat the global problem of tobacco exposure, in 2003 the WHO adopted the Framework Convention on Tobacco Control treaty. From this emerged a set of evidence-based policies with the goal of reducing the demand for tobacco, entitled MPOWER. MPOWER policies outline the following strategies for nations to reduce tobacco use: (1) monitor tobacco use and prevention policies; (2) protect individuals from tobacco smoke; (3) offer to help with tobacco cessation; (4) warn about tobacco-related dangers; (5) enforce bans on tobacco advertising; (6) raise taxes on tobacco; and (7) reduce the sale of cigarettes. More than half of all nations have implemented at least 1 MPOWER policy.[61]

Table 3-1. Deaths Caused by Tobacco Smoke Worldwide, by Sex

	Males and Females	Males	Females
Total number of deaths in 2015, millions	7.2 (6.5 to 7.8)	5.2 (4.7 to 5.7)	1.9 (1.7 to 2.2)
Percent change in total number from 1990 to 2015	21.5 (15.8 to 27.2)	26.4 (20.4 to 32.9)	9.9 (1.2 to 19.1)
Percent change in total number from 2005 to 2015	4.2 (0.9 to 7.6)	6.8 (3.1 to 10.7)	-2.3 (-7.5 to 3.7)
Mortality rate per 100 000 in 2015	110.7 (101.0 to 120.3)	177.2 (160.2 to 193.7)	55.2 (48.8 to 61.9)
Percent change in rate from 2005 to 2015	−20.3 (−22.8 to −17.7)	−18.9 (−21.7 to −16.0)	−25.2 (−29.1 to −20.5)
Percent change in rate from 1990 to 2015	−33.3 (−36.4 to −30.1)	−32.8 (−35.8 to −29.5)	−38.4 (−43.7 to −33.2)
PAF in 2015, %	12.8 (11.7 to 13.9)	16.9 (15.4 to 18.4)	7.8 (6.9 to 8.7)
Percent change in PAF from 1990 to 2015	4.4 (−0.1 to 8.5)	3.7 (−0.1 to 7.4)	−0.4 (−7.9 to 7.0)
Percent change in PAF from 2005 to 2015	0.1 (−2.4 to 2.6)	−0.1 (−2.4 to 2.2)	−3.0 (−7.4 to 2.2)

Rates are most current data available as of 2015. Rates are per 100 000 people. Values in parentheses represent 95% CIs. PAF indicates population attributable fraction.

Source: Global Burden of Disease Study 2015, Institute of Health Metrics and Evaluation.[62]

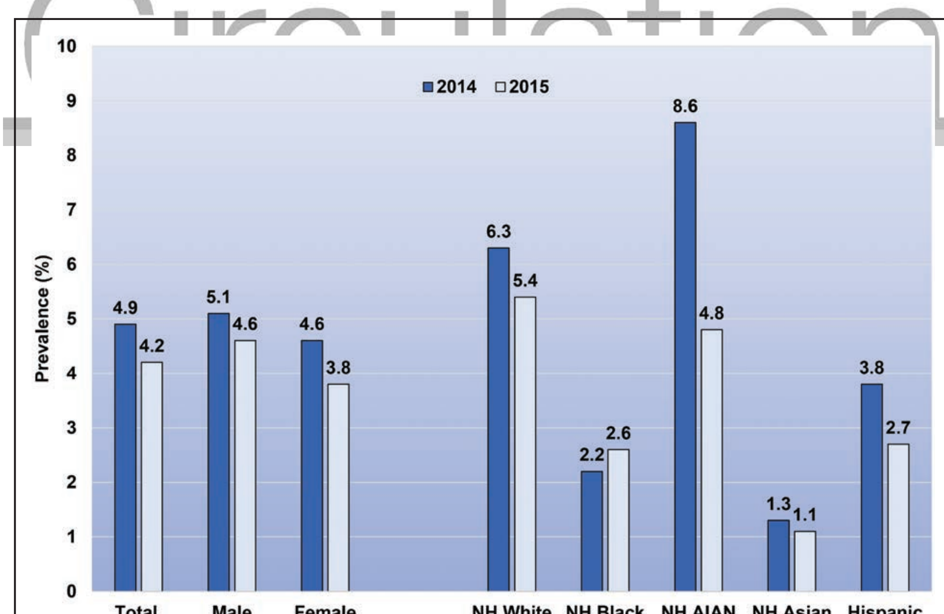

Chart 3-1. Prevalence (%) of cigarette use in the past month for adolescents aged 12 to 17 years by sex and race/ethnicity (NSDUH, 2014 and 2015). Because of methodological differences among the NSDUH, the Youth Risk Behavior Survey, the National Youth Tobacco Survey, and other surveys, percentages of cigarette smoking measured by these surveys are not directly comparable. Notably, school-based surveys might include students who are 18 years old, who are legally permitted to smoke and have higher rates of smoking.

AIAN indicates American Indian or Alaska Native; NH, non-Hispanic; and NSDUH, National Survey on Drug Use and Health.

Data derived from Substance Abuse and Mental Health Services Administration, NSDUH.[63]

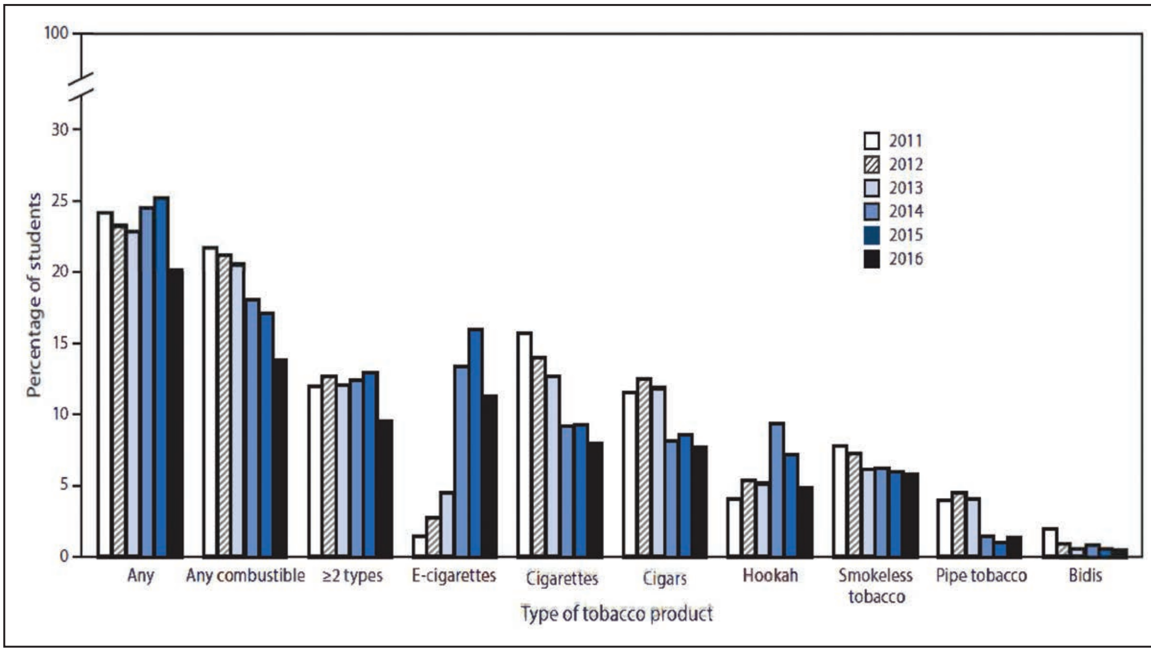

Chart 3-2. Estimated percentage of high school students who have used any tobacco products,* ≥2 tobacco products,†‡ and select tobacco products§ in the past 30 days (National Youth Tobacco Survey, 2011–2016).

*Any tobacco use is defined as past 30-day use of cigarettes, cigars, smokeless tobacco, electronic cigarettes (e-cigarettes), hookahs, pipe tobacco, and/or bidis. †Use of ≥2 tobacco products is defined as past 30-day use of ≥2 of the following product types: cigarettes, cigars, smokeless tobacco, e-cigarettes, hookahs, pipe tobacco, or bidis. ‡Use of ≥2 tobacco products demonstrated a nonlinear change ($P<0.05$). §E-cigarettes and hookahs demonstrated a linear increase ($P<0.05$). Cigarettes, cigars, and smokeless tobacco demonstrated a linear decrease ($P<0.05$). Pipe tobacco and bidis demonstrated a nonlinear decrease ($P<0.05$).
Data derived from the Centers for Disease Control and Prevention, National Youth Tobacco Survey.[64]

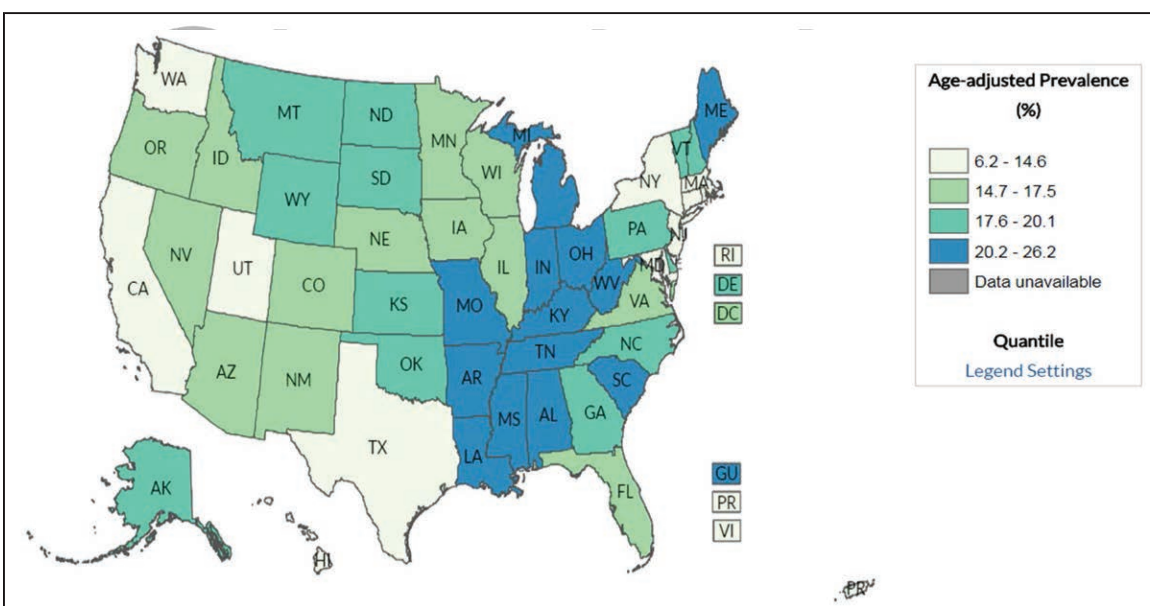

Chart 3-3. Age-adjusted prevalence (%) of current cigarette smoking for adults, by state: United States (BRFSS, 2016).

BRFSS indicates Behavior Risk Factor Surveillance System; GU, Guam; PR, Puerto Rico; and VI, Virgin Islands.
Data derived from the Centers for Disease Control and Prevention.[65]

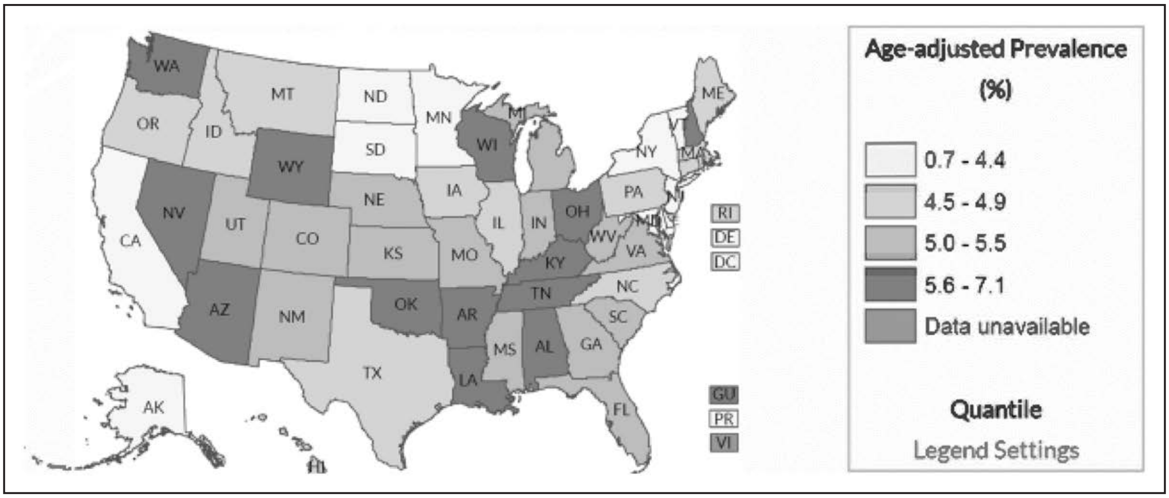

Chart 3-4. Prevalence (age-adjusted) of current e-cigarette use (BRFSS, 2016).
BRFSS indicates Behavior Risk Factor Surveillance System; GU, Guam; PR, Puerto Rico; and VI, Virgin Islands.

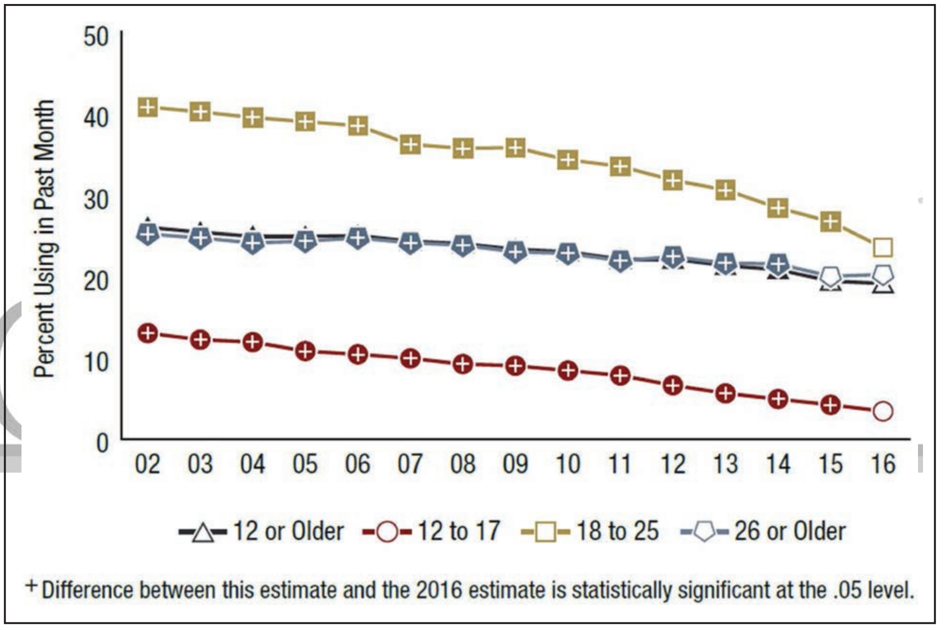

Chart 3-5. Past month cigarette use among people ≥12 years of age, by age group: percentages, 2002 to 2016 (NHIS, 2002–2016; NSDUH, 2002–2016).
NSDUH indicates National Survey on Drug Use and Health; and NHIS, National Health Interview Survey.
Data derived from the Centers for Disease Control and Prevention/National Center for Health Statistics and the Substance Abuse and Mental Health Services Administration (NSDUH).[63]

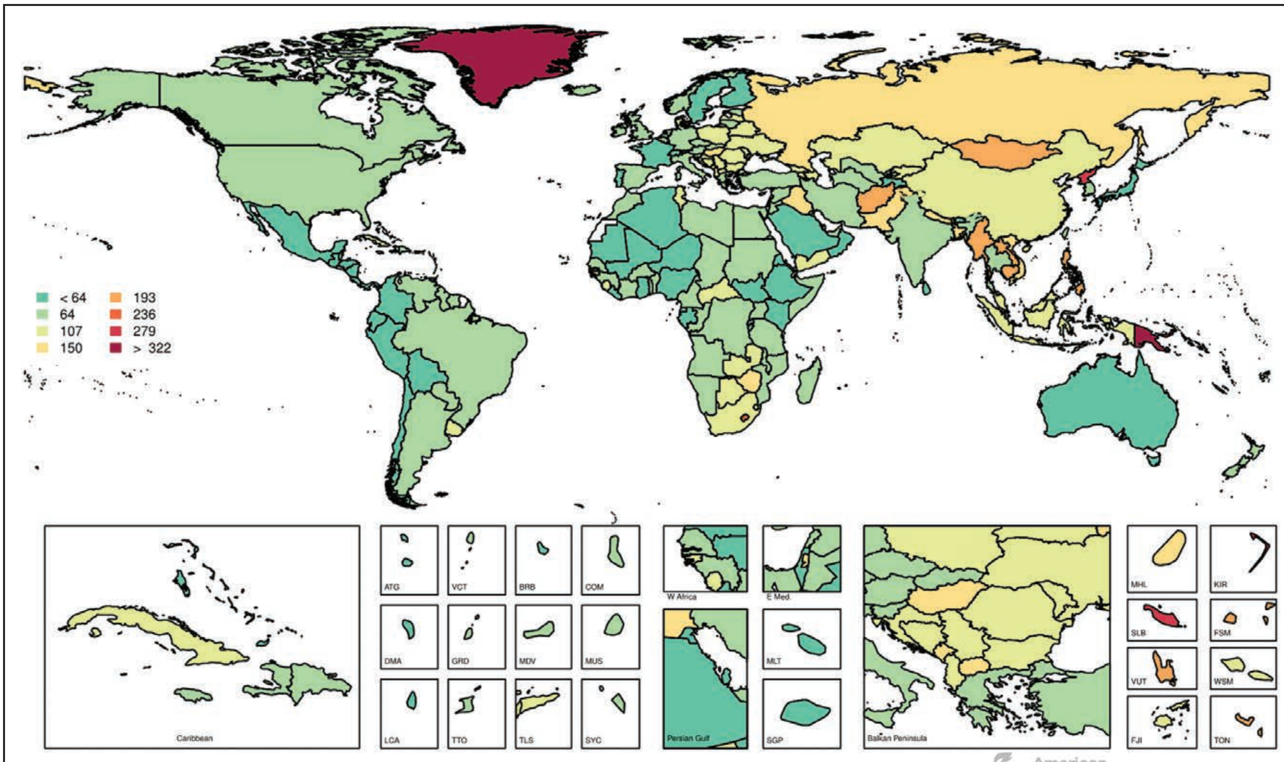

Chart 3-6. Age-standardized global mortality rates attributable to tobacco per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016 with permission.[57] Copyright © 2017, University of Washington.

REFERENCES

1. GBD 2016 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016 [published corrections appear in *Lancet*. 2017;390: E38 and *Lancet*. 2017;390:1736]. *Lancet*. 2017;390:1345–1422. doi: 10.1016/S0140-6736(17)32366-8
2. Thun MJ, Carter BD, Feskanich D, Freedman ND, Prentice R, Lopez AD, Hartge P, Gapstur SM. 50-Year trends in smoking-related mortality in the United States. *N Engl J Med*. 2013;368:351–364. doi: 10.1056/NEJMsa1211127
3. American Heart Association. My Life Check – Life's Simple 7. https://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check--lifes-simple-7. Accessed November 9, 2018.
4. Center for Behavioral Health Statistics and Quality. Key Substance Use and Mental Health Indicators in the United States: Results From the 2015 National Survey on Drug Use and Health. September 2016. HHS publication No. SMA 16-4984, NSDUH series H-51. https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.pdf. Accessed August 1, 2018.
5. Centers for Disease Control and Prevention, National Center for Health Statistics. National Health Interview Survey 2016 Data Release. https://www.cdc.gov/nchs/nhis/nhis_2016_data_release.htm. Accessed October 28, 2018.
6. Centers for Disease Control and Prevention (CDC). Electronic Nicotine Delivery Systems Key Facts. 2014. https://www.cdc.gov/tobacco/infographics/policy/pdfs/electronic-nicotine-delivery-systems-key-facts-infographic.pdf. Accessed June 8, 2016.
7. Kasza KA, Ambrose BK, Conway KP, Borek N, Taylor K, Goniewicz ML, Cummings KM, Sharma E, Pearson JL, Green VR, Kaufman AR, Bansal-Travers M, Travers MJ, Kwan J, Tworek C, Cheng YC, Yang L, Pharris-Ciurej N, van Bemmel DM, Backinger CL, Compton WM, Hyland AJ. Tobacco-product use by adults and youths in the United States in 2013 and 2014 [published correction appears in *N Engl J Med*. 2018;378:492]. *N Engl J Med*. 2017;376:342–353. doi: 10.1056/NEJMsa1607538
8. Jamal A, Gentzke A, Corey CG, Hu SS, Cullen KA, Apelberg BJ, Homa DM,King BA. Tobacco use among middle and high school students: United States, 2011–2016 [published correction appears in *MMWR Morb Mortal Wkly Rep*. 2017;66:765]. *MMWR Morb Mortal Wkly Rep*. 2017;66:23;597–603. doi: 10.15585/mmwr.mm6623a1
9. Mdodo R, Frazier EL, Dube SR, Mattson CL, Sutton MY, Brooks JT, Skarbinski J. Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys. *Ann Intern Med*. 2015;162:335–344. doi: 10.7326/M14-0954

9a. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health. BRFSS Prevalence & Trends Data. 2016. https://www.cdc.gov/brfss/brfssprevalence/index.html. Accessed October 28, 2018.

10. Jamal A, King BA, Neff LJ, Whitmill J, Babb SD, Graffunder CM. Current cigarette smoking among adults: United States, 2005-2015. *MMWR Morb Mortal Wkly Rep*. 2016;65:1205–1211. doi: 10.15585/mmwr.mm6544a2
11. Drake P, Driscoll AK, Mathews TJ. Cigarette smoking during pregnancy: United States, 2016. *NCHS Data Brief*. 2018 Feb;(305):1–8.
12. Watkins SL, Glantz SA, Chaffee BW. Association of noncigarette tobacco product use with future cigarette smoking among youth in the Population Assessment of Tobacco and Health (PATH) Study, 2013-2015. *JAMA Pediatr*. 2018;172:181–187. doi: 10.1001/jamapediatrics.2017.4173
13. Martins SS, Gorelick DA. Conditional substance abuse and dependence by diagnosis of mood or anxiety disorder or schizophrenia in the U.S. population. *Drug Alcohol Depend*. 2011;119:28–36. doi: 10.1016/j.drugalcdep.2011.05.010
14. US Burden of Disease Collaborators. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319:1444–1472. doi: 10.1001/jama.2018.0158
15. Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, McAfee T, Peto R. 21st-century hazards of smoking and benefits of

cessation in the United States. *N Engl J Med*. 2013;368:341–350. doi: 10.1056/NEJMsa1211128
16. US Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
17. Deleted in proof.
18. Mons U, Müezzinler A, Gellert C, Schöttker B, Abnet CC, Bobak M, de Groot L, Freedman ND, Jansen E, Kee F, Kromhout D, Kuulasmaa K, Laatikainen T, O'Doherty MG, Bueno-de-Mesquita B, Orfanos P, Peters A, van der Schouw YT, Wilsgaard T, Wolk A, Trichopoulou A, Boffetta P, Brenner H; on behalf of the CHANCES Consortium. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *BMJ*. 2015;350:h1551. doi: 10.1136/bmj.h1551
19. Zhang M, An Q, Yeh F, Zhang Y, Howard BV, Lee ET, Zhao J. Smoking-attributable mortality in American Indians: findings from the Strong Heart Study. *Eur J Epidemiol*. 2015;30:553–561. doi: 10.1007/s10654-015-0031-8
20. Holford TR, Meza R, Warner KE, Meernik C, Jeon J, Moolgavkar SH, Levy DT. Tobacco control and the reduction in smoking-related premature deaths in the United States, 1964-2012. *JAMA*. 2014;311:164–171. doi: 10.1001/jama.2013.285112
21. US Department of Health and Human Services. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General.* Atlanta, GA: Centers for Disease Control and Prevention; 2010.
22. Substance Abuse and Mental Health Services Administration. Key Substance Use and Mental Health Indicators in the United States: Results from the 2016 National Survey on Drug Use and Health. 2017. https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf. Accessed April 4, 2018.
23. Chang CM, Corey CG, Rostron BL, Apelberg BJ. Systematic review of cigar smoking and all cause and smoking related mortality. *BMC Public Health*. 2015;15:390. doi: 10.1186/s12889-015-1617-5
24. Rasmussen LD, Helleberg M, May MT, Afzal S, Kronborg G, Larsen CS, Pedersen C, Gerstoft J, Nordestgaard BG, Obel N. Myocardial infarction among Danish HIV-infected individuals: population-attributable fractions associated with smoking. *Clin Infect Dis*. 2015;60:1415–1423. doi: 10.1093/cid/civ013
25. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet*. 2011;378:1297–1305. doi: 10.1016/S0140-6736(11)60781-2
26. Peters SA, Huxley RR, Woodward M. Smoking as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 81 cohorts, including 3,980,359 individuals and 42,401 strokes. *Stroke*. 2013;44:2821–2828. doi: 10.1161/STROKEAHA.113.002342
27. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet*. 1996;348:498–505. doi: 10.1016/S0140-6736(95)12393-8
28. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet*. 1996;348:505–510. doi: 10.1016/S0140-6736(95)12394-6
29. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, Goldstein LB, Greenberg SM, Horvath SE, Iadecola C, Jauch EC, Moore WS, Wilson JA; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:3754–3832. doi: 10.1161/STR.0000000000000046
30. Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke. *Expert Rev Cardiovasc Ther*. 2010;8:917–932. doi: 10.1586/erc.10.56
31. Azar RR, Frangieh AH, Mroué J, Bassila L, Kasty M, Hage G, Kadri Z. Acute effects of waterpipe smoking on blood pressure and heart rate: a real-life trial. *Inhal Toxicol*. 2016;28:339–342. doi: 10.3109/08958378.2016.1171934
32. Yatsuya H, Folsom AR; and for the ARIC Investigators. Risk of incident cardiovascular disease among users of smokeless tobacco in the Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol*. 2010;172:600–605. doi: 10.1093/aje/kwq191
33. Bhatnagar A, Whitsel LP, Ribisl KM, Bullen C, Chaloupka F, Piano MR, Robertson RM, McAuley T, Goff D, Benowitz N; on behalf of the American Heart Association Advocacy Coordinating Committee, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Electronic cigarettes: a policy statement from the American Heart Association. *Circulation*. 2014;130:1418–1436. doi: 10.1161/CIR.0000000000000107
34. Bhatnagar A. E-cigarettes and cardiovascular disease risk: evaluation of evidence, policy implications, and recommendations. *Curr Cardiovasc Risk Rep*. 2016;10:24. doi: 10.1007/s12170-016-0505-6
35. Xu X, Bishop EE, Kennedy SM, Simpson SA, Pechacek TF. Annual healthcare spending attributable to cigarette smoking: an update. *Am J Prev Med*. 2015;48:326–333. doi: 10.1016/j.amepre.2014.10.012
36. Trends in State and Federal Cigarette Tax and Retail Price in the United States: 1970-2016. https://www.cdc.gov/tobacco/infographics/economics/pdfs/linegraph2017.pdf?s_cid=bb-osh-economics-graphic-001. Accessed October 28, 2018.
37. Kessel Schneider S, Buka SL, Dash K, Winickoff JP, O'Donnell L. Community reductions in youth smoking after raising the minimum tobacco sales age to 21. *Tob Control*. 2016;25:355–359. doi: 10.1136/tobaccocontrol-2014-052207
38. Morain SR, Winickoff JP, Mello MM. Have Tobacco 21 laws come of age? *N Engl J Med*. 2016;374:1601–1604. doi: 10.1056/NEJMp1603294
39. States and localities that have raised the minimum legal sale age for tobacco products to 21. https://www.tobaccofreekids.org/content/what_we_do/state_local_issues/sales_21/states_localities_MLSA_21.pdf. Accessed June 5, 2017.
40. Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting smoking among adults: United States, 2000-2015. *MMWR Morb Mortal Wkly Rep*. 2017;65:1457–1464. doi: 10.15585/mmwr.mm6552a1
41. Clinical Practice Guideline Treating Tobacco Use and Dependence Update Panel, Liaisons, and Staff. A clinical practice guideline for treating tobacco use and dependence: 2008 update: a U.S. Public Health Service report. *Am J Prev Med*. 2008;35:158–176. doi: 10.1016/j.amepre.2008.04.009
42. Eisenberg MJ, Windle SB, Roy N, Old W, Grondin FR, Bata I, Iskander A, Lauzon C, Srivastava N, Clarke A, Cassavar D, Dion D, Haught H, Mehta SR, Baril JF, Lambert C, Madan M, Abramson BL, Dehghani P; for the EVITA Investigators. Varenicline for smoking cessation in hospitalized patients with acute coronary syndrome. *Circulation*. 2016;133:21–30. doi: 10.1161/CIRCULATIONAHA.115.019634
43. Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, Ascher J, Russ C, Krishen A, Evins AE. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet*. 2016;387:2507–2520. doi: 10.1016/S0140-6735(16)30272-0
44. Schnoll RA, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, Gariti P, Wileyto EP, Hitsman B. Long-term nicotine replacement therapy: a randomized clinical trial. *JAMA Intern Med*. 2015;175:504–511. doi: 10.1001/jamainternmed.2014.8313
45. Halpern SD, French B, Small DS, Saulsgiver K, Harhay MO, Audrain-McGovern J, Loewenstein G, Brennan TA, Asch DA, Volpp KG. Randomized trial of four financial-incentive programs for smoking cessation. *N Engl J Med*. 2015;372:2108–2117. doi: 10.1056/NEJMoa1414293
46. Centers for Disease Control and Prevention (CDC). Quitting smoking among adults: United States, 2001–2010. *MMWR Morb Mortal Wkly Rep*. 2011;60:1513–1519.
47. Xu X, Alexander RL Jr, Simpson SA, Goates S, Nonnemaker JM, Davis KC, McAfee T. A cost-effectiveness analysis of the first federally funded antismoking campaign. *Am J Prev Med*. 2015;48:318–325. doi: 10.1016/j.amepre.2014.10.011
48. Antman E, Arnett D, Jessup M, Sherwin C. The 50th anniversary of the US Surgeon General's report on tobacco: what we've accomplished and where we go from here. *J Am Heart Assoc*. 2014;3:e000740. doi: 10.1161/JAHA.113.000740
49. Singh T, Marynak K, Arrazola RA, Cox S, Rolle IV, King BA. Vital signs: exposure to electronic cigarette advertising among middle school and high school students: United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2016;64:1403–1408. doi: 10.15585/mmwr.mm6452a3
50. Zhu SH, Sun JY, Bonnevie E, Cummins SE, Gamst A, Yin L, Lee M. Four hundred and sixty brands of e-cigarettes and counting:

implications for product regulation. *Tob Control*. 2014;23(suppl 3):iii3-iii9. doi: 10.1136/tobaccocontrol-2014-051670
51. Delnevo CD, Giovenco DP, Steinberg MB, Villanti AC, Pearson JL, Niaura RS, Abrams DB. Patterns of electronic cigarette use among adults in the United States. *Nicotine Tob Res*. 2016;18:715–719. doi: 10.1093/ntr/ntv237
52. Syamlal G, Jamal A, King BA, Mazurek JM. Electronic cigarette use among working adults: United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2016;65:557–561. doi: 10.15585/mmwr.mm6522a1
53. FDA's deeming regulations for e-cigarettes, cigars, and all other tobacco products. US Food & Drug Administration website. https://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm394909.htm. Accessed April 6, 2018.
54. Mackay DF, Irfan MO, Haw S, Pell JP. Meta-analysis of the effect of comprehensive smoke-free legislation on acute coronary events. *Heart*. 2010;96:1525–1530. doi: 10.1136/hrt.2010.199026
55. Tobacco and Genetics Consortium. Genome-wide meta-analyses identify multiple loci associated with smoking behavior. *Nat Genet*. 2010;42:441–447. doi: 10.1038/ng.571
56. Saleheen D, Zhao W, Young R, Nelson CP, Ho W, Ferguson JF, Rasheed A, Ou K, Nurnberg ST, Bauer RC, Goel A, Do R, Stewart AFR, Hartiala J, Zhang W, Thorleifsson G, Strawbridge RJ, Sinisalo J, Kanoni S, Sedaghat S, Marouli E, Kristiansson K, Hua Zhao J, Scott R, Gauguier D, Shah SH, Smith AV, van Zuydam N, Cox AJ, Willenborg C, Kessler T, Zeng L, Province MA, Ganna A, Lind L, Pedersen NL, White CC, Joensuu A, Edi Kleber M, Hall AS, März W, Salomaa V, O'Donnell C, Ingelsson E, Feitosa MF, Erdmann J, Bowden DW, Palmer CNA, Gudnason V, Faire U, Zalloua P, Wareham N, Thompson JR, Kuulasmaa K, Dedoussis G, Perola M, Dehghan A, Chambers JC, Kooner J, Allayee H, Deloukas P, McPherson R, Stefansson K, Schunkert H, Kathiresan S, Farrall M, Marcel Frossard P, Rader DJ, Samani NJ, Reilly MP. Loss of cardioprotective effects at the *ADAMTS7* locus as a result of gene-smoking interactions. *Circulation*. 2017;135:2336–2353. doi: 10.1161/CIRCULATIONAHA.116.022069
57. Global Burden of Disease Study 2016 (GBD 2016) results. Global Health Data Exchange website. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed May 1, 2018.
58. Ng M, Freeman MK, Fleming TD, Robinson M, Dwyer-Lindgren L, Thomson B, Wollum A, Sanman E, Wulf S, Lopez AD, Murray CJ, Gakidou E. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. *JAMA*. 2014;311:183–192. doi: 10.1001/jama.2013.284692
59. World Health Organization. Tobacco Fact Sheet. 2017. http://www.who.int/mediacentre/factsheets/fs339/en/. Accessed June 5, 2017.
60. Goodchild M, Nargis N, Tursan d'Espaignet E. Global economic cost of smoking-attributable diseases. *Tob Control*. 2017;27:58–64. doi: 10.1136/tobaccocontrol-2016-053305
61. World Health Organization. The WHO Framework Convention on Tobacco Control: An Overview. 2015. http://www.who.int/fctc/about/en/index.html. Accessed July 18, 2016.
62. Global Burden of Disease Study 2015 (GBD 2015) results. Global Health Data Exchange website. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed May 30, 2017.
63. Center for Behavioral Health Statistics and Quality. Behavioral Health Trends in the United States: Results From the 2014 National Survey on Drug Use and Health. 2015. http://www.samhsa.gov/data/. Accessed August 25, 2016.
64. National Youth Tobacco Survey (NYTS). Centers for Disease Control and Prevention website. http://www.cdc.gov/tobacco/data_statistics/surveys/nyts/. Accessed July 18, 2016.
65. State Tobacco Activities Tracking and Evaluation (STATE) System. Centers for Disease Control and Prevention website. http://www.cdc.gov/statesystem/cigaretteuseadult.html. Accessed July 18, 2016.

4. PHYSICAL INACTIVITY

See Charts 4-1 through 4-13

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Physical inactivity is a major risk factor for CVD and stroke.[1] Meeting the guidelines for PA is one of the AHA's 7 components of ideal cardiovascular health for both children and adults.[2] The AHA and 2008 federal guidelines for PA recommend that children get at least 60 minutes of PA daily (including aerobic and muscle- and bone-strengthening activity).[3] In 2015, on the basis of survey interviews,[4] only 27.1% of high school students reported achieving at least 60 minutes of daily PA, which is likely an overestimation of those actually meeting the guidelines.[5,6] The 2008 federal guidelines recommend that adults get at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic activity (or an equivalent combination) per week and perform muscle-strengthening activities at least 2 days per week.[3] In a nationally representative sample of adults, only 22.5% of adults reported participating in adequate leisure-time aerobic and muscle-strengthening activity to meet these criteria (Chart 4-1), but they were not asked to report activity accumulated during occupational, transportation, or domestic duties.[7] Being physically active is an important aspect of overall health. PA not only reduces premature mortality but also improves risk factors for CVD (such as HBP and high cholesterol) and reduces the likelihood of diseases related to CVD, including CHD, HF, stroke, type 2 DM, and sudden heart attacks.[3] Benefits from PA are seen for all ages and groups, including children and older adults, pregnant females, and people with disabilities and chronic conditions. Therefore, the 2008 federal guidelines recommend being as physically active as abilities and conditions allow and, if not currently meeting the recommendations, increasing PA gradually.[3] Ahead of the new 2018 federal guidelines, the Physical Activity Guidelines Advisory Committee published a report providing an even clearer message for individuals not meeting the 150 minutes of moderate PA per week guideline, stating that even small increases in moderate-intensity PA or replacing sedentary time with light-intensity PA could provide health benefits.[8]

Abbreviations Used in Chapter 4

AF	atrial fibrillation
AHA	American Heart Association
AMI	acute myocardial infarction
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
DBP	diastolic blood pressure
DM	diabetes mellitus
ED	emergency department
EF	ejection fraction
GBD	Global Burden of Disease
GED	General Educational Development
HBP	high blood pressure
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HR	hazard ratio
LDL-C	low-density lipoprotein cholesterol
LIFE	Lifestyle Interventions and Independence for Elders
MET	metabolic equivalent
MI	myocardial infarction
MSA	Metropolitan Statistical Area
NAVIGATOR	Long-term Study of Nateglinide + Valsartan to Prevent or Delay Type II Diabetes Mellitus and Cardiovascular Complications
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
OR	odds ratio
PA	physical activity
PAD	peripheral artery disease
PAR	population attributable risk
QALY	quality-adjusted life-year
RCT	randomized controlled trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SES	socioeconomic status
TC	total cholesterol
VTE	venous thromboembolism
WC	waist circumference
WHI	Women's Health Initiative
WHO	World Health Organization
YRBSS	Youth Risk Behavior Surveillance System

Defining and Measuring PA

There are 4 dimensions of PA (mode or type, frequency, duration, and intensity) and 4 common domains for adults (occupational, domestic, transportation, and leisure time).[5] For children, there are additional considerations of structured PA in schools and communities. The federal guidelines specify the suggested frequency, duration, and intensity of activity. Historically, recommendations on PA for health purposes have focused on leisure-time activity. However, because all domains of PA could have an impact on health, and because an increase in 1 domain can sometimes be compensated for by a decrease in another domain, ideally data will be collected on all dimensions and domains of PA.[5]

There are 2 broad categories of methods to assess PA: (1) subjective methods that use questionnaires and diaries/logs and (2) objective methods that use wearable monitors (pedometers, accelerometers, etc). Studies that compare the findings between subjective and objective methods have found that there is marked

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discordance between self-reported and measured PA, with respondents often overstating their PA, especially the intensity.[5,6]

Another consideration in the measurement of PA is that surveys often ask only about leisure-time PA, which represents PA obtained from a single domain. People who obtain high PA in other domains might be less likely to engage in leisure-time PA. Although they might meet the federal PA guidelines, people who spend considerable time and physical effort in occupational, domestic, or transportation activities/domains might be less likely to be identified as meeting the guidelines.

PA and cardiorespiratory fitness provide distinct metrics in assessment of CVD risk.[9] Poor cardiorespiratory (or aerobic) fitness might be a stronger predictor of adverse cardiometabolic and cardiovascular outcomes such as CHD, stroke, and HF than traditional risk factors.[10–12]Although many studies have shown that increasing the amount and quality of PA can improve cardiorespiratory fitness, other factors can contribute, such as a genetic predisposition to perform aerobic exercise.[13] Because cardiorespiratory fitness is directly measured and reflects both participation in PA and the state of physiological systems affecting performance, the relationship between cardiorespiratory fitness and clinical outcomes is stronger than the relationship of PA to a series of clinical outcomes.[9] Unlike health behaviors such as PA and risk factors that are tracked by federally funded programs (NHIS, NHANES, etc),[6,14] there are no national data on adult cardiorespiratory fitness, although the development of a national cardiorespiratory fitness registry has been proposed.[9] Such additional data on the cardiorespiratory fitness levels of Americans could give a fuller and more accurate picture of physical fitness levels.[9]

Prevalence

Youth

Meeting the Activity Recommendations (See Charts 4-2 through 4-4)

- On the basis of self-reported PA (YRBSS, 2015)[4]:
  - — The prevalence of high school students who met aerobic activity recommendations of ≥60 minutes of PA on all 7 days of the week was 27.1% nationwide and declined from 9th (31.0%) to 12th (23.5%) grades. At each grade level, the prevalence was higher in boys than in girls.
  - — More than double the percentage of high school–aged boys (36.0%) than girls (17.7%) reported having been physically active ≥60 minutes per day on all 7 days (Chart 4-2).
    - ▪ The prevalence of students meeting activity recommendations on ≥5 days per week was higher among NH white boys (62.0%), NH black boys (52.2%), and Hispanic boys (53.5%) than NH white girls (43.5%), NH black girls (33.4%), and Hispanic girls (33.1%) (Chart 4-2).
  - — 14.3% of students reported that they did not participate in ≥60 minutes of any kind of PA on any 1 of the previous 7 days. Girls were more likely than boys to report this level of inactivity (17.5% versus 11.1%), with black girls reporting the highest rate of inactivity (25.2%) (Chart 4-3).
- With regard to objectively measured moderate to vigorous PA (based on age-specific criteria for accelerometer cutpoints; NHANES, 2003–2004)[6]:
  - — Only 8% of 12- to 19-year-olds accumulated ≥60 minutes of moderate to vigorous PA on ≥5 days per week, whereas 42% of 6- to 11-year-olds achieved similar activity levels.[6]
  - — More boys than girls met PA recommendations (≥60 minutes of moderate to vigorous activity) on ≥5 days per week.[6]
- With regard to objectively measured cardiorespiratory fitness (NHANES, 2012)[15]:
  - — For adolescents aged 12 to 15 years, boys in all age groups were more likely to have adequate levels of cardiorespiratory fitness than girls (Chart 4-4).[15]
- With regard to self-reported muscle-strengthening activities (YRBSS, 2015)[4]:
  - — The proportion of high school students who participated in muscle-strengthening activities on ≥3 days of the week was 53.4% nationwide and declined from 9th grade (males 64.9%, females 48.2%) to 12th grade (males 59.9%, females 39.9%).
  - — More high school boys (63.7%) than girls (42.7%) reported having participated in muscle-strengthening activities on ≥3 days of the week.

Structured Activity Participation in Schools and Sports

- In 2015, only 29.8% of students attended physical education classes in school daily (33.8% of boys and 25.5% of girls; YRBSS).[4]
- Daily physical education class participation declined from the 9th grade (44.6% for boys, 39.5% for girls) through the 12th grade (27.9% for boys, 16.0% for girls; YRBSS).[4]
- Just over half (57.6%) of high school students played on at least 1 school or community sports team in the previous year: 53.0% of girls and 62.2% of boys (YRBSS).[4]

Television/Video/Computers
(See Chart 4-5)

Research suggests that screen time (watching television or using a computer) can lead to less PA among children.[16] In addition, television viewing time is associated with poor nutritional choices, overeating, and weight gain (Chapter 5, Nutrition).

- In 2015 (YRBSS)[4]:
  - — Nationwide, 41.7% of high school students used a computer for activities other than school work (eg, videogames or other computer games) for ≥3 hours per day on an average school day.
  - — The prevalence of using computers ≥3 hours per day (for activities other than school work) was highest among NH black girls (48.4%), followed by Hispanic girls (47.4%), Hispanic boys (45.1%), NH black boys (41.2%), NH white boys (38.9%), and NH white girls (38.3%) (Chart 4-5).
  - — The prevalence of watching television ≥3 hours per day was highest among NH black girls (41.5%) and boys (37.0%), followed by Hispanic girls (29.2%) and boys (27.4%) and NH white boys (21.4%) and girls (18.8%).
- A report from the Kaiser Family Foundation (using data from 2009) reported that 8- to 18-year-olds spent an average of 33 minutes per day talking on the phone and 49 minutes using their phone to access media (music, games, or videos).[17] In addition to other cell phone use, 7th to 12th graders spent an average of 95 minutes per day text messaging. Surveys such as YRBSS have not historically asked about cell phone use specifically and are thus likely underestimates of total screen-time use.

Adults

Meeting the Activity Recommendations
(See Charts 4-1 and 4-6 through 4-10)

- With regard to self-reported leisure-time aerobic and muscle-strengthening PA (NHIS, 2016)[7]:
  - — 22.5% of adults met the 2008 federal PA guidelines for both aerobic and strengthening activity, an important component of overall physical fitness, based on only reporting leisure-time activity (Chart 4-1).
- For self-reported leisure-time aerobic PA (NHIS, 2016)[7]:
  - — The age-adjusted proportion who reported meeting the 2008 aerobic PA guidelines for Americans (≥150 minutes of moderate PA or 75 minutes of vigorous PA or an equivalent combination each week) through leisure-time activities was 59.7% and 53.6% for NH white males and females, 51.0% and 39.1% for NH black males and females, and 46.4% and 41.8% for Hispanic males and females, respectively. Among both males and females, NH whites were more likely to meet the PA aerobic guidelines with leisure-time activity than NH blacks and Hispanics. For each racial/ethnic group, males had higher PA than females (Chart 4-6).
  - — Among adults ≥25 years of age, 32.4% of participants with no high school diploma, 40.8% of those with a high school diploma or GED high school equivalency credential, 51.4% of those with some college, and 64.9% of those with a bachelor's degree or higher met the federal guidelines for aerobic PA through leisure-time activities (Chart 4-7).
- Adults residing in urban areas (metropolitan statistical areas) are more likely to meet the federal aerobic PA guidelines through leisure-time activities than those residing in rural areas (53.7% versus 46.2%) (Chart 4-8).[7]
- Adults living below 200% of the poverty level are less likely to meet the federal PA guidelines through leisure-time activities than adults living at >200% above the poverty level (Chart 4-9).[7]
- 13.5 % of people with disabilities and 24.3% of people without disabilities meet both the aerobic and muscle-strengthening guidelines (Chart 4-10).[7]
- In 2016, 26.9% of adults reported that they do not engage in leisure-time PA (no sessions of leisure time PA of ≥10 minutes in duration; Chart 4-11).[7]
- Among adults 20 to 59 years of age, 3.8% of males and 3.2% of females met recommendations to engage in moderate to vigorous PA for 30 minutes (in sessions of ≥10 minutes) on ≥5 of 7 days.[6] It is also important to consider that using data accumulated only in ≥10-minute bouts could remove up to 75% of moderate activity.[18]
  - — These data also revealed that rural US residents performed less moderate to vigorous PA than urban residents, but rural residents spent more time in lighter-intensity PA (accelerometer counts per minute: 760–2020) than their urban resident counterparts.[19]
  - — In a review examining self-reported versus directly measured PA (eg, accelerometers, pedometers, indirect calorimetry, doubly labeled water, heart rate monitor), 60% of respondents self-reported higher values of activity than what was measured by use of direct methods.[20] Among males, self-reported PA was 44% greater than directly measured values; among females, self-reported activity was 138% greater than directly measured PA.[20]

- With regard to objectively measured moderate to vigorous PA (accelerometer counts per minute >2020; NHANES, 2003–2004)[6]:
  — Among those ≥60 years of age, adherence to PA recommendations was 2.5% in males and 2.3% in females.[6]
  — In contrast to self-reported PA, which suggested that NH whites had the higher levels of PA,[14] data from objectively measured PA revealed that Hispanic participants had higher total PA and moderate to vigorous PA compared with NH white or black participants (≥20 years old).[6,21]
- Levels of activity declined sharply after the age of 50 years in all groups.[18] In a recent study of almost 5000 British males, in those with low PA in midlife, retirement and the development of cardiovascular-related conditions were identified as factors predicting a decrease in PA over 20 years of follow-up, but for males who were more active in middle age, retirement was observed to be a time of increasing PA.[22]
- A Nielsen Report using data from 2017 reported that adults spent an average of 5 hours 5 minutes per day watching television (including live television and other television-connected devices such as DVDs or playing video games on a console) and an hour and a half each day on computers or tablets.[23] Adult smartphone app/web use was reported as 2 hours 28 minutes per day using data collected from 12 500 smartphone users in 2017.[23] These technology use behaviors could influence time spent in PA and sedentary time.
  — Of particular concern, black adults spent an average of 7 hours 13 minutes per day watching television. Black and Hispanic adults had the highest smartphone use compared with other racial/ethnic groups.[23]

Structured Activity Participation in Leisure-Time, Domestic, Occupational, and Transportation Activities

- Individuals from urban areas who participated in NHANES 2003 to 2006 reported participating in more transportation activity, but rural individuals reported spending more time in household PA and more total PA than urban individuals, possibly explaining the higher levels of light activity of rural individuals observed by objective methods.[19]
- At this time, it is unclear which construct of PA (domestic, occupational, or transportation) contributes to the higher objectively measured PA[21] but lower subjectively measured PA[14] for Hispanic individuals, or whether these differences are caused by overreporting or underreporting of leisure-time PA.
- A 1-day assessment indicated that the mean prevalence of any active transportation was 10.3% using 2012 data from the American Time Use Study. NH whites reported the lowest active transport, only 9.2%, of any racial/ethnic group. Roughly 11.0% of Hispanics, 13.4% of NH blacks, and 15.0% of other NH individuals reported participating in any active transportation on the previous day.[24]

Mortality

Self-Reported Physical Inactivity and Mortality

- Physical inactivity is the fourth-leading risk factor for global death, responsible for 1 to 2 million deaths annually.[25,26] The adjusted population attributable fraction for achieving <150 minutes of moderate to vigorous PA per week was 8.0% for all-cause and 4.6% for major CVD in a study of 17 low-, middle-, and high-income countries in 130 843 participants without preexisting CVD.[27]
- A similar analysis in the US using NHIS data from 1990 to 1991 (N=67 762) found that after 20 years of follow-up, 8.7% of all-cause mortality was attributed to levels of PA that were <150 minutes of moderate-intensity equivalent activity per week.[28]
- A study of US adults that linked a large, nationally representative sample of 10 535 participants (NHANES) to death records found that meeting the aerobic PA guidelines reduced all-cause mortality, with an HR of 0.64 (95% CI, 0.52–0.79), after adjustment for potential confounding factors. Furthermore, for adults not meeting the aerobic PA guidelines, engaging in muscle-strengthening activity ≥2 times a week was associated with a 44% lower adjusted HR for all-cause mortality.[29]
- A meta-analysis of 9 cohort studies, representing 122 417 patients, found that as little as 15 minutes of daily moderate to vigorous PA reduced all-cause mortality in adults ≥60 years of age. This protective effect of PA was dose dependent; the most rapid reduction in mortality per minute of added PA was for those at the lowest levels of PA. These findings suggest that older adults can benefit from PA time far below the amount recommended by the federal guidelines.[30]
- In a pooled study of >600 000 participants,[31] an inverse dose-response relationship was observed between level of self-reported leisure-time PA (HR, 0.80 [95% CI, 0.78–0.82] for less than the recommended minimum of the PA guidelines; HR, 0.69 [95% CI, 0.67–0.70] for 1–2 times the recommended minimum; and HR, 0.63 [95% CI, 0.62–0.65] for 2–3 times the minimum) and mortality, with the upper threshold for mortality benefit

occurring at 3 to 5 times the PA recommendations (HR, 0.61; 95% CI, 0.59–0.62). Furthermore, there was no evidence of harm associated with performing ≥10 times the recommended minimum (HR, 0.68; 95% CI, 0.59–0.78).[31]

- Similarly, a population-based cohort in New South Wales, Australia, of 204 542 adults followed up for an average of 6.5 years evaluated the relationship of PA to mortality risk. It found that compared with those who reported no moderate to vigorous PA, the adjusted HRs for all-cause mortality were 0.66 (95% CI, 0.61–0.71) for those reporting 10 to 149 min/wk, 0.53 (95% CI, 0.48–0.57) for those reporting 150 to 299 min/wk, and 0.46 (95% CI, 0.43–0.49) for those reporting ≥300 min/wk of activity.[32]
- In the Women's Health Study (N=28 879; mean age, 62 years), females participating in strength training (1–19, 20–59, and 60–149 min/wk compared with 0 min/wk) had lower risk of all-cause mortality (HR [95% CI], 0.73 [0.65–0.82], 0.71 [0.62–0.82], and 0.81 [0.67–0.97], respectively), but performing ≥150 min/wk strength training was not associated with lower risk of all-cause mortality (HR, 1.10; 95% CI, 0.77–1.56) because of very wide CIs.[33]
- A meta-analysis also revealed an association between participating in more transportation-related PA and lower all-cause mortality risk.[34] In contrast, higher occupational PA has been associated with higher mortality in males but not females.[35] It is unclear whether confounding factors such as fitness, SES, or other domains of PA might impact this relationship.
- In a longitudinal cohort study of 263 540 participants from the UK Biobank cohort, commuting by bicycle was associated with a lower risk of CVD mortality and all-cause mortality (HR, 0.48 and 0.59, respectively). Commuting by walking was associated with a lower risk of CVD mortality (HR, 0.64) but not all-cause mortality.[36]
- In a study involving 55 137 adults followed up over an average of 15 years, running even 5 to 10 min/d and at slow speeds (<6 mph) was associated with a markedly reduced risk of CVD and of death attributable to all causes.[37]
- In the Southern Community Cohort Study of 63 308 individuals followed up for >6.4 years, more time spent being sedentary (>12 h/d versus <5.76 h/d) was associated with a 20% to 25% increased risk of all-cause mortality in both black and white adults. Both PA (beneficial) and sedentary time (detrimental) were associated with mortality risk.[38]
- In a meta-analysis of 13 studies evaluating the association between sedentary time and all-cause mortality, higher sedentary time was associated with a 22% higher risk of all-cause mortality (HR, 1.22; 95% CI, 1.09–1.41). This association was more pronounced at lower levels of PA than at higher levels.[39]
- A meta-analysis that included >1 million participants across 16 studies compared the risk associated with sitting time and television viewing in physically active and inactive study participants. For inactive individuals (defined as the lowest quartile of PA), those sitting >8 h/d had a higher all-cause mortality risk than those sitting <4 h/d. For active individuals (top quartile for PA), sitting time was not associated with all-cause mortality, but active people who watched television ≥5 h/d did have higher mortality risk.[40]

Objectively Measured Physical Inactivity/ Sedentary Time and Mortality

- In a subsample of NHANES (participants with objectively measured PA and between the ages of 50 and 79 years [N=3029]), models that replaced sedentary time with 10 min/d of moderate to vigorous PA were associated with lower all-cause mortality (HR, 0.70; 95% CI, 0.57–0.85) after 5 to 8 years of follow-up. Even substituting in 10 min/d of light activity was associated with lower all-cause mortality (HR, 0.91; 95% CI, 0.86–0.96).[41]
- In an analysis from the Women's Health Study, objective measures of PA and sedentary behavior using an accelerometer were associated with all-cause mortality. The highest levels of overall PA volume, as measured by the accelerometer, were associated with 60% to 70% lower risk of all-cause mortality. This inverse association between overall PA and all-cause mortality was largely driven by the moderate to vigorous PA levels; light PA or sedentary behavior was not associated with mortality risk in this cohort after accounting for moderate to vigorous PA.[42]
- In a cohort study of 7985 middle- and older-aged US adults, the REGARDS study objectively measured total sedentary time (HR [95% CI] for highest versus lowest quartile of total sedentary time, 2.63 [1.60–4.30]) and longer sedentary bouts (HR, 1.96; 95% CI, 1.31–2.93) were both associated with higher risk of all-cause mortality.[43]

Cardiorespiratory Fitness and Mortality

- The Cooper Center Longitudinal Study, an analysis conducted on 16 533 participants, revealed that across all risk factor strata, the presence of low cardiorespiratory fitness was associated with a greater risk of CVD death over a mean follow-up of 28 years.[44]

- In a longitudinal cohort study from the UK Biobank data, the association between PA and all-cause mortality was strongest among those with lowest hand-grip strength and lowest cardiorespiratory fitness, which suggests that strength and possibly cardiorespiratory fitness could moderate the association between PA and mortality.[45]
- In a retrospective cohort study of 57 085 individuals who were clinically referred for stress testing (but without established CAD or HF), cardiorespiratory fitness–associated "biologic age" was a stronger predictor of mortality over 10 years of follow-up than chronological age.[46]

Secular Trends

Youth

In 2015 (YRBSS)[4]:

- Among students nationwide, there was a significant increase in the number of individuals reporting participation in muscle-strengthening activities on ≥3 days per week, from 47.8% in 1991 to 53.4% in 2015; however, the prevalence did not change substantively from 2013 (51.7%) to 2015 (53.4%).
- A significant increase occurred in the number of youth reporting having used computers not for school work for ≥3 h/d compared with 2003 (22.1% versus 41.7% in 2015). The prevalence increased from 2003 to 2009 (22.1% versus 24.9%) and then increased more rapidly from 2009 to 2015 (24.9% versus 41.7%).
  - From 2004 to 2009, the Kaiser Family Foundation reported that the proportion of 8- to 18-year-olds who owned their own cell phone increased from 39% to 66%,[17] which could also contribute to higher exposure to screen time in children.
- Nationwide, the number of high school students who reported attending physical education classes at least once per week did not change substantively between 2013 (48.0%) and 2015 (51.6%).
  - The number of high school students reporting attending daily physical education classes changed in nonlinear ways over time. Attendance initially decreased from 1991 to 1995 (from 41.6% to 25.4%) and did not substantively change between 1995, 2013, and 2015 (25.4%, 29.4%, and 29.8%, respectively).
- The prevalence of high school students playing ≥1 team sport in the past year did not substantively change between 2013 (54.0%) and 2015 (57.6%). In 2012, the prevalence of adolescents aged 12 to 15 years with adequate levels of cardiorespiratory fitness (based on age- and sex-specific standards) was 42.2% (Chart 4-3), down from 52.4% in 1999 to 2000.[15]

Adults (See Charts 4-11 and 4-12)

- The prevalence of physical inactivity among adults ≥18 years of age, overall and by sex, has decreased from 1998 to 2016, with the largest drop occurring in the past decade, from 40.2% to 26.9% between 2005 and 2016, respectively (Chart 4-11).[7,47] The prevalence of physical inactivity has surpassed the target for Healthy People 2020, which was 32.6%.[47]
- A 2.3% decline in physical inactivity between 1980 and 2000 was estimated to have prevented or postponed ≈17 445 deaths (≈5%) attributable to CHD in the United States.[48]
- The age-adjusted percentage of US adults who reported meeting both the muscle-strengthening and aerobic guidelines increased from 14.4% in 1998 to 21.4% in 2015 (Chart 4-12).[14] The percentage of US adults who reported meeting the aerobic guideline increased from 40.1% in 1998 to 49.7% in 2015.[14,49]
- Although it appears that leisure-time PA has been increasing in recent years, trends in technology behavior could influence both PA and sedentary time. Nielsen reports of adult smartphone app/web use comparing data collected in 2012 and 2014 (48 min/d and 1 hour 25 minutes per day, respectively)[47] to 2017 (2 hours 28 minutes per day)[50] suggest extreme increases in use over the past few years. Although they acknowledge that there were inconsistent methods in data collection among these different reports, the reported changes in technology behavior over such a short period of time are striking.
  - During this time period, from 2012 to 2017, television viewing decreased from 5 hours 28 minutes per day to 5 hours 5 minutes per day. Time spent on a computer decreased from 1 hour 3 minutes to <52 minutes in 2017. However, in 2017, tablet use was also measured and contributed to screen time, at 34 min/d.
  - The relationships between changes in technology habits and sedentary time have not been measured systematically.

Complications of Physical Inactivity: The Cardiovascular Health Impact

Youth

- In a study from the NHANES cohort, of participants aged 6 to 17 years with objective measurement of PA levels by accelerometer, young participants with the highest levels of PA had lower SBP, lower glucose levels, and lower insulin levels than participants in the lowest PA group.[51]

- Similarly, a higher amount of objectively measured sedentary duration assessed by accelerometer among children aged 10 to 14 years old is associated with greater odds of hypertriglyceridemia and cardiometabolic risk.[52]
- For elementary school children, engagement in organized sports for ≈1 year was associated with lower clustered cardiovascular risk.[53]
- In a study of 36 956 Brazilian adolescents, self-reported higher moderate to vigorous PA levels and lower screen time were associated with lower cardiometabolic risk. Furthermore, the association of screen time with cardiometabolic risk was modified by BMI. In contrast, the association between moderate to vigorous PA and cardiometabolic risk was independent of BMI.[54]
- In a prospective study of 700 Norwegian 10-year-old children with objective measures of PA, higher levels of moderate PA at baseline were associated with lower triglyceride levels and lower insulin resistance at 7-month follow-up. In contrast, sedentary time duration was not associated with cardiometabolic risk factors on follow-up.[55]

Adults

Cardiovascular and Metabolic Risk

- A review of the US Preventive Services Task Force recommendations examined the evidence on whether relevant counseling interventions for a healthful diet and PA in primary care modify intermediate physiological outcomes. It was concluded that after 12 to 24 months, intensive lifestyle counseling for individuals selected because of risk factors reduced TC levels by an average of 0.14 mmol/L, LDL-C levels by 0.10 mmol/L, triglyceride levels by 0.09 mmol/L, SBP by 2.06 mm Hg, DBP by 1.30 mm Hg, fasting glucose by 0.10 mmol/L, DM incidence by an RR of 0.54, and weight by a standardized difference of 0.24.[56]
- Results from NHANES 2011 to 2014 demonstrated that the prevalence of low HDL-C was higher among adults who reported not meeting PA guidelines (21.0%) than among adults meeting guidelines (17.7%).[57]
- Engaging in active transport to work has been associated with lower cardiovascular risk factors.
  - In a large Swedish cohort of 23 732 individuals, bicycling to work at baseline was associated with a lower odds of developing incident obesity, hypertension, hypertriglyceridemia, and impaired glucose tolerance at 10 years' follow-up than among those using passive modes of transportation.[58]
- A total of 120 to 150 min/wk of moderate-intensity activity, compared with none, can reduce the risk of developing metabolic syndrome.[3]
- Even lighter-intensity activities, such as yoga, were reported to improve BMI, BP, triglycerides, LDL-C, and HDL-C but not fasting blood glucose in a meta-analysis of 32 RCTs comparing yoga to nonexercise control groups.[59]
- In a sample of 466 605 participants in the China Kadoorie Biobank study, a 1-SD (1.5 h/d) increase in sedentary time was associated with a 0.19-U higher BMI, a 0.57-cm larger WC, and 0.44% more body fat. Both higher sedentary leisure time and lower PA were independently associated with an increased BMI.[60]
- In a dose-response meta-analysis of 22 studies with 330 222 participants evaluating the association between PA levels and risk of hypertension, each 10 MET h/wk higher level of leisure time PA was associated with a 6% lower risk of hypertension (RR, 0.94; 95% CI, 0.92–0.96)].[61]
- In a meta-analysis of 17 trials with 5075 pregnant female participants that evaluated the effects of exercise during pregnancy, aerobic exercise for ≈30 to 60 minutes 2 to 7 times per week during pregnancy was associated with significantly lower risk of gestational hypertensive disorders (RR, 0.70; 95% CI, 0.53–0.83).[62]
- In a population-based study of Hispanic/Latino adults with objective assessment of sedentary time, higher levels of sedentary time were associated with lower levels of HDL, higher triglycerides, and higher measures of insulin resistance after adjustment for PA levels. Furthermore, the accrual of prolonged and uninterrupted bouts of sedentary time was particularly associated with greater abnormalities in measures of glucose regulation.[63,64]

Cardiovascular Events

- In a dose-response meta-analysis of 9 prospective cohort studies (N=720 425), higher levels of sedentary time were associated with greater risk of CVD in a nonlinear relationship (HR for highest versus lowest sedentary time, 1.14; 95% CI, 1.09–1.19).[65]
- A study of the factors related to declining CVD among Norwegian adults ≥25 years of age found that increased PA (≥1 hour of strenuous PA per week) accounted for 9% of the decline in hospitalized and nonhospitalized fatal and nonfatal CHD events.[66]
- In a study that followed 1.1 million females in the United Kingdom without prior vascular disease

for an average of 9 years, those who reported moderate activity were found to be at lower risk of CHD, a cerebrovascular event, or a thrombotic event. However, strenuous PA was not found to be as beneficial as moderate PA.[67]

- In a prospective cohort study of 168916 participants from 17 countries, compared with low levels of self-reported PA (<150 min/wk of moderate-intensity PA), moderate (150–750 min/wk) and high (>750 min/wk) levels of PA were associated with a graded lower risk of major cardiovascular events (HR [95% CI] high versus low: 0.75 [0.69–0.82]; moderate versus low: 0.86 [0.78–0.93]; high versus moderate: 0.88 [0.82–0.94]) over an average 6.9 years of follow-up time.[27]
- In the 2-year LIFE study of older adults (mean age, 78.9 years), higher levels of PA, measured by accelerometer, were associated with lower risk of adverse cardiovascular events.[68]
- In a dose-response meta-analysis of 12 prospective cohort studies (n=370460), there was an inverse dose-dependent association between PA levels and risk of HF. PA levels at the guideline-recommended minimum (500 MET min/wk) were associated with 10% lower risk of HF. PA at twice and 4 times the guideline-recommended levels was associated with 19% and 35% lower risk of HF, respectively.[69]
- Furthermore, a recent individual level pooled analysis of 3 large cohort studies demonstrated that the strong, dose-dependent association between higher PA levels and lower risk of HF is largely driven by lower risk of HF with preserved EF but not HF with reduced EF.[70]
- In a large clinical trial (NAVIGATOR) involving 9306 people with impaired glucose tolerance, ambulatory activity as assessed by pedometer at baseline and 12 months was found to be inversely associated with risk of a cardiovascular event.[71]
- Domains of PA, other than leisure time, are understudied and often overlooked. A meta-analysis reported a protective relation of transportation activity to cardiovascular risk, which was greater in women.[72] However, higher occupational PA has recently been associated with higher MI incidence in males 19 to 70 years old.[35,73] These relationships require further investigation, because a protective association of occupational activity with MI has been reported in young males (19–44 years).[73]
- A recent analysis from the Rotterdam Study evaluated the contribution of specific PA types on CVD-free life expectancy. Higher levels of cycling were associated with a greater CVD-free life span in males (3.1 years) and females (2.4 years). Furthermore, high domestic work in females (2.4 years) and high gardening in males (2 years) was also associated with an increased CVD-free life span.[74]
- Cardiorespiratory fitness and PA levels are important determinants of HF risk in the general population. In the Cooper Center Longitudinal Study population, higher levels of cardiorespiratory fitness in midlife were associated with lower risk of HF, MI, and stroke.[75]
  - — The inverse association between higher fitness levels and risk of HF (HR per 1-MET higher fitness level, 0.79; 95% CI, 0.75–0.83 for males) was stronger than observed for risk of MI (HR, 0.91; 95% CI, 0.87–0.95).[75]
  - — Cardiorespiratory fitness accounted for 47% of the HF risk associated with higher BMI levels.[11]
  - — Improvement in cardiorespiratory fitness in middle age was also strongly associated with lower risk of HF among the Cooper Center Longitudinal Study participants (HR per 1-MET increase in fitness levels, 0.83; 95% CI, 0.74–0.93).[76]
- Lower levels of cardiorespiratory fitness have also been associated with higher risk of HF in a recent study of 21080 veterans, with a 91% higher risk of HF noted among low-fit participants (HR, 1.91; 95% CI, 1.74–2.09).[77]
- In a Swedish cohort of 773925 young males without history of VTE, cardiorespiratory fitness was associated with a reduced risk of VTE (HR, 0.81; 95% CI, 0.78–0.85) at ≥20 years of follow-up.[78]
- In 5962 veterans, lower exercise capacity was associated with a higher risk of developing AF. For every 1-MET increase in exercise capacity, the risk of developing AF was 21% lower (HR, 0.79; 95% CI, 0.76–0.82).[79]

Secondary Prevention

- A Cochrane systematic review of 63 studies concluded that exercise-based cardiac rehabilitation programs for CHD patients reduced cardiovascular mortality and hospital admissions but not overall mortality.[80]
- In a prospective study that monitored 902 HF patients (with preserved or reduced EF) for 3 years, reporting participation in any PA (≥1 min/wk) was associated with a lower risk of cardiac death and all-cause death than no PA. Less television screen time (<2 versus >4 h/d) was also associated with lower all-cause death.[81]
- In a prospective cohort study of 15486 participants with stable CAD from 39 countries, higher levels of PA were associated with lower

risk of mortality such that doubling the exercise volume was associated with 10% lower risk of all-cause mortality after adjustment for potential confounders.[82]
  — Among 1746 CAD patients followed up for 2 years, those who remained inactive or became inactive had a 4.9- and 2.4-fold higher risk of cardiac death, respectively, than patients who remained at least irregularly active during the follow-up period.[83]
  — In a prospective cohort study of 3307 individuals with CHD, participants who maintained high PA levels over longitudinal follow-up had a lower risk of mortality than those who were inactive over time (HR, 0.64; 95% CI, 0.50–0.83).[84]
- In a cohort of patients with HF and preserved EF, compared with high levels of self-reported PA, poor and intermediate levels were associated with higher risk of HF hospitalization (HR [95% CI], 1.93 [1.16–3.22] for poor versus high PA and 1.84 [1.02–3.31] for intermediate versus high PA) and cardiovascular mortality (HR [95% CI], 4.36 [1.37–13.83] for poor versus high PA and 4.05 [1.17–14.04] for intermediate versus high PA).[85]
- Using data from a registry of stable outpatients with symptomatic coronary disease, cerebrovascular disease, or PAD, the mortality rate of patients with a recent MI was significantly lower in patients who participated in supervised (N=593) versus unsupervised (N=531) exercise programming.[86]
- Early mortality after a first MI was lower for patients who had higher exercise capacity before the MI event. Every 1-MET-higher exercise capacity before the MI was associated with an 8% to 10% lower risk of mortality at 28 days, 90 days, and 365 days after MI.[87] A study of 3572 patients with recent MI demonstrated significant sex differences in PA after AMI. Females were more likely to be inactive than males within 12 months after the AMI episode (OR, 1.37; 95% CI, 1.21–1.55).[88]
- A recent study of participants included in the WHI observational study who experienced a clinical MI during the study demonstrated that compared with those who maintained low PA levels after the MI event, participants had lower risk of mortality with improvement in PA levels (HR, 0.54; 95% CI, 0.36–0.86) or with sustained high PA levels (HR, 0.52; 95% CI, 0.36–0.73).[89]
- Among 2370 individuals with CVD who responded to the Taiwan National Health Interview Survey, achieving more total PA, leisure-time PA, and domestic and work-related PA was associated with lower mortality at 7-year follow-up.[90]

Costs

- The economic consequences of physical inactivity are substantial. Using data derived primarily from WHO publications and data warehouses, one study estimated that economic costs of physical inactivity account for 1.5% to 3.0% of total direct healthcare expenditures in developed countries such as the United States.[91]
- A global analysis of 142 countries (93.2% of the world's population) concluded that physical inactivity cost healthcare systems $53.8 billion in 2013, including $9.7 billion paid by individual households.[92]
- A study of American adults reported that inadequate levels of aerobic PA (after adjustment for BMI) were associated with an estimated 11.1% of aggregate healthcare expenditures (including expenditures for inpatient, outpatient, ED, office-based, dental, vision, home health, prescription drug, and other services).[93]
- An evaluation of healthcare costs based on the cardiovascular risk factor profile (including ≥30 minutes of moderate to vigorous PA ≥5 times per week) found that among adults aged ≥40 years with CVD, the highest marginal expenditures ($2853 in 2012) were for those not meeting the PA guidelines. Healthcare costs included hospitalizations, prescribed medications, outpatient visits (hospital outpatient visits and office-based visits), ED visits, and other expenditures (dental visits, vision aid, home health care, and other medical supplies).[94]
- A systematic review of population-based interventions to encourage PA found that improving biking trails, distributing pedometers, and school-based PA were most cost-effective.[95]
- Interventions and community strategies to increase PA have been shown to be cost-effective in terms of reducing medical costs[96]:
  — Nearly $3 in medical cost savings is realized for every $1 invested in building bike and walking trails.
  — The incremental cost-effectiveness ratio ranges from $14 000 to $69 000 per QALY gained from interventions such as pedometer or walking programs compared with no intervention, especially in high-risk groups.

Strategies to Prevent Physical Inactivity

The US Surgeon General has introduced "Step It Up!, a Call to Action to Promote Walking and Walkable

Communities" in recognition of the importance of PA.[97] There are roles for communities, schools, and worksites.

Communities

- Community-level interventions have been shown to be effective in promoting increased PA. Communities can encourage walking with street design that includes sidewalks, improved street lighting, and landscaping design that reduces traffic speed to improve pedestrian safety. Higher neighborhood walkability has been associated with lower prevalence of overweight, obesity, and lower incidence of DM.[98] Moving to a walkable neighborhood was associated with a lower risk for incident hypertension in the Canadian Community Health Survey.[99]
- Community-wide campaigns include a variety of strategies such as media coverage, risk factor screening and education, community events, and policy or environmental changes.
- Educating the public on the recommended PA guidelines could increase adherence. In a study examining awareness of current US PA guidelines, only 33% of respondents had direct knowledge of the recommended dosage of PA (ie, frequency/duration).[100]

Schools

- Schools can provide opportunities for PA through physical education, recess, before- and after-school activity programs, and PA breaks.[101]
- According to the School Health Policies and Practices Study, <5% of elementary schools and junior and senior high schools required daily physical education in 2014.[47]
- In 2012, the School Health Policies and Practices Study also reported that 58.9% of school districts required regular elementary school recess.[47]
- Healthy afterschool programs and active school day policies have been shown to be cost-effective solutions to increase PA and prevent childhood obesity.[102]

Worksites

- Worksites can offer access to on-site exercise facilities or employer-subsidized off-site exercise facilities to encourage PA among employees.
- Worksite interventions for sedentary occupations, such as providing "activity-permissive" workstations and email contacts that promote breaks, have reported increased occupational light activity, and the more adherent individuals observed improvements in cardiometabolic outcomes.[103,104]

Family History and Genetics

- It is clear that environmental factors can play a role in PA and sedentary behavior and the context in which these behaviors occur. However, PA and sedentary behavior can also be determined in part by genetics, with heritability estimates of up to 47%, although few loci have been identified or replicated.[105,106]

Global Burden (See Chart 4-13)

- Physical inactivity is responsible for 12.2% of the global burden of MI after accounting for other CVD risk factors such as cigarette smoking, DM, hypertension, abdominal obesity, lipid profile, excessive alcohol intake, and psychosocial factors.[107]
- Worldwide, the prevalence of physical inactivity (35%) is now greater than the prevalence of smoking (26%). On the basis of the HRs associated with these 2 behaviors (1.57 for smoking and 1.28 for inactivity), it was concluded that the PAR was greater for inactivity (9%) than for smoking (8.7%). Inactivity was estimated to be responsible for 5.3 million deaths compared with 5.1 million deaths for smoking.[108]
- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories. Mortality rates attributable to low PA are high in Eastern Europe, the North Africa/Middle East region, and the Pacific Island countries (Chart 4-13).[109]

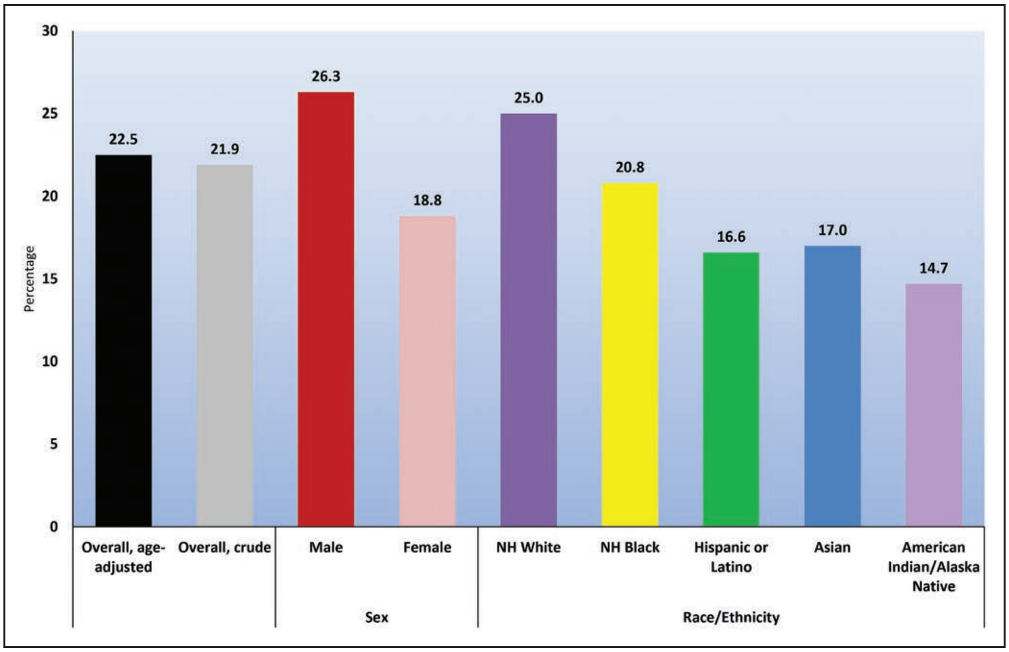

Chart 4-1. Prevalence of meeting both the aerobic and muscle-strengthening guidelines for the 2008 Physical Activity Guidelines for Americans among adults ≥18 years of age, overall and by sex and race/ethnicity.
Data are age adjusted for adults ≥18 years of age.
NH indicates non-Hispanic.
Source: National Health Interview Survey, 2016 (National Center for Health Statistics).[7]

American Heart Association.

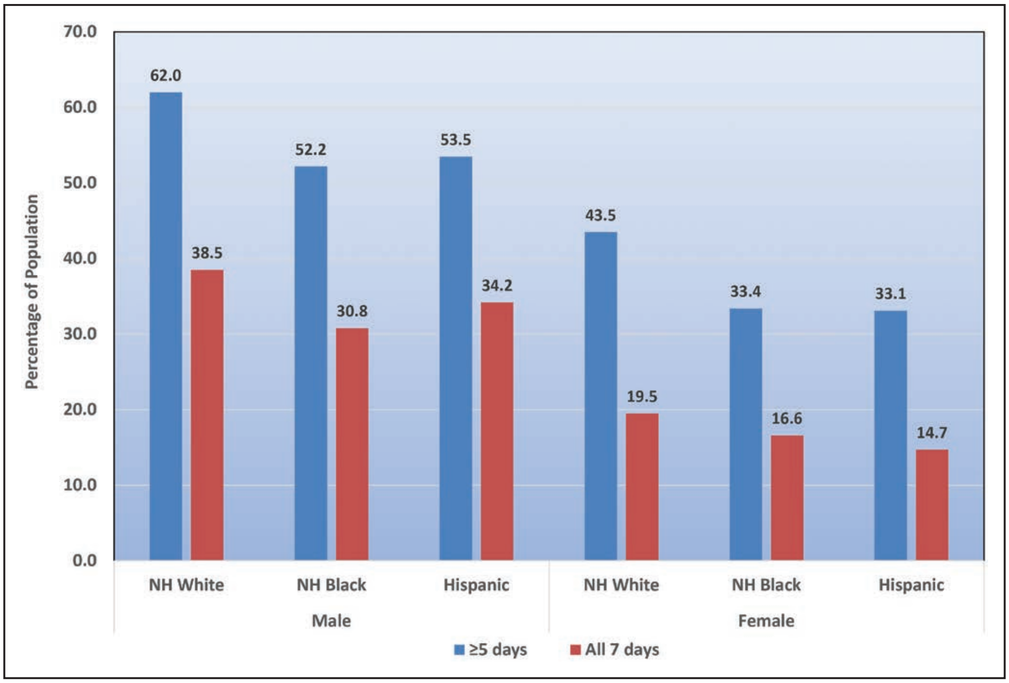

Chart 4-2. Prevalence of students in grades 9 to 12 who were active at least 60 min/d on all 7 days by race/ethnicity and sex.
"Currently recommended levels" was defined as activity that increased their heart rate and made them breathe hard some of the time for a total of ≥60 min/d on all 7 days preceding the survey.
NH indicates non-Hispanic.
Source: Youth Risk Behavior Surveillance Survey, 2015.[4]

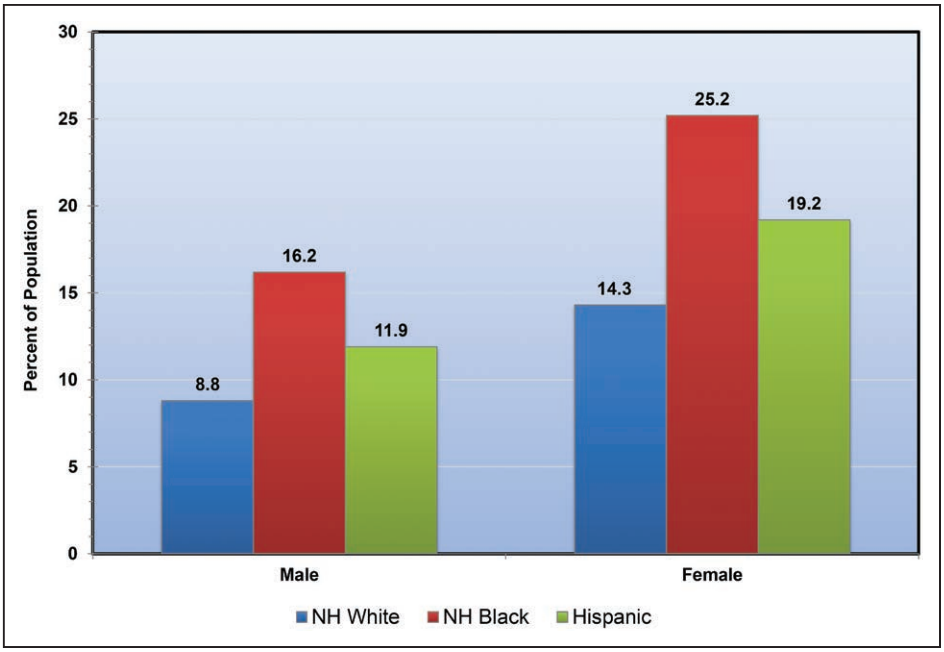

Chart 4-3. Prevalence of students in grades 9 to 12 who did not participate in ≥60 minutes of physical activity on any day in the past 7 days by race/ethnicity and sex.
NH indicates non-Hispanic.
Source: Youth Risk Behavior Surveillance Survey, 2015.[4]

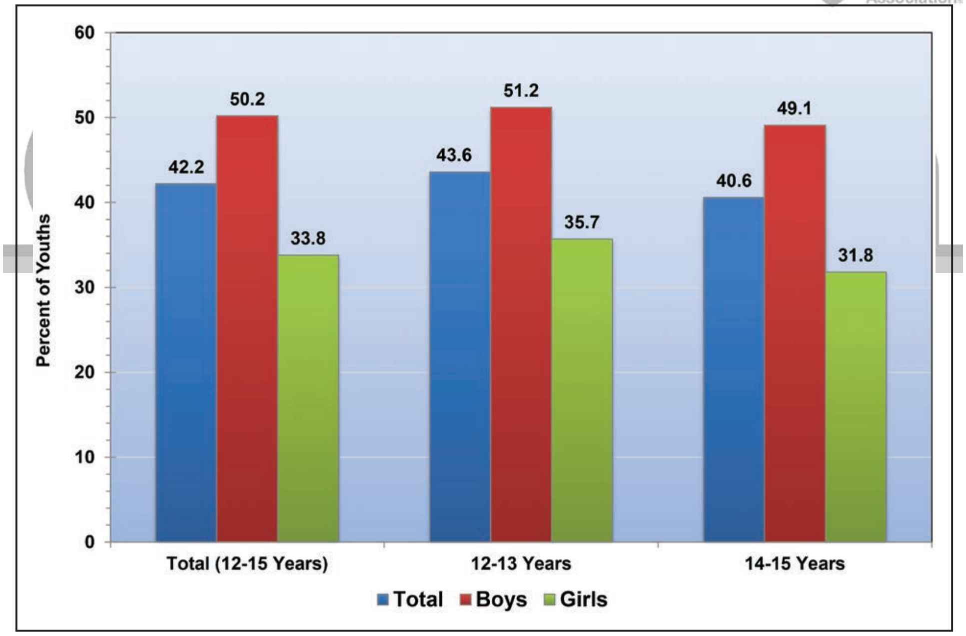

Chart 4-4. Prevalence of children 12 to 15 years of age who had adequate levels of cardiorespiratory fitness by sex and age (NHANES, National Youth Fitness Survey, 2012).
NHANES indicates National Health and Nutrition Examination Survey.
Source: NHANES, National Youth Fitness Survey, 2012.[15]

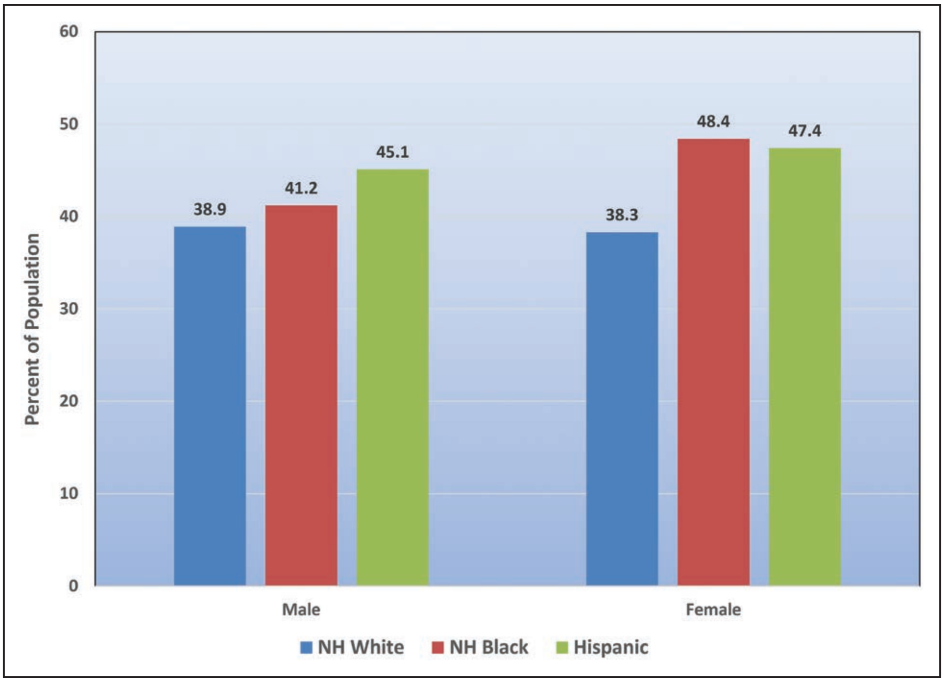

Chart 4-5. Percentage of students in grades 9 to 12 who used a computer* for ≥3 hours on an average school day by race/ethnicity and sex.
NH indicates non-Hispanic.
*For something other than school work.
Source: Youth Risk Behavior Surveillance Survey, 2015.[4]

American Heart Association.

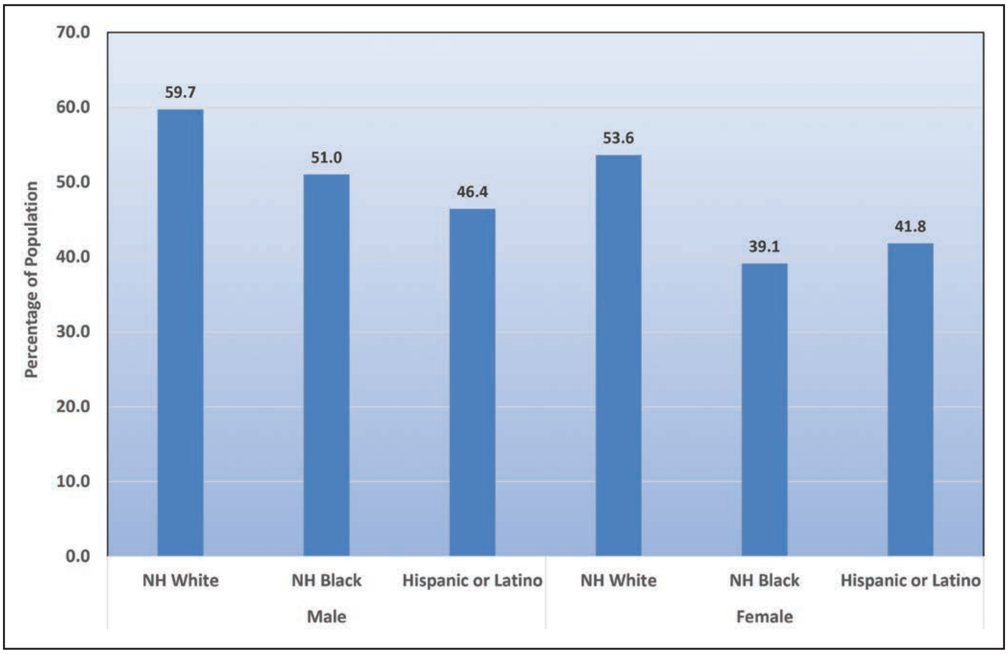

Chart 4-6. Prevalence of meeting the aerobic guideline of the 2008 Physical Activity Guidelines for Americans among adults ≥18 years of age by race/ethnicity and sex (NHIS, 2016).
Percentages are age adjusted. The aerobic guidelines of the 2008 Federal Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time physical activity for ≥150 min/wk or vigorous activity ≥75 min/wk or an equivalent combination.
NH indicates non-Hispanic; and NHIS, National Health Interview Survey.
Source: NHIS, 2016 (National Center for Health Statistics).[7]

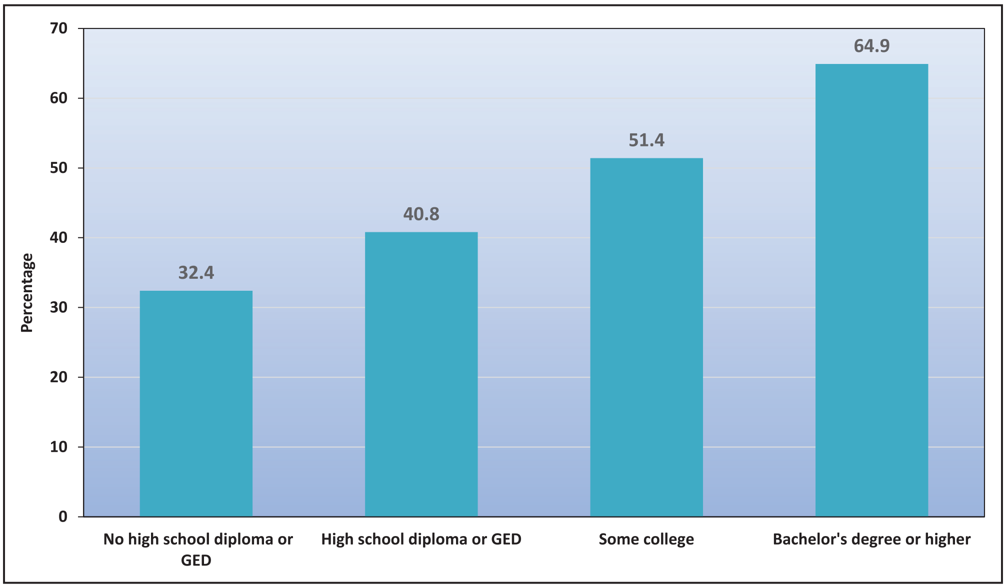

Chart 4-7. Prevalence of meeting the aerobic guideline of the 2008 Physical Activity Guidelines for Americans among adults ≥25 years of age by educational attainment (NHIS, 2016).

Percentages are age adjusted. The aerobic guidelines of the 2008 Federal Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time physical activity for ≥150 min/wk or vigorous activity ≥75 min/wk or an equivalent combination.

GED indicates General Educational Development; and NHIS, National Health Interview Survey.

Source: NHIS, 2016 (National Center for Health Statistics).[7]

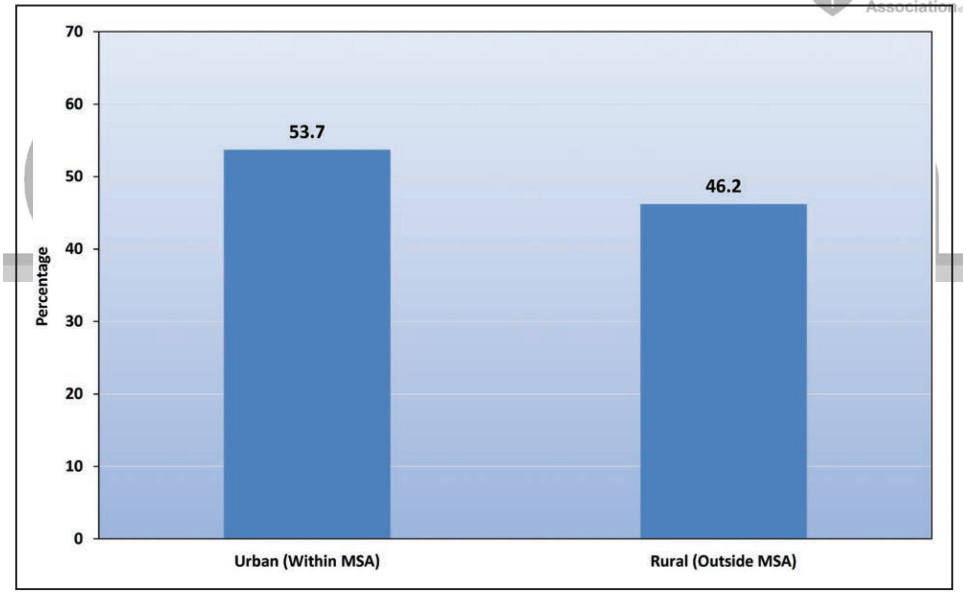

Chart 4-8. Prevalence of meeting the aerobic guideline for the 2008 Physical Activity Guidelines for Americans among adults ≥18 years of age by location of residence (NHIS, 2016).

Percentages are age adjusted. The aerobic guidelines of the 2008 Federal Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time physical activity for ≥150 min/wk or vigorous activity ≥75 min/wk or an equivalent combination.

MSA indicates metropolitan statistical area; and NHIS, National Health Interview Survey.

Source: NHIS, 2016 (National Center for Health Statistics).[7]

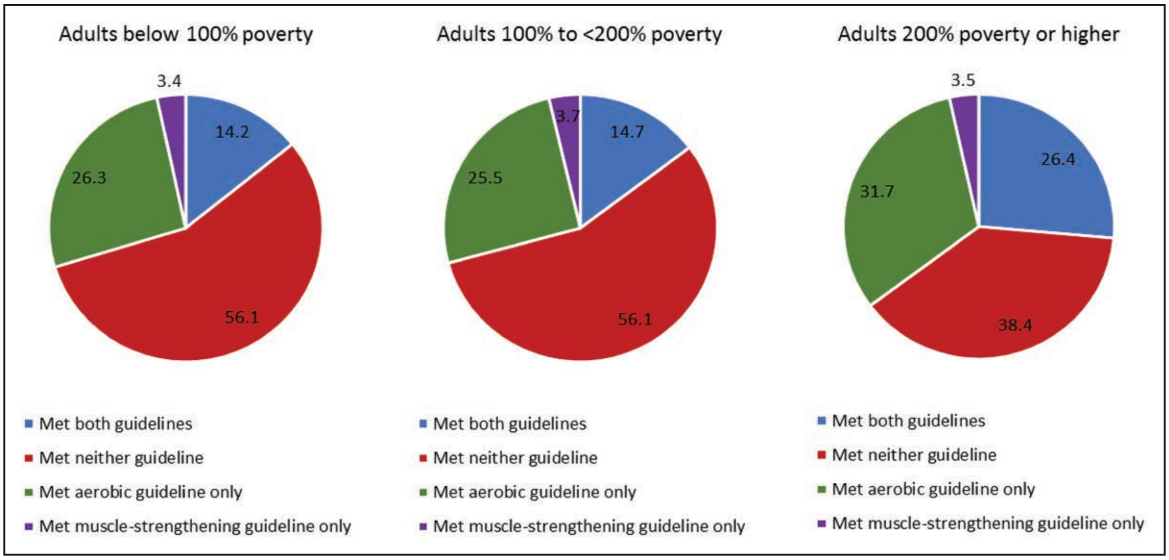

Chart 4-9. Prevalence of meeting the aerobic and muscle-strengthening guidelines for the 2008 Physical Activity Guidelines for Americans among adults ≥18 years of age by poverty level and type of activity (NHIS, 2016).

Percentages are age adjusted. The aerobic guidelines of the 2008 Federal Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time physical activity for ≥150 min/wk or vigorous activity ≥75 min/wk or an equivalent combination and performing muscle-strengthening activities at least 2 days per week. NHIS indicates National Health Interview Survey.

Source: NHIS, 2016 (National Center for Health Statistics).[7]

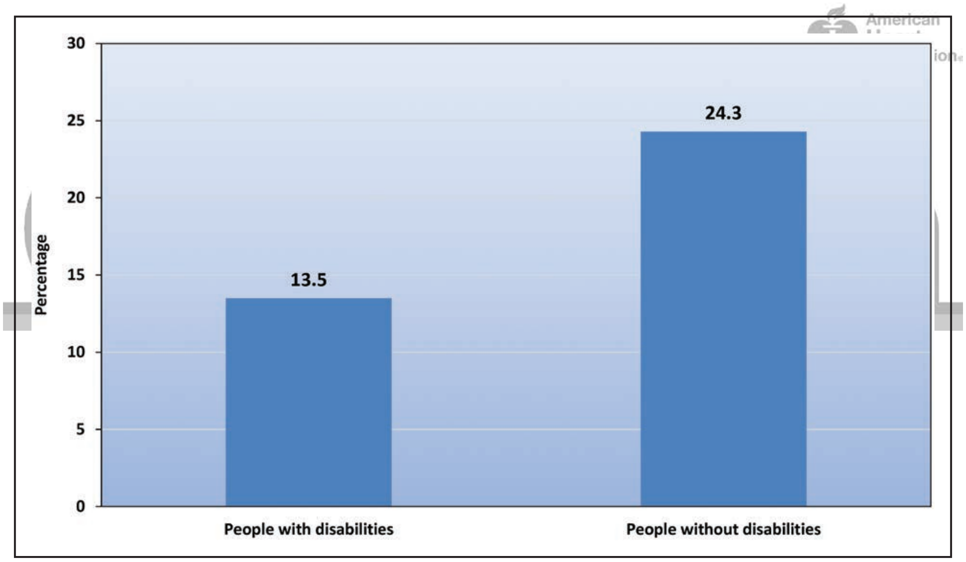

Chart 4-10. Prevalence of meeting both the aerobic and muscle-strengthening guidelines for the 2008 Physical Activity Guidelines for Americans among adults ≥18 years of age by disability status.

Percentages are age adjusted. The aerobic guidelines of the 2008 Federal Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time physical activity for ≥150 min/wk or vigorous activity ≥75 min/wk or an equivalent combination.

Source: National Health Interview Survey, 1998 to 2016 (National Center for Health Statistics).[7]

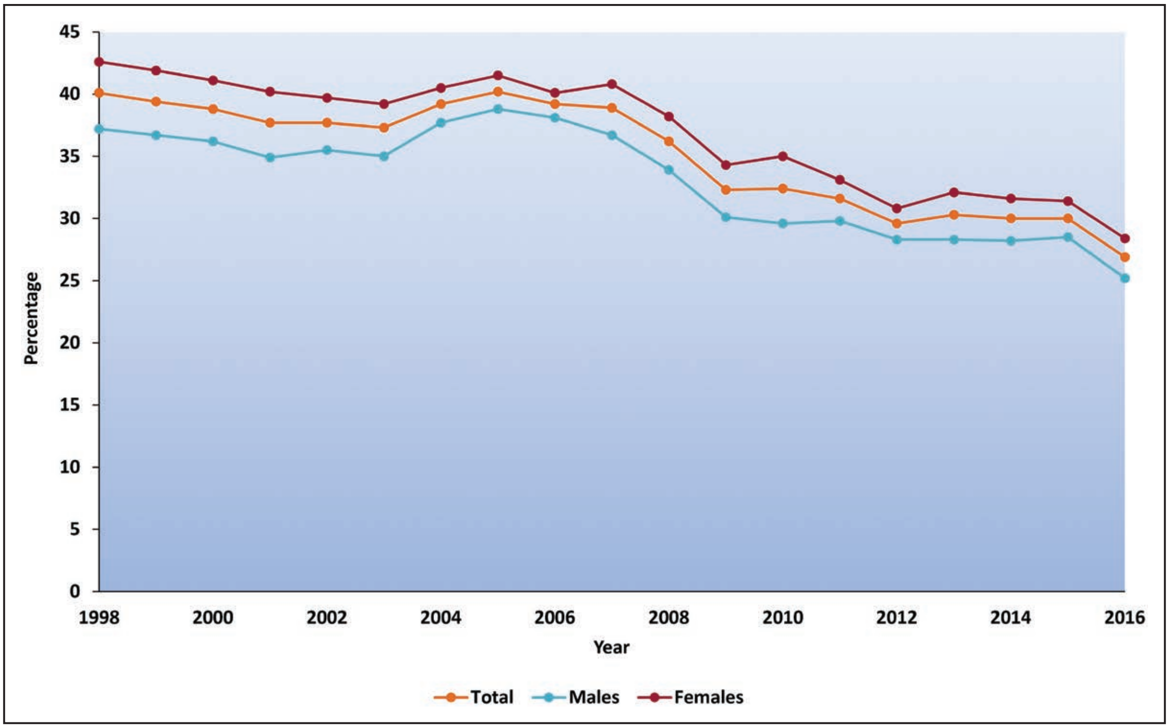

Chart 4-11. Trends in the prevalence of physical inactivity among adults ≥18 years of age, overall and by sex (NHIS, 1998–2016).
Percentages are age adjusted. Physical inactivity is defined as reporting no engagement in leisure-time physical activity in bouts lasting ≥10 minutes.
NHIS indicates National Health Interview Survey.
Source: NHIS, 1998 to 2016 (National Center for Health Statistics).[7]

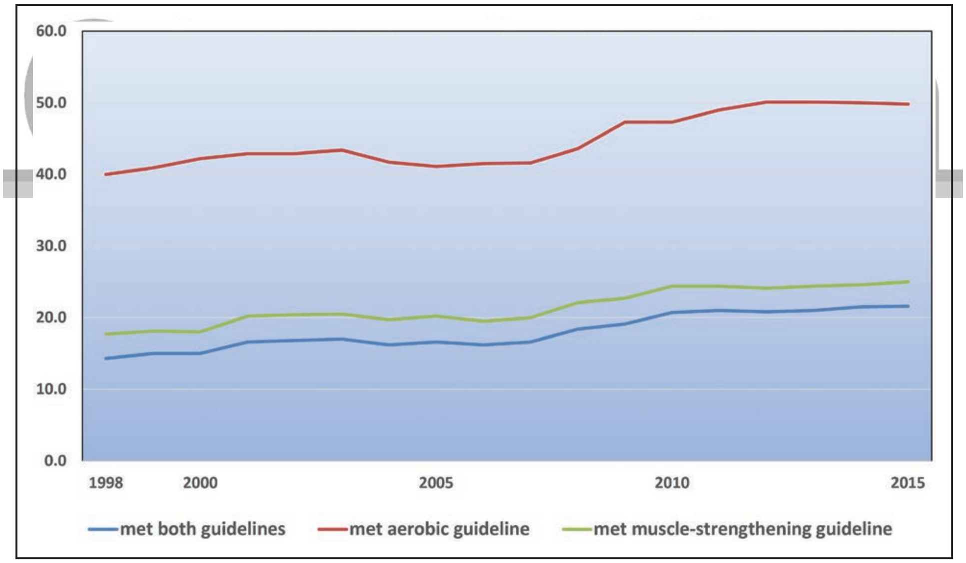

Chart 4-12. Trends in meeting the physical activity guidelines of the 2008 Federal Physical Activity Guidelines for Americans through leisure-time activity only among adults ≥18 years of age by type of activity (NHIS, 1998–2015).
Source: NHIS, 1998 to 2015 (National Center for Health Statistics).

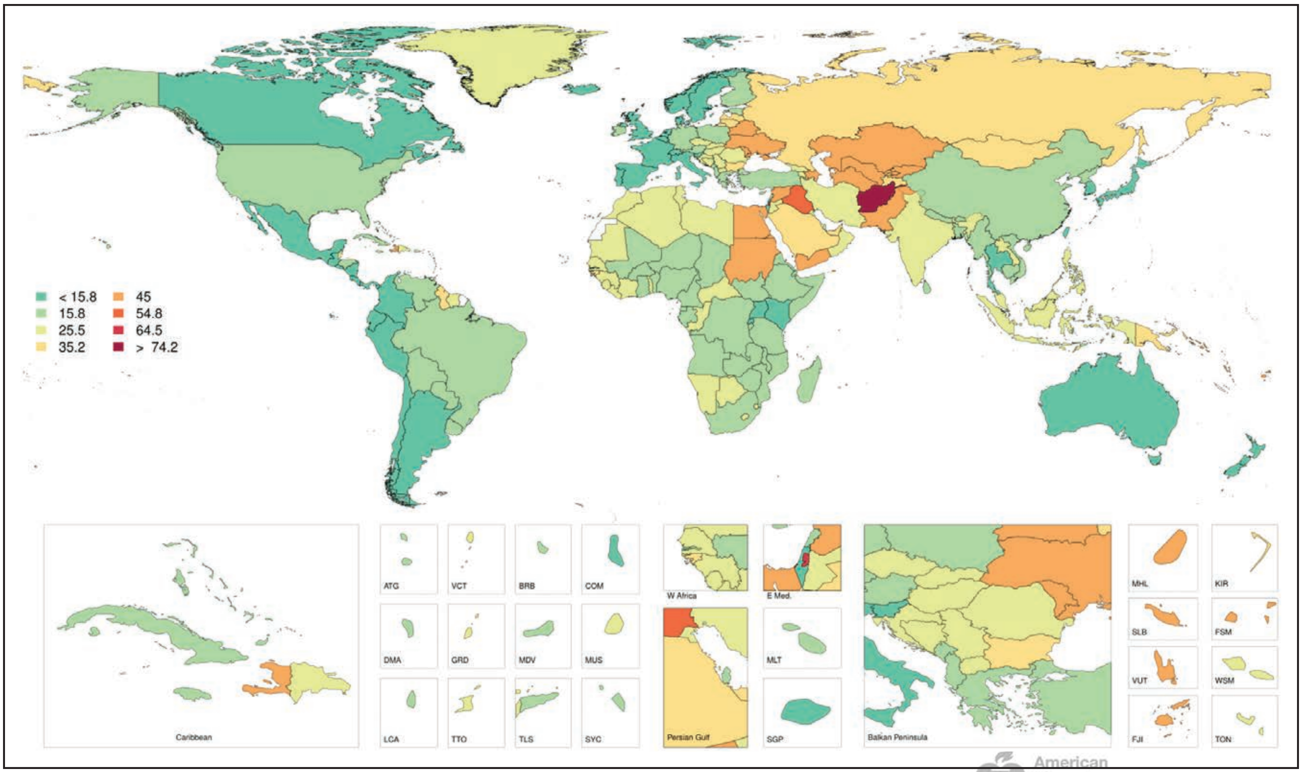

Chart 4-13. Age-standardized global mortality rates attributable to low physical activity per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016 with permission.[109] Copyright © 2017, University of Washington.

REFERENCES

1. Artinian NT, Fletcher GF, Mozaffarian D, Kris-Etherton P, Van Horn L, Lichtenstein AH, Kumanyika S, Kraus WE, Fleg JL, Redeker NS, Meininger JC, Banks J, Stuart-Shor EM, Fletcher BJ, Miller TD, Hughes S, Braun LT, Kopin LA, Berra K, Hayman LL, Ewing LJ, Ades PA, Durstine JL, Houston-Miller N, Burke LE; on behalf of the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122:406–441. doi: 10.1161/CIR.0b013e3181e8edf1
2. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
3. US Department of Health and Human Services. *2008 Physical Activity Guidelines for Americans*. October 2008. ODPHP publication No. U0036. http://www.health.gov/paguidelines/pdf/paguide.pdf. Accessed September 7, 2018.
4. Kann L, McManus T, Harris WA, Shanklin SL, Flint KH, Hawkins J, Queen B, Lowry R, Olsen EO, Chyen D, Whittle L, Thornton J, Lim C, Yamakawa Y, Brener N, Zaza S. Youth Risk Behavior Surveillance: United States, 2015 [published correction appears in *MMWR Morb Mortal Wkly Rep*. 2016;65:610]. *MMWR Surveill Summ*. 2016;65:1–174. doi: 10.15585/mmwr.ss6506a1
5. Strath SJ, Kaminsky LA, Ainsworth BE, Ekelund U, Freedson PS, Gary RA, Richardson CR, Smith DT, Swartz AM; on behalf of the American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health and Cardiovascular, Exercise, Cardiac Rehabilitation and Prevention Committee of the Council on Clinical Cardiology, and Council on Cardiovascular and Stroke Nursing. Guide to the assessment of physical activity: clinical and research applications: a scientific statement from the American Heart Association. *Circulation*. 2013;128:2259–2279. doi: 10.1161/01.cir.0000435708.67487.da
6. Troiano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc*. 2008;40:181–188. doi: 10.1249/mss.0b013e31815a51b3
7. National Center for Health Statistics. National Health Interview Survey, 2016. Public-use data file and documentation. https://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHIS/2016/srvydesc.pdf. Accessed September 7, 2018.
8. 2018 Physical Activity Guidelines Advisory Committee. *2018 Physical Activity Guidelines Advisory Committee Scientific Report*. Washington, DC: US Department of Health and Human Services; 2018.
9. Kaminsky LA, Arena R, Beckie TM, Brubaker PH, Church TS, Forman DE, Franklin BA, Gulati M, Lavie CJ, Myers J, Patel MJ, Piña IL, Weintraub WS, Williams MA; on behalf of the American Heart Association Advocacy Coordinating Committee, Council on Clinical Cardiology, and Council on Nutrition, Physical Activity and Metabolism. The importance of cardiorespiratory fitness in the United States: the need for a national registry: a policy statement from the American Heart Association. *Circulation*. 2013;127:652–662. doi: 10.1161/CIR.0b013e31827ee100
10. Ross R, Blair SN, Arena R, Church TS, Després JP, Franklin BA, Haskell WL, Kaminsky LA, Levine BD, Lavie CJ, Myers J, Niebauer J, Sallis R, Sawada SS, Sui X, Wisløff U; on behalf of the American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Cardiovascular and Stroke Nursing; Council on Functional Genomics and Translational Biology; Stroke Council. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation*. 2016;134:e653–e699. doi: 10.1161/CIR.0000000000000461

11. Pandey A, Cornwell WK 3rd, Willis B, Neeland IJ, Gao A, Leonard D, DeFina L, Berry JD. Body mass index and cardiorespiratory fitness in mid-life and risk of heart failure hospitalization in older age: findings from the Cooper Center Longitudinal Study. *JACC Heart Fail*. 2017;5:367–374. doi: 10.1016/j.jchf.2016.12.021
12. Andersen K, Rasmussen F, Held C, Neovius M, Tynelius P, Sundstrom J. Exercise capacity and muscle strength and risk of vascular disease and arrhythmia in 1.1 million young Swedish men: cohort study. *BMJ*. 2015;351:h4543. doi: 10.1136/bmj.h4543
13. DeFina LF, Haskell WL, Willis BL, Barlow CE, Finley CE, Levine BD, Cooper KH. Physical activity versus cardiorespiratory fitness: two (partly) distinct components of cardiovascular health? *Prog Cardiovasc Dis*. 2015;57:324–329. doi: 10.1016/j.pcad.2014.09.008
14. National Center for Health Statistics. National Health Interview Survey, 2015. Public-use data file, documentation, and NCHS tabulations. https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2016_SHS_Table_A-14.pdf. Accessed September 7, 2018
15. Gahche J, Fakhouri T, Carroll DD, Burt VL, Wang CY, Fulton JE. Cardiorespiratory fitness levels among U.S. youth aged 12–15 years: United States, 1999–2004 and 2012. *NCHS Data Brief*. 2014;(153):1–8.
16. Lieberman DA, Chamberlin B, Medina E, Jr., Franklin BA, Sanner BM, Vafiadis DK; on behalf of the Power of Play: Innovations in Getting Active Summit Planning Committee. The Power of Play: Innovations in Getting Active Summit 2011: a science panel proceedings report from the American Heart Association. *Circulation* 2011;123:2507–2516. doi: 10.1161/CIR.0b013e318219661d
17. Rideout VJ, Foehr UG, Roberts DF. *Generation M2: Media in the Lives of 8-18-Year-Olds: A Kaiser Family Foundation Study.* Menlo Park, CA: Henry J. Kaiser Family Foundation; 2010.
18. Luke A, Dugas LR, Durazo-Arvizu RA, Cao G, Cooper RS. Assessing physical activity and its relationship to cardiovascular risk factors: NHANES 2003-2006. *BMC Public Health*. 2011;11:387. doi: 10.1186/1471-2458-11-387
19. Fan JX, Wen M, Kowaleski-Jones L. Rural-urban differences in objective and subjective measures of physical activity: findings from the National Health and Nutrition Examination Survey (NHANES) 2003-2006. *Prev Chronic Dis*. 2014;11:E141. doi: 10.5888/pcd11.140189
20. Prince SA, Adamo KB, Hamel ME, Hardt J, Connor Gorber S, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. *Int J Behav Nutr Phys Act*. 2008;5:56. doi: 10.1186/1479-5868-5-56
21. Hawkins MS, Storti KL, Richardson CR, King WC, Strath SJ, Holleman RG, Kriska AM. Objectively measured physical activity of USA adults by sex, age, and racial/ethnic groups: a cross-sectional study. *Int J Behav Nutr Phys Act*. 2009;6:31. doi: 10.1186/1479-5868-6-31
22. Aggio D, Papachristou E, Papacosta O, Lennon LT, Ash S, Whincup PH, Wannamethee SG, Jefferis BJ. Trajectories of self-reported physical activity and predictors during the transition to old age: a 20-year cohort study of British men. *Int J Behav Nutr Phys Act*. 2018;15:14. doi: 10.1186/s12966-017-0642-4
23. Nielsen Comparable Metrics Report Q2 2017. http://www.nielsen.com/content/dam/corporate/us/en/reports-downloads/2017-reports/q2-2017-comparable-metrics-report.pdf. Accessed September 7, 2018.
24. Whitfield GP, Paul P, Wendel AM. Active transportation surveillance: United States, 1999-2012. *MMWR Surveill Summ*. 2015;64:1–17.
25. GBD 2013 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386:2287–2323. doi: 10.1016/S0140-6736(15)00128-2
26. World Health Organization. *Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks.* Geneva, Switzerland: World Health Organization; 2009.
27. Lear SA, Hu W, Rangarajan S, Gasevic D, Leong D, Iqbal R, Casanova A, Swaminathan S, Anjana RM, Kumar R, Rosengren A, Wei L, Yang W, Chuangshi W, Huaxing L, Nair S, Diaz R, Swidon H, Gupta R, Mohammadifard N, Lopez-Jaramillo P, Oguz A, Zatonska K, Seron P, Avezum A, Poirier P, Teo K, Yusuf S. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study [published correction appears in *Lancet*. 2017;390:2626]. *Lancet*. 2017;390:2643–2654. doi: 10.1016/S0140-6736(17)31634-3
28. Carlson SA, Adams EK, Yang Z, Fulton JE. Percentage of deaths associated with inadequate physical activity in the United States. *Prev Chronic Dis*. 2018;15:E38. doi: 10.5888/pcd18.170354
29. Zhao G, Li C, Ford ES, Fulton JE, Carlson SA, Okoro CA, Wen XJ, Balluz LS. Leisure-time aerobic physical activity, muscle-strengthening activity and mortality risks among US adults: the NHANES linked mortality study. *Br J Sports Med*. 2014;48:244–249. doi: 10.1136/bjsports-2013-092731
30. Hupin D, Roche F, Gremeaux V, Chatard JC, Oriol M, Gaspoz JM, Barthélémy JC, Edouard P. Even a low-dose of moderate-to-vigorous physical activity reduces mortality by 22% in adults aged ≥60 years: a systematic review and meta-analysis. *Br J Sports Med*. 2015;49:1262–1267. doi: 10.1136/bjsports-2014-094306
31. Arem H, Moore SC, Patel A, Hartge P, Berrington de Gonzalez A, Visvanathan K, Campbell PT, Freedman M, Weiderpass E, Adami HO, Linet MS, Lee IM, Matthews CE. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. *JAMA Intern Med*. 2015;175:959–967. doi: 10.1001/jamainternmed.2015.0533
32. Gebel K, Ding D, Chey T, Stamatakis E, Brown WJ, Bauman AE. Effect of moderate to vigorous physical activity on all-cause mortality in middle-aged and older Australians [published correction appears in *JAMA Intern Med*. 2015;175:1248]. *JAMA Intern Med*. 2015;175:970–977. doi: 10.1001/jamainternmed.2015.0541
33. Kamada M, Shiroma EJ, Buring JE, Miyachi M, Lee IM. Strength training and all-cause, cardiovascular disease, and cancer mortality in older women: a cohort study. *J Am Heart Assoc*. 2017;6:e007677. doi: 10.1161/JAHA.117.007677
34. Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose-response meta-analysis of cohort studies. *Int J Epidemiol*. 2011;40:1382–1400. doi: 10.1093/ije/dyr112
35. Holtermann A, Marott JL, Gyntelberg F, Søgaard K, Suadicani P, Mortensen OS, Prescott E, Schnohr P. Occupational and leisure time physical activity: risk of all-cause mortality and myocardial infarction in the Copenhagen City Heart Study: a prospective cohort study. *BMJ Open*. 2012;2:e000556. doi: 10.1136/bmjopen-2011-000556
36. Celis-Morales CA, Lyall DM, Welsh P, Anderson J, Steell L, Guo Y, Maldonado R, Mackay DF, Pell JP, Sattar N, Gill JMR. Association between active commuting and incident cardiovascular disease, cancer, and mortality: prospective cohort study. *BMJ*. 2017;357:j1456. doi: 10.1136/bmj.j1456
37. Lee DC, Pate RR, Lavie CJ, Sui X, Church TS, Blair SN. Leisure-time running reduces all-cause and cardiovascular mortality risk [published correction appears in *J Am Coll Cardiol*. 2014;64:1537]. *J Am Coll Cardiol*. 2014;64:472–481. doi: 10.1016/j.jacc.2014.04.058
38. Matthews CE, Cohen SS, Fowke JH, Han X, Xiao Q, Buchowski MS, Hargreaves MK, Signorello LB, Blot WJ. Physical activity, sedentary behavior, and cause-specific mortality in black and white adults in the Southern Community Cohort Study. *Am J Epidemiol*. 2014;180:394–405. doi: 10.1093/aje/kwu142
39. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis [published correction appears in *Ann Intern Med*. 2015;163:400]. *Ann Intern Med*. 2015;162:123–132. doi: 10.7326/M14-1651
40. Ekelund U, Steene-Johannessen J, Brown WJ, Fagerland MW, Owen N, Powell KE, Bauman A, Lee IM; Lancet Physical Activity Series 2 Executive Committee; Lancet Sedentary Behaviour Working Group. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women [published correction appears in *Lancet*. 2016;388:e6]. *Lancet*. 2016;388:1302–1310. doi: 10.1016/S0140-6736(16)30370-1
41. Fishman EI, Steeves JA, Zipunnikov V, Koster A, Berrigan D, Harris TA, Murphy R. Association between objectively measured physical activity and mortality in NHANES. *Med Sci Sports Exerc*. 2016;48:1303–1311. doi: 10.1249/MSS.0000000000000885
42. Lee IM, Shiroma EJ, Evenson KR, Kamada M, LaCroix AZ, Buring JE. Accelerometer-measured physical activity and sedentary behavior in relation to all-cause mortality: the Women's Health Study. *Circulation*. 2018;137:203–205. doi: 10.1161/CIRCULATIONAHA.117.031300
43. Diaz KM, Howard VJ, Hutto B, Colabianchi N, Vena JE, Safford MM, Blair SN, Hooker SP. Patterns of sedentary behavior and mortality in U.S. middle-aged and older adults: a national cohort study. *Ann Intern Med*. 2017;167:465–475. doi: 10.7326/M17-0212
44. Wickramasinghe CD, Ayers CR, Das S, de Lemos JA, Willis BL, Berry JD. Prediction of 30-year risk for cardiovascular mortality by fitness and risk factor levels: the Cooper Center Longitudinal Study. *Circ Cardiovasc Qual Outcomes*. 2014;7:597–602. doi: 10.1161/CIRCOUTCOMES.113.000531

45. Celis-Morales CA, Lyall DM, Anderson J, Iliodromiti S, Fan Y, Ntuk UE, Mackay DF, Pell JP, Sattar N, Gill JM. The association between physical activity and risk of mortality is modulated by grip strength and cardiorespiratory fitness: evidence from 498 135 UK-Biobank participants. *Eur Heart J*. 2017;38:116–122. doi: 10.1093/eurheartj/ehw249
46. Blaha MJ, Hung RK, Dardari Z, Feldman DI, Whelton SP, Nasir K, Blumenthal RS, Brawner CA, Ehrman JK, Keteyian SJ, Al-Mallah MH. Age-dependent prognostic value of exercise capacity and derivation of fitness-associated biologic age. *Heart*. 2016;102:431–437. doi: 10.1136/heartjnl-2015-308537
47. National Center for Health Statistics. Chapter 33: Physical Activity. *Healthy People 2020 Midcourse Review*. Hyattsville, MD; US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2016. DHHS publication No. 2017-1042.
48. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med*. 2007;356:2388–2398. doi: 10.1056/NEJMsa053935
49. National Center for Health Statistics. *Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities.* Hyattsville, MD: National Center for Health Statistics; 2016. http://www.cdc.gov/nchs/data/hus/hus15.pdf. Accessed September 7, 2018.
50. *Shifts in Viewing: The Cross-Platform Report: September 2014*. New York, NY: Nielsen Company; 2014. http://www.nielsen.com/content/dam/corporate/us/en/reports-downloads/2014%20Reports/q2-2014-cross-platform-report-shifts-in-viewing.pdf. Accessed September 7, 2018.
51. Jenkins GP, Evenson KR, Herring AH, Hales D, Stevens J. Cardiometabolic correlates of physical activity and sedentary patterns in U.S. youth. *Med Sci Sports Exerc*. 2017;49:1826–1833. doi: 10.1249/MSS.0000000000001310
52. Bailey DP, Charman SJ, Ploetz T, Savory LA, Kerr CJ. Associations between prolonged sedentary time and breaks in sedentary time with cardiometabolic risk in 10-14-year-old children: the HAPPY study. *J Sports Sci*. 2017;35:2164–2171. doi: 10.1080/02640414.2016.1260150
53. Hebert JJ, Klakk H, Møller NC, Grøntved A, Andersen LB, Wedderkopp N. The prospective association of organized sports participation with cardiovascular disease risk in children (the CHAMPS Study-DK). *Mayo Clin Proc*. 2017;92:57–65. doi: 10.1016/j.mayocp.2016.08.013
54. Cureau FV, Ekelund U, Bloch KV, Schaan BD. Does body mass index modify the association between physical activity and screen time with cardiometabolic risk factors in adolescents? Findings from a country-wide survey. *Int J Obes (Lond)*. 2017;41:551–559. doi: 10.1038/ijo.2016.210
55. Skrede T, Stavnsbo M, Aadland E, Aadland KN, Anderssen SA, Resaland GK, Ekelund U. Moderate-to-vigorous physical activity, but not sedentary time, predicts changes in cardiometabolic risk factors in 10-y-old children: the Active Smarter Kids Study. *Am J Clin Nutr*. 2017;105:1391–1398. doi: 10.3945/ajcn.116.150540
56. LeFevre ML; U.S. Preventive Services Task Force. Behavioral counseling to promote a healthful diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2014;161:587–593. doi: 10.7326/M14-1796
57. Zwald ML, Akinbami LJ, Fakhouri TH, Fryar CD. Prevalence of low high-density lipoprotein cholesterol among adults, by physical activity: United States, 2011–2014. *NCHS Data Brief*. 2017;(276):1–8.
58. Grontved A, Koivula RW, Johansson I, Wennberg P, Østergaard L, Hallmans G, Renström F, Franks PW. Bicycling to work and primordial prevention of cardiovascular risk: a cohort study among Swedish men and women. *J Am Heart Assoc*. 2016;5:e004413. doi: 10.1161/jaha.116.004413
59. Chu P, Gotink RA, Yeh GY, Goldie SJ, Hunink MG. The effectiveness of yoga in modifying risk factors for cardiovascular disease and metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials. *Eur J Prev Cardiol*. 2016;23:291–307. doi: 10.1177/2047487314562741
60. Du H, Bennett D, Li L, Whitlock G, Guo Y, Collins R, Chen J, Bian Z, Hong LS, Feng S, Chen X, Chen L, Zhou R, Mao E, Peto R, Chen Z; China Kadoorie Biobank Collaborative Group. Physical activity and sedentary leisure time and their associations with BMI, waist circumference, and percentage body fat in 0.5 million adults: the China Kadoorie Biobank study. *Am J Clin Nutr*. 2013;97:487–496. doi: 10.3945/ajcn.112.046854
61. Liu X, Zhang D, Liu Y, Sun X, Han C, Wang B, Ren Y, Zhou J, Zhao Y, Shi Y, Hu D, Zhang M. Dose-response association between physical activity and incident hypertension: a systematic review and meta-analysis of cohort studies. *Hypertension*. 2017;69:813–820. doi: 10.1161/HYPERTENSIONAHA.116.08994
62. Magro-Malosso ER, Saccone G, Di Tommaso M, Roman A, Berghella V. Exercise during pregnancy and risk of gestational hypertensive disorders: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2017;96:921–931. doi: 10.1111/aogs.13151
63. Qi Q, Strizich G, Merchant G, Sotres-Alvarez D, Buelna C, Castañeda SF, Gallo LC, Cai J, Gellman MD, Isasi CR, Moncrieft AE, Sanchez-Johnsen L, Schneiderman N, Kaplan RC. Objectively measured sedentary time and cardiometabolic biomarkers in US Hispanic/Latino adults: the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Circulation*. 2015;132:1560–1569. doi: 10.1161/CIRCULATIONAHA.115.016938
64. Diaz KM, Goldsmith J, Greenlee H, Strizich G, Qi Q, Mossavar-Rahmani Y, Vidot DC, Buelna C, Brintz CE, Elfassy T, Gallo LC, Daviglus ML, Sotres-Alvarez D, Kaplan RC. Prolonged, uninterrupted sedentary behavior and glycemic biomarkers among US Hispanic/Latino adults: the HCHS/SOL (Hispanic Community Health Study/Study of Latinos). *Circulation*. 2017;136:1362–1373. doi: 10.1161/CIRCULATIONAHA.116.026858
65. Pandey A, Salahuddin U, Garg S, Ayers C, Kulinski J, Anand V, Mayo H, Kumbhani DJ, de Lemos J, Berry JD. Continuous dose-response association between sedentary time and risk for cardiovascular disease: a meta-analysis. *JAMA Cardiol*. 2016;1:575–583. doi: 10.1001/jamacardio.2016.1567
66. Mannsverk J, Wilsgaard T, Mathiesen EB, Løchen ML, Rasmussen K, Thelle DS, Njølstad I, Hopstock LA, Bønaa KH. Trends in modifiable risk factors are associated with declining incidence of hospitalized and non-hospitalized acute coronary heart disease in a population. *Circulation*. 2016;133:74–81. doi: 10.1161/CIRCULATIONAHA.115.016960
67. Armstrong ME, Green J, Reeves GK, Beral V, Cairns BJ; on behalf of the Million Women Study Collaborators. Frequent physical activity may not reduce vascular disease risk as much as moderate activity: large prospective study of women in the United Kingdom. *Circulation*. 2015;131:721–729. doi: 10.1161/CIRCULATIONAHA.114.010296
68. Cochrane SK, Chen SH, Fitzgerald JD, Dodson JA, Fielding RA, King AC, McDermott MM, Manini TM, Marsh AP, Newman AB, Pahor M, Tudor-Locke C, Ambrosius WT, Buford TW; for the LIFE Study Research Group. Association of accelerometry-measured physical activity and cardiovascular events in mobility-limited older adults: the LIFE (Lifestyle Interventions and Independence for Elders) Study. *J Am Heart Assoc*. 2017;6:e007215. doi: 10.1161/JAHA.117.007215
69. Pandey A, Garg S, Khunger M, Darden D, Ayers C, Kumbhani DJ, Mayo HG, de Lemos JA, Berry JD. Dose-response relationship between physical activity and risk of heart failure: a meta-analysis. *Circulation*. 2015;132:1786–1794. doi: 10.1161/CIRCULATIONAHA.115.015853
70. Pandey A, LaMonte M, Klein L, Ayers C, Psaty BM, Eaton CB, Allen NB, de Lemos JA, Carnethon M, Greenland P, Berry JD. Relationship between physical activity, body mass index, and risk of heart failure. *J Am Coll Cardiol*. 2017;69:1129–1142. doi: 10.1016/j.jacc.2016.11.081
71. Yates T, Haffner SM, Schulte PJ, Thomas L, Huffman KM, Bales CW, Califf RM, Holman RR, McMurray JJ, Bethel MA, Tuomilehto J, Davies MJ, Kraus WE. Association between change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance (NAVIGATOR trial): a cohort analysis. *Lancet*. 2014;383:1059–1066. doi: 10.1016/S0140-6736(13)62061-9
72. Hamer M, Chida Y. Active commuting and cardiovascular risk: a meta-analytic review. *Prev Med*. 2008;46:9–13. doi: 10.1016/j.ypmed.2007.03.006
73. Johnsen AM, Alfredsson L, Knutsson A, Westerholm PJ, Fransson EI. Association between occupational physical activity and myocardial infarction: a prospective cohort study. *BMJ Open*. 2016;6:e012692. doi: 10.1136/bmjopen-2016-012692
74. Dhana K, Koolhaas CM, Berghout MA, Peeters A, Ikram MA, Tiemeier H, Hofman A, Nusselder W, Franco OH. Physical activity types and life expectancy with and without cardiovascular disease: the Rotterdam Study. *J Public Health (Oxf)*. 2017;39:e209–e218. doi: 10.1093/pubmed/fdw110
75. Berry JD, Pandey A, Gao A, Leonard D, Farzaneh-Far R, Ayers C, DeFina L, Willis B. Physical fitness and risk for heart failure and coronary artery disease. *Circ Heart Fail*. 2013;6:627–634. doi: 10.1161/CIRCHEARTFAILURE.112.000054
76. Pandey A, Patel M, Gao A, Willis BL, Das SR, Leonard D, Drazner MH, de Lemos JA, DeFina L, Berry JD. Changes in mid-life fitness predicts heart failure risk at a later age independent of interval development of cardiac and noncardiac risk factors: the Cooper Center Longitudinal Study. *Am Heart J*. 2015;169:290–297.e1. doi: 10.1016/j.ahj.2014.10.017
77. Myers J, Kokkinos P, Chan K, Dandekar E, Yilmaz B, Nagare A, Faselis C, Soofi M. Cardiorespiratory fitness and reclassification of risk for incidence of heart failure: the Veterans Exercise Testing Study. *Circulation Heart Fail*. 2017;10:e003780. doi: 10.1161/CIRCHEARTFAILURE.116.003780
78. Zöller B, Ohlsson H, Sundquist J, Sundquist K. Cardiovascular fitness in young males and risk of unprovoked venous thromboembolism in adulthood. *Ann Med*. 2017;49:176–184. doi: 10.1080/07853890.2016.1252057

79. Faselis C, Kokkinos P, Tsimploulis A, Pittaras A, Myers J, Lavie CJ, Kyritsi F, Lovic D, Karasik P, Moore H. Exercise capacity and atrial fibrillation risk in veterans: a cohort study. *Mayo Clin Proc*. 2016;91:558–566. doi: 10.1016/j.mayocp.2016.03.002
80. Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. *J Am Coll Cardiol*. 2016;67:1–12. doi: 10.1016/j.jacc.2015.10.044
81. Doukky R, Mangla A, Ibrahim Z, Poulin MF, Avery E, Collado FM, Kaplan J, Richardson D, Powell LH. Impact of physical inactivity on mortality in patients with heart failure. *Am J Cardiol*. 2016;117:1135–1143. doi: 10.1016/j.amjcard.2015.12.060
82. Stewart RAH, Held C, Hadziosmanovic N, Armstrong PW, Cannon CP, Granger CB, Hagström E, Hochman JS, Koenig W, Lonn E, Nicolau JC, Steg PG, Vedin O, Wallentin L, White HD; STABILITY Investigators. Physical activity and mortality in patients with stable coronary heart disease. *J Am Coll Cardiol*. 2017;70:1689–1700. doi: 10.1016/j.jacc.2017.08.017
83. Lahtinen M, Toukola T, Junttila MJ, Piira OP, Lepojärvi S, Kääriäinen M, Huikuri HV, Tulppo MP, Kiviniemi AM. Effect of changes in physical activity on risk for cardiac death in patients with coronary artery disease. *Am J Cardiol*. 2018;121:143–148. doi: 10.1016/j.amjcard.2017.10.002
84. Moholdt T, Lavie CJ, Nauman J. Sustained physical activity, not weight loss, associated with improved survival in coronary heart disease [published correction appears in *J Am Coll Cardiol*. 2018;71:1499]. *J Am Coll Cardiol*. 2018;71:1094–1101. doi: 10.1016/j.jacc.2018.01.011
85. Hegde SM, Claggett B, Shah AM, Lewis EF, Anand I, Shah SJ, Sweitzer NK, Fang JC, Pitt B, Pfeffer MA, Solomon SD. Physical activity and prognosis in the TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist). *Circulation*. 2017;136:982–992. doi: 10.1161/CIRCULATIONAHA.117.028002
86. Coll-Fernández R, Coll R, Muñoz-Torrero JF, Aguilar E, Ramón Álvarez L, Sahuquillo JC, Yeste M, Jiménez PE, Mujal A, Monreal M; FRENA Investigators. Supervised versus non-supervised exercise in patients with recent myocardial infarction: a propensity analysis. *Eur J Prev Cardiol*. 2016;23:245–252. doi: 10.1177/2047487315578443
87. Shaya GE, Al-Mallah MH, Hung RK, Nasir K, Blumenthal RS, Ehrman JK, Keteyian SJ, Brawner CA, Qureshi WT, Blaha MJ. High exercise capacity attenuates the risk of early mortality after a first myocardial infarction: the Henry Ford Exercise Testing (FIT) Project. *Mayo Clin Proc*. 2016;91:129–139. doi: 10.1016/j.mayocp.2015.11.012
88. Minges KE, Strait KM, Owen N, Dunstan DW, Camhi SM, Lichtman J, Geda M, Dreyer RP, Bueno H, Beltrame JF, Curtis JP, Krumholz HM. Gender differences in physical activity following acute myocardial infarction in adults: a prospective, observational study. *Eur J Prev Cardiol*. 2017;24:192–203. doi: 10.1177/2047487316679905
89. Gorczyca AM, Eaton CB, LaMonte MJ, Manson JE, Johnston JD, Bidulescu A, Waring ME, Manini T, Martin LW, Stefanick ML, He K, Chomistek AK. Change in physical activity and sitting time after myocardial infarction and mortality among postmenopausal women in the Women's Health Initiative-Observational Study. *J Am Heart Assoc*. 2017;6:e005354. doi: 10.1161/JAHA.116.005354
90. Ku PW, Chen LJ, Fox KR, Chen YH, Liao Y, Lin CH. Leisure-time, domestic, and work-related physical activity and their prospective associations with all-cause mortality in patients with cardiovascular disease. *Am J Cardiol*. 2018;121:177–181. doi: 10.1016/j.amjcard.2017.10.003
91. Oldridge NB. Economic burden of physical inactivity: healthcare costs associated with cardiovascular disease. *Eur J Cardiovasc Prev Rehabil*. 2008;15:130–139. doi: 10.1097/HJR.0b013e3282f19d42
92. Ding D, Lawson KD, Kolbe-Alexander TL, Finkelstein EA, Katzmarzyk PT, van Mechelen W, Pratt M; Lancet Physical Activity Series 2 Executive Committee. The economic burden of physical inactivity: a global analysis of major non-communicable diseases. *Lancet*. 2016;388:1311–1324. doi: 10.1016/S0140-6736(16)30383-X
93. Carlson SA, Fulton JE, Pratt M, Yang Z, Adams EK. Inadequate physical activity and health care expenditures in the United States. *Prog Cardiovasc Dis*. 2015;57:315–323. doi: 10.1016/j.pcad.2014.08.002
94. Valero-Elizondo J, Salami JA, Ogunmoroti O, Osondu CU, Aneni EC, Malik R, Spatz ES, Rana JS, Virani SS, Blankstein R, Blaha MJ, Veledar E, Nasir K. Favorable cardiovascular risk profile is associated with lower healthcare costs and resource utilization: the 2012 Medical Expenditure Panel Survey. *Circ Cardiovasc Qual Outcomes*. 2016;9:143–153. doi: 10.1161/CIRCOUTCOMES.115.002616
95. Laine J, Kuvaja-Köllner V, Pietilä E, Koivuneva M, Valtonen H, Kankaanpää E. Cost-effectiveness of population-level physical activity interventions: a systematic review. *Am J Health Promot*. 2014;29:71–80. doi: 10.4278/ajhp.131210-LIT-622
96. Weintraub WS, Daniels SR, Burke LE, Franklin BA, Goff DC Jr, Hayman LL, Lloyd-Jones D, Pandey DK, Sanchez EJ, Schram AP, Whitsel LP; on behalf of the American Heart Association Advocacy Coordinating Committee; Council on Cardiovascular Disease in the Young; Council on the Kidney in Cardiovascular Disease; Council on Epidemiology and Prevention; Council on Cardiovascular Nursing; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Clinical Cardiology, and Stroke Council. Value of primordial and primary prevention for cardiovascular disease: a policy statement from the American Heart Association. *Circulation*. 2011;124:967–990. doi: 10.1161/CIR.0b013e3182285a81
97. *Step It Up! The Surgeon General's Call to Action to Promote Walking and Walkable Communities.* Washington, DC: US Dept of Health and Human Services, Office of the Surgeon General; 2015.
98. Creatore MI, Glazier RH, Moineddin R, Fazli GS, Johns A, Gozdyra P, Matheson FI, Kaufman-Shriqui V, Rosella LC, Manuel DG, Booth GL. Association of neighborhood walkability with change in overweight, obesity, and diabetes. *JAMA*. 2016;315:2211–2220. doi: 10.1001/jama.2016.5898
99. Chiu M, Rezai MR, Maclagan LC, Austin PC, Shah BR, Redelmeier DA, Tu JV. Moving to a highly walkable neighborhood and incidence of hypertension: a propensity-score matched cohort study. *Environ Health Perspect*. 2016;124:754–760. doi: 10.1289/ehp.1510425
100. Bennett GG, Wolin KY, Puleo EM, Mâsse LC, Atienza AA. Awareness of national physical activity recommendations for health promotion among US adults. *Med Sci Sports Exerc*. 2009;41:1849–1855. doi: 10.1249/MSS.0b013e3181a52100
101. Centers for Disease Control and Prevention and SHAPE America–Society of Health and Physical Educators. *Strategies for Recess in Schools.* Atlanta, GA; Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2017.
102. Cradock AL, Barrett JL, Kenney EL, Giles CM, Ward ZJ, Long MW, Resch SC, Pipito AA, Wei ER, Gortmaker SL. Using cost-effectiveness analysis to prioritize policy and programmatic approaches to physical activity promotion and obesity prevention in childhood. *Prev Med*. 2017;95(suppl):S17–S27. doi: 10.1016/j.ypmed.2016.10.017
103. Carr LJ, Leonhard C, Tucker S, Fethke N, Benzo R, Gerr F. Total worker health intervention increases activity of sedentary workers. *Am J Prev Med*. 2016;50:9–17. doi: 10.1016/j.amepre.2015.06.022
104. Healy GN, Winkler EAH, Eakin EG, Owen N, Lamontagne AD, Moodie M, Dunstan DW. A cluster RCT to reduce workers' sitting time: impact on cardiometabolic biomarkers. *Med Sci Sports Exerc*. 2017;49:2032–2039. doi: 10.1249/MSS.0000000000001328
105. Young DR, Hivert MF, Alhassan S,Camhi SM, Ferguson JF, Katzmarzyk PT, Lewis CE, Owen N, Perry CK, Siddique J, Yong CM; on behalf of the Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Functional Genomics and Translational Biology; and Stroke Council. Sedentary behavior and cardiovascular morbidity and mortality: a science advisory from the American Heart Association. *Circulation*. 2016;134:e262–279. doi: 10.1161/CIR.0000000000000440
106. den Hoed M, Brage S, Zhao JH, Westgate K, Nessa A, Ekelund U, Spector TD, Wareham NJ, Loos RJ. Heritability of objectively assessed daily physical activity and sedentary behavior. *Am J Clin Nutr*. 2013;98:1317–1325. doi: 10.3945/ajcn.113.069849
107. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952. doi: 10.1016/S0140-6736(04)17018-9
108. Wen CP, Wu X. Stressing harms of physical inactivity to promote exercise. *Lancet*. 2012;380:192–193. doi: 10.1016/S0140-6736(12)60954-4
109. Global Burden of Disease Study 2016. Global Burden of Disease Study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed September 7, 2018.

5. NUTRITION

See Table 5-1 and Charts 5-1 through 5-8

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This chapter of the Update highlights national dietary habits, focusing on key foods, nutrients, dietary patterns, and other dietary factors related to cardiometabolic health. It is intended to examine current intakes, trends and changes in intakes, and estimated effects on disease to support and further stimulate efforts to monitor and improve dietary habits in relation to cardiovascular health.

Prevalence and Trends in the AHA 2020 Healthy Diet Metrics (See Table 5-1 and Charts 5-1 and 5-2)

The AHA's 2020 Impact Goals prioritize improving cardiovascular health,[1] which includes following a healthy diet pattern characterized by 5 primary and 3 secondary metrics (Table 5-1) that should be consumed within the context that is appropriate in energy balance and consistent with a DASH-type eating plan.[1]

Abbreviations Used in Chapter 5

AHA	American Heart Association
BMI	body mass index
BP	blood pressure
CER	cost-effectiveness ratio
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
DALY	disability-adjusted life-year
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
DM	diabetes mellitus
GBD	Global Burden of Disease
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HEI	Healthy Eating Index
HF	heart failure
HR	hazard ratio
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
MI	myocardial infarction
MUFA	monounsaturated fatty acid
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
PA	physical activity
PREDIMED	Prevención con Dieta Mediterránea
PUFA	polyunsaturated fatty acid
RCT	randomized controlled trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SBP	systolic blood pressure
SCD	sudden cardiac death
SES	socioeconomic status
SFA	saturated fatty acid
SNAP	Supplemental Nutrition Assistance Program
SNP	single-nucleotide polymorphism
SSB	sugar-sweetened beverage
TC	total cholesterol
TOHP	Trials of Hypertension Prevention
WHI	Women's Health Initiative

The AHA scoring system for ideal, intermediate, and poor diet patterns uses a binary-based scoring system, which awards 1 point for meeting the ideal target for each metric and 0 points otherwise.[2] For better consistency with other dietary pattern scores such as DASH, an alternative continuous scoring system has been developed to measure small improvements over time toward the AHA ideal target levels (Table 5-1). The dietary targets remain the same, and progress toward each of these targets is assessed by use of a more granular range of 1 to 10 (rather than 0 to 1).

Using the alternative scoring system, the mean AHA healthy diet score improved between 2003 to 2004 and 2011 to 2012 in the United States in both children and adults.[3] In children, the poor diet (<40% adherence), based on the AHA healthy diet score, decreased from 69.2% to 54.6%. In adults, the prevalence of a poor diet decreased from 50.3% to 41.0%.[4] Improvements were largely attributable to increased whole grain consumption and decreased SSB consumption in both children and adults.[4] Among adults, other significant improvements included increased consumption of nuts, seeds, and legumes (0.54 to 0.81 servings/d) and decreased consumption of 100% fruit juice (0.43 to 0.32 servings/d) and white potatoes (0.39 to 0.32 servings/d).[4] No major improvements in consumption of sodium, fish, fruits and vegetables, processed meats, and saturated fat were noted.

Smaller improvements in AHA healthy diet scores were seen in minority groups and those with lower income or education (Charts 5-1 and 5-2).[4] For example, the proportion with a poor diet (<40% adherence) decreased from 50.5% to 35.7% in adults with income-to-poverty ratio ≥3.0, but only from 67.8% to 60.6% in adults with income-to-poverty ratio <1.3 (Chart 5-2).

Global Trends in Key Dietary Factors

Globally, between 1999 and 2010, SSB intake increased in several countries.[5] SSB consumption was highest in the Caribbean, with adults consuming on average 2 servings per day, and lowest in East Asia, at 0.20 servings per day. Adults in the United States had the 26th-highest consumption among 187 countries.

A number of countries and US cities have implemented SSB taxes.[6] In Mexico, a 1 peso per liter excise tax was implemented in January 2014. In a study using store purchase data from 6645 Mexican households, posttax volume of beverages purchased decreased by 5.5% in 2014 and by 9.7% in 2015 compared with

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predicted volume of beverages purchased based on pretax trends. Although all socioeconomic groups experienced declines in SSB purchases, the lowest socioeconomic group had the greatest decline in SSB purchases (9.0% in 2014 and 14.3% in 2015).[7] In Berkeley, CA, a 1 cent per ounce SSB excise tax was implemented in January 2015.[8] Using store-level data, posttax year 1 SSB sales declined by 9.6% compared with predicted SSB sales based on pretax trends. By comparison, SSB sales increased by 6.9% in non-Berkeley stores in adjacent cities.

In 2010, mean sodium intake among adults worldwide was 3950 mg/d.[9] Across world regions, mean sodium intakes were highest in Central Asia (5510 mg/d) and lowest in eastern sub-Saharan Africa (2180 mg/d). Across countries, the lowest observed mean national intakes were ≈1500 mg/d. Between 1990 and 2010, global mean sodium intake appeared to remain relatively stable, although data on trends in many world regions were suboptimal.[9]

In a systematic review of population-level sodium initiatives, reduction in mean sodium intake occurred in 5 of 10 initiatives.[10] Successful population-level sodium initiatives tended to use multiple strategies and included structural activities, such as food product reformulation. For example, Finland initiated a nationwide campaign in the late 1970s through public education, collaboration with the food industry, and salt labeling legislation. From 1979 to 2002, mean 24-hour urine sodium excretion in population-based samples decreased in Finnish males (5.1 to 3.9 g/d) and females (4.1 to 3.0 g/d), with concurrent decreases in mean SBP and prevalence of hypertension.[11,12] Similarly, the United Kingdom initiated a nationwide salt reduction program in 2003 to 2004 that included consumer awareness campaigns, progressively lower salt targets for various food categories, clear nutritional labeling, and working with industry to reformulate foods. Mean sodium intake in the United Kingdom decreased by 15% from 2003 to 2011,[13] along with concurrent decreases in BP (3.0/1.4 mm Hg) in patients not taking antihypertensive medication, stroke mortality (42%), and CHD mortality (40%) (*P*<0.001 for all comparisons); these findings remained statistically significant after adjustment for changes in demographics, BMI, and other dietary factors.

Dietary Habits in the United States: Current Intakes

Foods and Nutrients

Adults

The average dietary consumption by US adults of selected foods and nutrients related to cardiometabolic health based on data from 2011 to 2012 NHANES is detailed below[3]:

- Consumption of whole grains was 1.1 servings per day by NH white males and females, 0.8 to 0.9 servings per day by NH black males and females, and 0.6 to 0.8 servings per day by Mexican American males and females. For each of these groups, <10% of adults in 2011 to 2012 met guidelines of ≥3 servings per day.
- Fruit consumption ranged from 1.0 to 1.6 servings per day in these racial or ethnic subgroups: ≈9% of NH whites, 7% of NH blacks, and 6% of Mexican Americans met guidelines of ≥2 cups per day. When 100% fruit juices were included, the number of servings increased and the proportions of adults consuming ≥2 cups per day nearly doubled in NH whites, doubled in NH blacks, and more than doubled in Mexican Americans.
- Nonstarchy vegetable consumption ranged from 1.7 to 2.7 servings per day. Across all racial/ethnic subgroups, NH white females were the only group meeting the target of consuming ≥2.5 cups per day.
- Consumption of fish and shellfish was lowest among Mexican American females and white females (0.8 and 1.0 servings per week, respectively) and highest among NH black females and NH black and Mexican American males (1.9 and 1.7 servings per week, respectively). Generally, only 15% to 27% of adults in each sex and racial or ethnic subgroup consumed ≥2 servings per week.
- Weekly consumption of nuts and seeds was ≈3.5 servings among NH whites and 2.5 servings among NH blacks and Mexican Americans. Approximately 1 in 4 whites, 1 in 6 NH blacks, and 1 in 8 Mexican Americans met guidelines of ≥4 servings per week.
- Consumption of unprocessed red meats was higher in males than in females, up to 4.8 servings per week in Mexican American males.
- Consumption of processed meats was lowest among Mexican American females (1.1 servings per week) and highest among NH black and NH white males (≈2.5 servings per week). Between 57% (NH white males) and 79% (Mexican American females) of adults consumed ≤2 servings per week.
- Consumption of SSBs ranged from 6.8 servings per week among NH white females to nearly 12 servings per week among Mexican American males. Females generally consumed less than males. Some adults, from 33% of Mexican American males to 65% of NH white females, consumed <36 oz/wk.
- Consumption of sweets and bakery desserts ranged from 3.9 servings per week (Mexican

American males) to >7 servings per week (white females). Approximately 1 in 3 adults (1 in 2 Mexican American males) consumed <2.5 servings per week.

- Consumption of eicosapentaenoic acid and docosahexaenoic acid ranged from 0.058 to 0.117 g/d in each sex and racial or ethnic subgroup. Fewer than 8% of NH whites, 14% of NH blacks, and 11% of Mexican Americans consumed ≥0.250 g/d.
- One-third to one-half of adults in each sex and racial or ethnic subgroup consumed <10% of total calories from saturated fat, and approximately one-half to two-thirds consumed <300 mg of dietary cholesterol per day.
- Only ≈7% to 10% of NH whites, 4% to 5% of blacks, and 13% to 14% of Mexican Americans consumed ≥28 g of dietary fiber per day.
- Only ≈6% to 8% of adults in each age and racial or ethnic subgroup consumed <2.3 g of sodium per day. Estimated mean sodium intake in the US by 24-hour urinary excretion was 4205 mg/d for males and 3039 mg/d for females in 2013 to 2014. Estimates of sodium intake by race, sex, and source are shown in Charts 5-3 and 5-4.[14] Sodium added to food outside the home accounts for more than two-thirds of total sodium intake in the United States (Chart 5-4).[15] Top sources of sodium intake vary by race/ethnicity, with the largest contributor being yeast breads for NH whites, sandwiches for NH blacks, burritos and tacos for Hispanics, and soups for NH Asians.[16]

Children and Teenagers

On the basis of NHANES 2011 to 2012, the average dietary consumption by US children and teenagers of selected foods and nutrients related to cardiometabolic health is detailed below[3]:

- Whole grain consumption was <1 serving per day in all age and sex groups, with <5% of all children in different age and sex subgroups meeting guidelines of ≥3 servings per day.[17]
- Fruit consumption was low and decreased with age: 1.7 to 1.9 servings per day in younger boys and girls (5–9 years of age), 1.4 servings per day in adolescent boys and girls (10–14 years of age), and 0.9 to 1.3 servings per day in teenage boys and girls (15–19 years of age). The proportion meeting guidelines of ≥2 cups per day was also low and decreased with age: ≈8% to 14% in those 5 to 9 years of age, 3% to 8% in those 10 to 14 years of age, and 5% to 6% in those 15 to 19 years of age. When 100% fruit juices were included, the number of servings consumed increased by ≈50%, and proportions consuming ≥2 cups per day increased to nearly 25% of those 5 to 9 years of age, 20% of those 10 to 14 years of age, and 15% of those 15 to 19 years of age.
- Nonstarchy vegetable consumption was low, ranging from 1.1 to 1.5 servings per day, with <1.5% of children in different age and sex subgroups meeting guidelines of ≥2.5 cups per day.
- Consumption of fish and shellfish was low, ranging between 0.3 and 1.0 servings per week in all age and sex groups. Among all ages, only 7% to 14% of youths consumed ≥2 servings per week.
- Consumption of nuts, seeds, and beans ranged from 1.1 to 2.7 servings per week among different age and sex groups, and generally <15% of children in different age and sex subgroups consumed ≥4 servings per week.
- Consumption of unprocessed red meats was higher in boys than in girls and increased with age, up to 3.6 and 2.5 servings per week in 15- to 19-year-old boys and girls, respectively.
- Consumption of processed meats ranged from 1.4 to 2.3 servings per week, and the majority of children consumed <2 servings per week of processed meats.
- Consumption of SSBs was higher in boys than in girls in the 5- to 9-year-old (7.7±6.2 versus 6.0±3.8 servings per week) and 10- to 14-year-old (11.6±5.3 versus 9.7±7.9 servings per week) groups, but it was higher in girls than in boys in the 15- to 19-year-old group (14±6.0 versus 12.4±5.8 servings per week). Only about half of children 5 to 9 years of age and one-quarter of boys 15 to 19 years of age consumed <4.5 servings per week.
- Consumption of sweets and bakery desserts was higher among 5- to 9-year-old and 10- to 14-year-old boys and girls and modestly lower (4.7 to 6 servings per week) among 15- to 19-year-olds. A minority of children in all age and sex subgroups consumed <2.5 servings per week.
- Consumption of eicosapentaenoic acid and docosahexaenoic acid was low, ranging from 0.034 to 0.065 g/d in boys and girls in all age groups. Fewer than 7% of children and teenagers at any age consumed ≥0.250 g/d.
- Consumption of SFAs was ≈11% of calories in boys and girls in all age groups, and average consumption of dietary cholesterol ranged from ≈210 to 270 mg/d, increasing with age. Approximately 25% to 40% of youths consumed <10% energy from SFAs, and ≈70% to 80% consumed <300 mg of dietary cholesterol per day.

- Consumption of dietary fiber ranged from ≈14 to 16 g/d. Fewer than 3% of children in all age and sex subgroups consumed ≥28 g/d.
- Consumption of sodium ranged from 3.1 to 3.5 g/d. Only 2% to 11% of children in different age and sex subgroups consumed <2.3 g/d.

Impact on US Mortality (See Chart 5-5)

Comparable risk assessment methods and nationally representative data were used to estimate the impact of 10 specific dietary factors on cardiometabolic mortality in the United States in 2002 and 2012 (Chart 5-5).[18] In 2012, 318 656 (45.4%) of 702 308 cardiometabolic deaths were estimated to be attributable to poor dietary habits. The largest numbers of deaths attributable to diet were estimated to be from high sodium intake (66 508; 9.5% of all cardiometabolic deaths), low consumption of nuts/seeds (59 374; 8.5%), high consumption of processed meats (57 766; 8.2%), low intake of seafood omega-3 fats (54 626; 7.8%), low consumption of vegetables (53 410; 7.6%) and fruits (52 547; 7.5%), and high consumption of SSBs (51 694; 7.4%). Between 2002 and 2012, population-adjusted US cardiometabolic deaths decreased by 26.5%, with declines in estimated diet-associated cardiometabolic deaths for PUFAs (−20.8%), nuts/seeds (−18.0%), and SSBs (−14.5%) and increases in diet-associated cardiometabolic deaths for sodium (5.8%) and unprocessed red meats (14.4%). Estimated cardiometabolic mortality related to whole grains, fruits, vegetables, seafood, omega-3 fats, and processed meats remained relatively stable.

Cost (See Chart 5-6)

The US Department of Agriculture reported that the Consumer Price Index for all food increased by 0.9% in 2017.[19] Prices for foods eaten at home decreased by 0.2% in 2017, whereas prices for foods eaten away from home increased by 2.3%.[12] Using data from Euromonitor International, the US Department of Agriculture calculated the share of consumer expenditures attributed to food in multiple countries in 2016. The proportion of consumer expenditures spent on food ranged from 6.3% in the United States to 9.1% in Canada, 23.1% in Mexico, and 58.9% in Nigeria (Chart 5-6).[20]

Cost of a Healthy Diet

- A meta-analysis of price comparisons of healthy versus unhealthy diet patterns found that the healthiest diet patterns cost, on average, ≈$1.50 more per person per day to consume.[21]
- In an assessment of snacks served at YMCA after-school programs from 2006 to 2008, healthful snacks were ≈50% more expensive ($0.26 per snack) than less healthful snacks.[22]
- In a 1-year (2013–2014) RCT of 30 after-school programs in South Carolina, site leaders in the intervention group received assistance in establishing snack budgets and menus and identifying low-cost outlets to purchase snacks that met healthy eating standards. The intervention was successful in increasing the number of days fruits and vegetables were served (3.9 versus 0.7 d/wk) and decreasing the number of days SSBs (0.1 versus 1.8 d/wk) and sugary foods (0.3 versus 2.7 d/wk) were served.[23] Cost in the intervention group was minimized by identifying low-cost grocery outlets or large bulk warehouse stores; cost increased by $0.02 per snack in the intervention group compared with a $0.01 per snack decrease in the control group.

Cost-Effectiveness of Sodium Reduction

- In a cost-effectiveness analysis using the Coronary Heart Disease Policy Model, a 1.2-g/d reduction in dietary sodium was projected to reduce US annual cases of incident CHD by 60 000 to 120 000, stroke by 32 000 to 66 000, and total mortality by 44 000 to 92 000.[24] The projected benefits would be greater in blacks than in nonblacks. If accomplished through a regulatory intervention, estimated savings in healthcare costs would be $10 billion to $24 billion annually.[24]
- A global cost-effectiveness analysis modeled the cost-effectiveness of a so-called soft regulation national policy to reduce sodium intake in countries around the world, based on the United Kingdom experience (government-supported industry agreements, government monitoring of industry compliance, public health campaign).[25] Model estimates were based on sodium intake, BP, and CVD data from 183 countries. Country-specific cost data were used to estimate the CER, defined as purchasing power parity adjusted international dollars (I$, equivalent to country-specific purchasing power of $1 US) per DALY saved over 10 years. Globally, the estimated average CER was I$204 per DALY (95% CI, I$149–I$322) saved. The estimated CER was highly favorable in high-, middle-, and low-income countries.

Secular Trends

Trends in Dietary Patterns (See Chart 5–7)

In addition to individual foods and nutrients, overall dietary patterns can be another useful tool for assessing diet quality.[26] Different dietary patterns have been defined, such as Mediterranean, DASH-type, HEI-2010, Alternate HEI, Western, prudent, and vegetarian patterns. The original DASH diet was low fat; a higher-MUFA DASH-type diet is even more healthful and similar to a traditional Mediterranean dietary pattern.[27]

Between 1999 and 2010, the average Alternate HEI–2010 score of US adults improved from 39.9 to 46.8.[28] This was related to reduced intake of *trans* fat (accounting for more than half of the improvement), SSBs, and fruit juice, as well as an increased intake of whole fruit, whole grains, PUFAs, and nuts and legumes. Adults with greater family income and education had higher scores, and the gap between low and high SES widened over time, from 3.9 points in 1999 to 2000 to 7.8 points in 2009 to 2010.

Between 1999 and 2012, the mean HEI-2010 score in US children and adolescents aged 2 to 18 years improved from 42.5 to 50.9.[29] One-third of the improvement was attributable to reduction in empty calorie intake; other HEI categories that improved included whole grains, fruit, seafood and plant proteins, greens and beans, and fatty acids (Chart 5-7). Participants in the National School Lunch Program and the School Breakfast Program had lower HEI-2010 scores than nonparticipants. There was also a trend toward lower HEI-2010 in SNAP participants after the 2003 to 2004 cycle. HEI-2010 scores were consistently lower from 1999 to 2012 in NH blacks (39.6–48.4) than in NH whites (42.1–50.2) and were highest in Mexican Americans (44.1–51.9). In a study that used household store purchase data (N=98 256 household-by-quarter observations), SNAP participants purchased more calories from SSBs (15–20 kcal per person per day), more sodium (174–195 mg per person per day), and fewer calories from fiber (−0.52 kcal per person per day) than income-eligible and higher-income nonparticipants.[30]

The impact of the October 2009 Special Supplemental Nutrition Program for Women, Infants, and Children food package revision (more fruits, vegetables, whole grains, and lower-fat milk) was examined using 2003 to 2008 and 2011 to 2012 NHANES data in 2- to 4-year-old children from low-income households.[31] The Women, Infants, and Children food package revisions were associated with significant improvements in HEI-2010 score (3.7-higher HEI points; 95% CI, 0.6–6.9), with the greatest improvement coming from a 3.4-fold increase (95% CI, 1.3–9.4) in the greens and beans category.

Worldwide, 2 separate, relatively uncorrelated dietary patterns can be characterized, 1 by greater intakes of health-promoting foods (eg, fruits, vegetables, nuts, fish) and 1 by lower intakes of less optimal foods (eg, processed meats, SSBs).[32] In 2010, compared with low-income nations, high-income nations had better diet patterns based on healthful foods but substantially worse diet patterns based on unhealthful foods. Between 1990 and 2010, both types of dietary patterns improved in high-income Western countries but worsened or did not improve in low-income countries in Africa and Asia. Middle-income countries showed the largest improvements in dietary patterns based on healthful foods but the largest deteriorations in dietary patterns based on unhealthful foods. Overall, global consumption of healthy foods improved but was outpaced by increased intake of unhealthy foods in most world regions.

Trends in Energy Intake

Until 1980, total energy intake remained relatively constant[33]; however, data from NHANES indicate that average energy intake among US adults increased from 1971, peaked at 2004, and has since stabilized. Average total energy intakes among US white adults in 1971, 2004, and 2010 were 1992, 2283, and 2200 kcal/d, respectively. Average total energy intakes among US black adults in 1971, 2004, and 2010 were 1780, 2169, and 2134 kcal/d, respectively. This rise in energy intake was primarily attributable to increased carbohydrate intake, particularly of starches, refined grains, and sugars.[34,35]

In a study using 4 nationally representative US Department of Agriculture surveys of food intake among US children,[36] average portion sizes among US children increased for many foods between 1977 and 2006. For example, pizza portion size increased from 406 to 546 calories, with much of this increase occurring from the 1990s to the 2000s. Portion sizes for other foods increased, including Mexican food (from 373 to 512 calories), cheeseburgers (from 380 to 473 calories), soft drinks (from 121 to 155 calories), fruit drinks (from 106 to 133 calories), and salty snacks (from 124 to 165 calories). French fry portion sizes increased at fast food locations but not stores and restaurants. Soft drink and pizza portion sizes increased at all food sources (stores, restaurants, and fast food locations).

In a quantitative analysis using various US surveys between 1977 and 2010, the relationships of national changes in energy density, portion sizes, and number of daily eating/drinking occasions to changes in total energy intake were assessed.[37] Total energy intake increased by 108 kcal/day over this time period. Changes in energy density were not consistently linked to energy intake over time. Rather, main contributors to temporal changes in caloric intake included an increase in the number of eating occasions from 3.9 to 5.1 from 1977 to 2010 and decreases in average portion size of foods and beverages since 1989 to 1991.

Cardiovascular Health Impact of Dietary Patterns

Cardiovascular and Metabolic Risk

- In a systematic review and meta-analysis, RCTs in children demonstrated reductions in BMI gain when SSBs were replaced with noncaloric beverages, and RCTs in adults showed weight gain when SSBs were added.[38]
- In a meta-analysis of 61 trials (N=2582), tree nut consumption lowered TC by 4.7 mg/dL, LDL-C by 4.8 mg/dL, apolipoprotein B by 3.7 mg/dL, and triglycerides by 2.2 mg/dL. No heterogeneity by nut type was observed.[39]
- After intentional weight loss in 21 overweight/obese young adults, an isocaloric low-carbohydrate diet resulted in smaller declines in total energy expenditure than a low-fat diet, with a mean difference of >300 kcal/d.[40]
- In a randomized trial of 609 nondiabetic participants with BMI 28 to 40 kg/m^2 that compared the effects of healthy low-fat versus healthy low-carbohydrate weight loss diets, weight loss at 12 months did not differ between groups. Neither genotype pattern (3 SNP multilocus genotype responsiveness pattern) nor insulin secretion (30 minutes after glucose challenge) modified the effects of diet on weight loss.[41]
- In the PREDIMED RCT, 7447 adults with type 2 DM or ≥3 CVD risk factors were randomized to 3 arms: Mediterranean diet supplemented by extra-virgin olive oil, Mediterranean diet supplemented with nuts, or control diet (advice to reduce dietary fat).[42] A significantly smaller decrease in central adiposity occurred in the Mediterranean diet with olive oil arm (−0.55 cm; 95% CI, −1.16 to −0.06) and the Mediterranean diet with nuts arm (−0.94 cm; 95% CI, −1.60 to −0.27) than in the control arm. In a subgroup analysis of 3541 patients in PREDIMED without DM, HRs for incident DM were 0.60 (95% CI, 0.43–0.85) for the Mediterranean diet with olive oil arm and 0.82 (0.61–1.10) for the Mediterranean diet with nuts arm compared with the control arm.
- In a randomized crossover trial of 118 overweight omnivores at low-moderate CVD risk, a reduced-calorie lacto-ovo vegetarian diet was compared to a reduced-calorie Mediterranean diet by providing face-to-face, individual counseling sessions. Both diets were equally successfully in reducing body weight and fat mass. LDL-C, uric acid, and vitamin B12 were lower during the vegetarian diet, whereas triglycerides were lower during the Mediterranean diet, without substantial differences between oxidative stress markers and inflammatory cytokines.[43]
- In a meta-analysis of 34 RCTs with modest reduction of sodium for ≥4 weeks, a 100-mmol/d (2300-mg/d) reduction in sodium was associated with a 5.8-mm Hg lower SBP.[44] The effects of sodium reduction on BP were stronger in individuals who were older, hypertensive, and black.[45,46]
- Compared with a usual Western diet, a DASH-type dietary pattern with low sodium reduced SBP by 5.3, 7.5, 9.7, and 20.8 mm Hg in adults with baseline SBP <130, 130–139, 140–149, and ≥150 mm Hg, respectively.[47]
- Compared with a higher-carbohydrate DASH diet, a DASH-type diet with higher protein lowered BP by 1.4 mm Hg, LDL by 3.3 mg/dL, and triglycerides by 16 mg/dL but also lowered HDL by 1.3 mg/dL. Compared with a higher-carbohydrate DASH diet, a DASH-type diet with higher unsaturated fat lowered BP by 1.3 mm Hg, increased HDL by 1.1 mg/dL, and lowered triglycerides by 10 mg/dL.[48] The DASH-type diet higher in unsaturated fat also improved glucose-insulin homeostasis compared with the higher-carbohydrate DASH diet.[49]
- In a systematic review and meta-analysis of controlled clinical trials of dietary pattern interventions, the DASH diet had the largest net effect on SBP (−7.6 mm Hg) and DBP (−4.2 mm Hg), whereas the Mediterranean diet had an effect on DBP (−1.4 mm Hg) but not SBP.[50]
- In a meta-analysis of 60 randomized controlled feeding trials, consumption of 1% of calories from SFAs in place of carbohydrates raised LDL-C concentrations but also raised HDL-C and lowered triglycerides, with no significant effects on apolipoprotein B concentrations.[51]
- In a randomized crossover trial of 92 adults with abdominal obesity, LDL was highest after a butter-rich diet, followed by a cheese-rich diet, high-carbohydrate diet, MUFA-rich diet, and PUFA-rich diet. The butter-rich and cheese-rich diets similarly increased HDL (+4.7% and +3.8%, respectively), compared with the high-carbohydrate diet.[52]
- In a meta-analysis of RCTs, consumption of 1% of calories from *trans* fat in place of SFAs, MUFAs, or PUFAs, respectively, increased the ratio of TC to HDL-C by 0.031, 0.054, and 0.67; increased apolipoprotein B levels by 3, 10, and 11 mg/L; decreased apolipoprotein A-1 levels by 7, 5, and 3 mg/L; and increased lipoprotein(a) levels by 3.8, 1.4, and 1.1 mg/L.[53]
- In a meta-analysis of 70 RCTs, consumption of eicosapentaenoic acid and docosahexaenoic acid lowered BP by 1.5/1.0 mm Hg.[54]
- A meta-analysis of 102 randomized controlled feeding trials evaluated the effects of exchanging different dietary fats and carbohydrates on markers of glucose-insulin homeostasis.[55] Replacing

5% energy from carbohydrates with SFAs generally had no significant effects, whereas replacing carbohydrates with unsaturated fats lowered both HbA_{1c} and insulin. On the basis of "gold standard" short-term insulin response in 10 trials, PUFAs improved insulin secretion compared with carbohydrates, SFAs, and even MUFAs.

Cardiovascular Events

Fats and Carbohydrates

- In the WHI RCT (N=48 835), reduction of total fat consumption from 37.8% energy (baseline) to 24.3% energy (at 1 year) and 28.8% energy (at 6 years) had no effect on incidence of CHD (RR, 0.98; 95% CI, 0.88–1.09), stroke (RR, 1.02; 95% CI, 0.90–1.15), or total CVD (RR, 0.98; 95% CI, 0.92–1.05) over a mean follow up of 8.1 years.[56] This was consistent with null results of 4 prior RCTs and multiple large prospective cohort studies that indicated little effect of total fat consumption on CVD risk.[57]
- In a meta-analysis of 21 studies, SFA consumption was not associated with increased risk of CHD, stroke, or total CVD.[58] In comparison, in a pooled individual-level analysis of 11 prospective cohort studies, the specific exchange of PUFA consumption in place of SFAs was associated with lower CHD risk, with 13% lower risk for each 5% energy exchange (RR, 0.87; 95% CI, 0.70–0.97).[59] These findings are consistent with a meta-analysis of RCTs in which increased PUFA consumption in place of SFAs reduced CHD events, with 10% lower risk for each 5% energy exchange (RR, 0.90; 95% CI, 0.83–0.97).[60] Replacing SFAs with MUFAs was not significantly associated with CHD risk.[59]
- In a meta-analysis of 13 prospective cohort studies, increased intake of PUFAs was associated with lower risk of CHD, whether it replaced SFAs or carbohydrates.[61]
- In a meta-analysis of prospective cohort studies, each 2% of calories from *trans* fat was associated with a 23% higher risk of CHD (RR, 1.23; 95% CI, 1.11–1.37).[62]
- In meta-analyses of prospective cohort studies, greater consumption of refined complex carbohydrates, starches, and sugars, as assessed by glycemic index or load, was associated with significantly higher risk of CHD and DM. When the highest category was compared with the lowest category, risk of CHD was 36% greater (glycemic load: RR, 1.36; 95% CI, 1.13–1.63) and risk of DM was 40% greater (glycemic index: RR, 1.40; 95% CI, 1.23–1.59).[63,64]
- In a prospective cohort study of urban Chinese females (N=64 328), high glycemic index and glycemic load were associated with increased risk of stroke. Compared with the lowest 10th percentiles, risks for the 90th percentiles of glycemic index and glycemic load were 1.19 (95% CI, 1.04–1.36) and 1.27 (95% CI, 1.04–1.54), respectively.[65]

Foods and Beverages

- In meta-analyses of prospective cohort studies, each daily serving of fruits or vegetables was associated with a 4% lower risk of CHD (RR, 0.96; 95% CI, 0.93–0.99), a 5% lower risk of stroke (RR, 0.95; 95% CI, 0.92–0.97), and a 4% lower risk of cardiovascular mortality (RR, 0.96; 95% CI, 0.92–0.99).[66–68]
- In a prospective study of 512 891 adults in China (only 18% consumed fresh fruit daily), individuals who ate fresh fruit daily had 40% lower risk of CVD death (RR, 0.60; 95% CI, 0.54–0.67), 34% lower risk of incident CHD (RR, 0.66; 95% CI, 0.58–0.75), 25% lower risk of ischemic stroke (RR, 0.75; 95% CI, 0.72–0.79), and 36% lower risk of hemorrhagic stroke (RR, 0.64; 95% CI, 0.56–0.74).[69]
- In a meta-analysis of 45 prospective studies, whole grain intake was associated with a lower risk of CHD (HR, 0.81; 95% CI, 0.75–0.87) and CVD (HR, 0.78, 95% CI, 0.73–0.85) but was not significantly associated with stroke (HR, 0.88; 95% CI, 0.75–1.03).[70]
- In a meta-analysis of 16 prospective cohort studies, fish consumption was associated with significantly lower risk of CHD mortality.[71] Compared with no consumption, consumption of an estimated 0.250 g/d of long-chain omega-3 fatty acids was associated with 35% lower risk of CHD death ($P<0.001$).
- Among 16 479 males and females in the REGARDS study, individuals who consumed ≥2 servings of fried fish per week had a greater risk of CVD over 5.1 years of follow-up than those who consumed <1 serving per month (HR, 1.63; 95% CI, 1.11–2.40).[72]
- In a meta-analysis of prospective cohort and case-control studies from multiple countries, consumption of unprocessed red meat was not significantly associated with incidence of CHD. In contrast, each 50-g serving per day of processed meats (eg, sausage, bacon, hot dogs, deli meats) was associated with a higher incidence of CHD (RR, 1.42; 95% CI, 1.07–1.89).[73]
- In a study of 169 310 female nurses and 41 526 male physicians, consumption of 1 serving of nuts ≥5 times per week was associated with lower risk of CVD (HR, 0.86; 95% CI, 0.79, 0.93) and CHD (HR, 0.80; 95% CI, 0.72, 0.89), compared with those who never or almost never consumed nuts. Results were largely consistent for peanuts, tree nuts, and walnuts.[74]

- In a meta-analysis of 5 prospective observational studies, consumption of legumes (beans) was associated with lower incidence of CHD (RR per 4 weekly 100-g servings, 0.86; 95% CI, 0.78–0.94).[75]
- Results from a meta-analysis of 17 prospective observational studies showed that neither dairy consumption nor dairy fat was significantly associated with higher or lower risk of CHD.[76]
- In a meta-analysis of 15 country-specific observational cohorts, consumption of butter had small or neutral overall associations with mortality, CVDs, and DM.[77]

Sodium and Potassium

- Nearly all observational studies demonstrate an association between higher estimated sodium intakes (eg, >4000 mg/d) and a higher risk of CVD events, in particular stroke.[78–84] Some studies have also observed higher CVD risk at estimated low intakes (eg, <3000 g/d), which suggests a potential J-shaped relationship with risk.
- An AHA science advisory suggested that variation in methodology might account for inconsistencies in the relationship between sodium and CVD in observational studies. Increased risk at low sodium intake in some observational studies could be related to reverse causation (illness causing low intake), imprecise estimation of sodium intake through a single dietary recall or a single urine excretion.[82]
- Post hoc analyses of the TOHP with 10 to 15 years of follow-up found that participants randomized to sodium reduction had a 25% decrease in CVD risk (RR, 0.75; 95% CI, 0.57–0.99) compared with those randomized to control.[83]
- In an observational analysis of TOHP participants not assigned to an active sodium reduction intervention, sodium-potassium ratio was linearly associated with risk of CVD over 10 to 15 years of follow-up (RR, 1.24 per unit; 95% CI, 1.05–1.46; *P*=0.01).[83]
- In a longer-term (median 24 years) post hoc analysis of the TOHP (median of five 24-hour urine measurements), every 1-U increase in sodium-potassium ratio was associated with a 13% higher risk of death (HR, 1.13; 95% CI, 1.01–1.27; *P*=0.04).[84]

Dietary Supplement Trends and Outcomes

Use of dietary supplements is common in the United States among both adults and children despite lack of evidence to support the use of most dietary supplements in reducing risks of CVD or death[85]:

- Approximately half of US adults in 2007 to 2010 used ≥1 dietary supplement, with the most common supplement being multivitamin-multimineral products (32% of males and females reporting such use).[86] Supplement use is associated with older age, white race, higher education, greater PA, moderate alcohol consumption, lower BMI, abstinence from smoking, having health insurance, and higher intake of most vitamins and minerals from food.[87,88]
- A meta-analysis of 4 RCTs and 27 prospective cohort and nested case-control studies found no significant effect of calcium supplements or calcium plus vitamin D supplements with CVD events or mortality.[89]
- Observational studies have found that the antioxidants vitamin C, beta-carotene, and vitamin E are associated with lower risk of CHD and mortality, but RCTs providing antioxidant supplementation have demonstrated no benefit on CVD outcomes or mortality.[90–95]
- A 2017 AHA scientific advisory statement summarized available evidence and suggested fish oil supplementation only for secondary prevention of CHD and SCD (Class IIa recommendation) and for secondary prevention of outcomes in patients with HF (Class IIa recommendation).[96]
- A meta-analysis of 77 917 participants in 10 RCTs with ≥500 participants treated for ≥1 year found that fish oil supplementation (eicosapentaenoic acid dose range 226–1800 mg/d; docosahexaenoic acid dose range 0–1700 mg/d) had no significant effect on CHD death (RR, 0.94; 95% CI, 0.81–1.03), nonfatal MI (RR, 0.97; 95% CI, 0.87–1.08), or any CHD events (RR, 0.97; 95% CI, 0.93–1.01).[97]

Dietary Patterns

The 2015 US Dietary Guidelines Advisory Committee summarized the evidence for benefits of healthful diet patterns on a range of cardiometabolic and other disease outcomes.[17] They concluded that a healthy dietary pattern is higher in vegetables, fruits, whole grains, low-fat or nonfat dairy, seafood, legumes, and nuts; moderate in alcohol (among adults); lower in red and processed meat; and low in sugar-sweetened foods and drinks and refined grains. The 2015 US Dietary Guidelines also describe a healthy vegetarian dietary pattern, which includes more legumes, soy products, nuts and seeds, and whole grains but does not include meats, poultry, or seafood.[17]

- In a meta-analysis of 8 observational studies (3 Seventh-day Adventist cohorts [N=110 723] and 5 other cohorts [N=72 598]), vegetarians had a 40% lower risk of CHD in the Seventh-day Adventist studies (RR, 0.60; 95% CI, 0.43–0.80) and a 16% lower risk of CHD (RR, 0.84; 95% CI, 0.74–0.96) in the other studies.[98]

- In a cohort of 200 272 US males and females, greater adherence to a plant-based dietary pattern, defined by higher intake of plant-based foods and low intake of animal based foods, was associated with a 20% lower risk of DM (HR, 0.80; 95% CI, 0.74–0.87).[99]
- In a cohort of 380 296 US males and females, greater versus lower adherence to a Mediterranean dietary pattern was associated with a 22% lower cardiovascular mortality (RR, 0.78; 95% CI, 0.69–0.87).[100] Similar findings have been seen for the Mediterranean dietary pattern and risk of incident CHD and stroke[101] and for the DASH-type dietary pattern.[102]
- In a cohort of 72 113 US female nurses, a dietary pattern characterized by higher intakes of vegetables, fruits, legumes, fish, poultry, and whole grains was associated with a 28% lower cardiovascular mortality (RR, 0.72; 95% CI, 0.60–0.87), whereas a dietary pattern characterized by higher intakes of processed meat, red meat, refined grains, french fries, and sweets/desserts was associated with a 22% higher cardiovascular mortality (RR, 1.22; 95% CI, 1.01–1.48).[103] Similar findings have been seen in other cohorts and for other outcomes, including development of DM and metabolic syndrome.[104–110]
- The observational findings for benefits of a healthy food–based dietary pattern have been confirmed in 2 randomized clinical trials, including a small secondary prevention trial in France among patients with recent MI[111] and a large primary prevention trial in Spain among patients with CVD risk factors.[42] The latter trial, PREDIMED, demonstrated an ≈30% reduction in the risk of stroke, MI, and death attributable to cardiovascular causes in those patients randomized to Mediterranean-style diets supplemented with extra-virgin olive oil or mixed nuts.[42]

Family History and Genetics

- Although the interaction between genetics and nutrition is complex, genetic factors may contribute to food preferences and modulate the association between dietary components and adverse cardiovascular health outcomes.[112,113]

Nutrition and Disparities in CVD Health

- Societal and environmental factors independently associated with diet quality, adiposity, or weight gain include education, income, race/ethnicity, and (at least cross-sectionally) neighborhood availability of supermarkets.[114–116]
- Other local food-environment characteristics, such as availability of grocery stores (ie, smaller stores than supermarkets), convenience stores, and fast food restaurants, are not consistently associated with diet quality or adiposity and could be linked to social determinants of health for CVD.[117]
- Disparities may be driven in part by overabundance of unhealthy food options. In a study of neighborhood-level data from 4 US cities (Birmingham, AL, Chicago, IL, Minneapolis, MN, and Oakland, CA), past neighborhood-level income was inversely associated with current density of convenience stores.[118] In low-income neighborhoods, the percentage of white population was inversely associated with density of fast food restaurants and smaller grocery stores.
- In a study using NHANES and Nielsen Homescan data to examine disparities in calories from store-bought consumer packaged goods over time, calories from store-bought beverages decreased between 2003 to 2006 and 2009 to 2012. However, the decline in calories from consumer packaged goods was slower for NH blacks, Mexican Americans, and lowest-income households.[119]

Global Burden (See Chart 5-8)

- A report from the GBD Study estimated the impact of 14 specific dietary factors on mortality worldwide in 2005 to 2015. In 2015, a total of 6.9 million male deaths (237.4 deaths per 100 000) and 5.2 million female deaths (147.0 deaths per 100 000) worldwide were estimated to be attributable to poor dietary habits. The population attributable fraction was 22.4% for males and 20.7% for females. Although the estimated mortality rate attributable to poor dietary factors decreased by 15.0% in the worldwide population from 2005 to 2015, the population attributable fraction increased by 7.9% over the same time period.[120]
- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories. Mortality rates attributable to dietary risks were highest in Eastern Europe, Russia, and Central Asia (Chart 5-8).[121]

Table 5-1. AHA Dietary Targets and Healthy Diet Score for Defining Cardiovascular Health

	AHA Target	Consumption Range for Alternative Healthy Diet Score*	Alternative Scoring Range*
Primary dietary metrics†			
Fruits and vegetables	≥4.5 cups/d‡	0 to ≥4.5 cups/d‡	0–10
Fish and shellfish	2 or more 3.5-oz servings/wk (≥200 g/wk)	0 to ≥7 oz/wk	0–10
Sodium	≤1500 mg/d	≤1500 to >4500 mg/d	10–0
SSBs	≤36 fl oz/wk	≤36 to >210 fl oz/wk	10–0
Whole grains	3 or more 1-oz-equivalent servings/d	0 to ≥3 oz/d	0–10
Secondary dietary metrics†			
Nuts, seeds, and legumes	≥4 servings/wk (nuts/seeds: 1 oz; legumes: ½ cup)	0 to ≥4 servings/d	0–10
Processed meats	2 or fewer 1.75-oz servings/wk (≤100 g/wk)	≤3.5 to >17.5 oz/wk	10–0
Saturated fat	≤7% energy	≤7 to >15 (% energy)	10–0
AHA Diet Score (primary)	Ideal: 4 or 5 dietary targets (≥80%) Intermediate: 2 or 3 dietary targets (40%–79%) Poor: <2 dietary targets (<40%)	Sum of scores for primary metrics	0 (worst) to 100 (best)§ Ideal: 80–100 Intermediate: 40–79 Poor: <40
AHA Diet Score (secondary)	Ideal: 4 or 5 dietary targets (≥80%) Intermediate: 2 or 3 dietary targets (40%–79%) Poor: <2 dietary targets (<40%)	Sum of scores for primary and secondary metrics	0 (worst) to 100 (best)§ Ideal: 80–100 Intermediate: 40–79 Poor: <40

AHA indicates American Heart Association; and SSBs, sugar-sweetened beverages.

*Consistent with other dietary pattern scores, the highest score (10) was given for meeting or exceeding the AHA target (eg, at least 4.5 cups of fruits and vegetables per day; no more than 1500 mg/d of sodium), and the lowest score (0) was given for zero intake (protective factors) or for very high intake (harmful factors). The score for each metric was scaled continuously within this range. For harmful factors, the level of high intake that corresponded to a zero score was identified as approximately the 90th percentile distribution of US population intake.

†Selected by the AHA based on evidence for likely causal effects on cardiovascular events, diabetes mellitus, or obesity; a general prioritization of food rather than nutrient metrics; consistency with US and AHA dietary guidelines; ability to measure and track these metrics in the US population; and parsimony, that is, the inclusion of as few components as possible that had minimal overlap with each other while at the same time having some overlap with the many other relevant dietary factors that were not included.[2] The AHA dietary metrics should be targeted in the context of a healthy diet pattern that is appropriate in energy balance and consistent with a DASH (Dietary Approaches to Stop Hypertension)-type eating plan, including but not limited to these metrics.

‡Including up to one 8-oz serving per day of 100% fruit juice and up to 0.42 cups/d (3 cups/wk) of starchy vegetables such as potatoes or corn.

§The natural range of the primary AHA Diet Score is 0 to 50 (5 components), and the natural range of the secondary AHA Diet Score is 0 to 80 (8 components). Both scores are then rescaled to a range of 0 to 100 for comparison purposes. The ideal range of the primary AHA Diet Score corresponds to the AHA scoring system of meeting at least 4 of 5 binary dietary targets (≥80%), the intermediate range corresponds to meeting 2 or 3 dietary targets (40%–79%), and the poor range corresponds to meeting <2 dietary targets (<40%). The same ranges are used for the secondary AHA Diet Score for consistency and comparison.

Sources: AHA's My Life Check – Life's Simple 7[1]; Lloyd-Jones et al[2]; Rehm et al.[4]

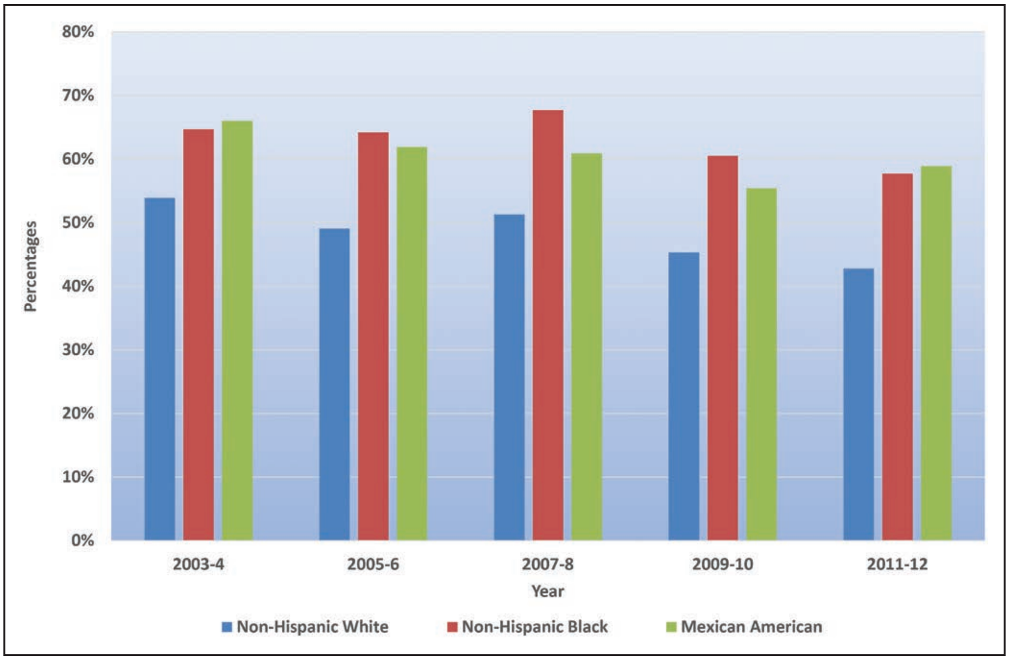


Chart 5-1. Trends in prevalence of poor AHA healthy diet score, by race/ethnicity.
Components of AHA healthy diet score are defined in Table 5-1. Poor diet was defined as <40% adherence, based on primary AHA continuous diet score.[4] AHA indicates American Heart Association.

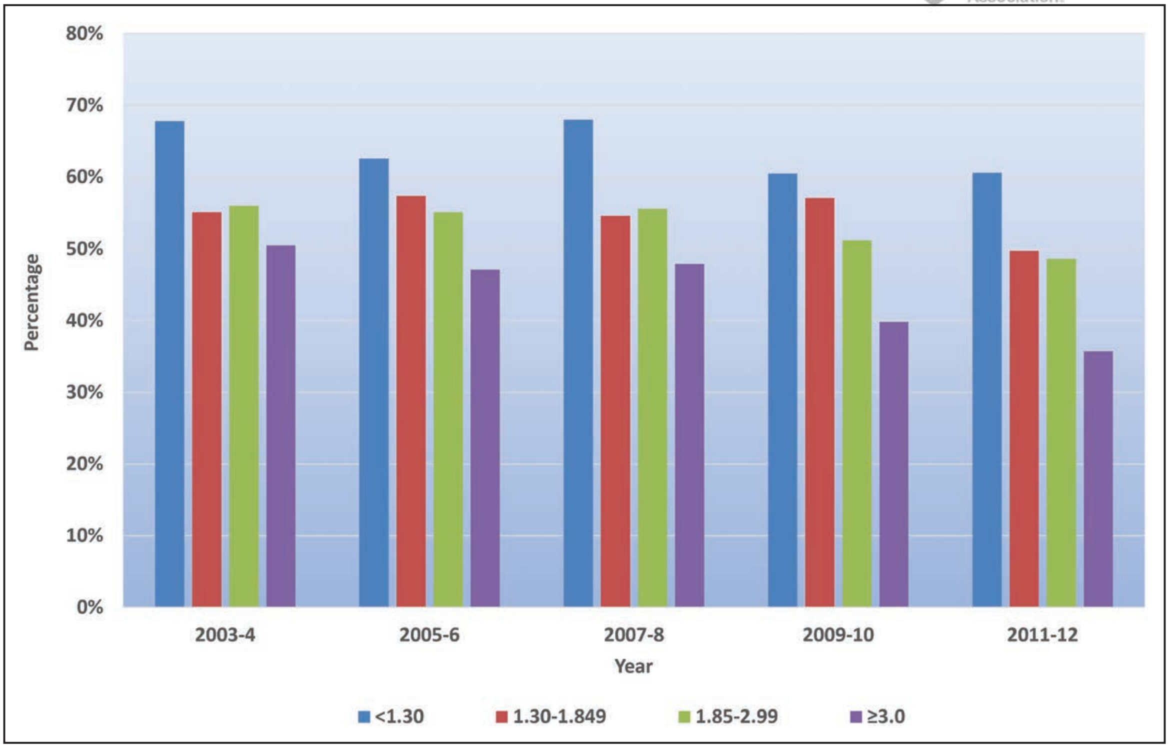


Chart 5-2. Trends in prevalence of poor AHA healthy diet score, by ratio of family income to poverty level (<1.30, 1.30–1.849, 1.85–2.99, ≥3.0).
Components of AHA healthy diet score are defined in Table 5-1. Poor diet was defined as <40% adherence, based on primary AHA continuous diet score.[4] AHA indicates American Heart Association.

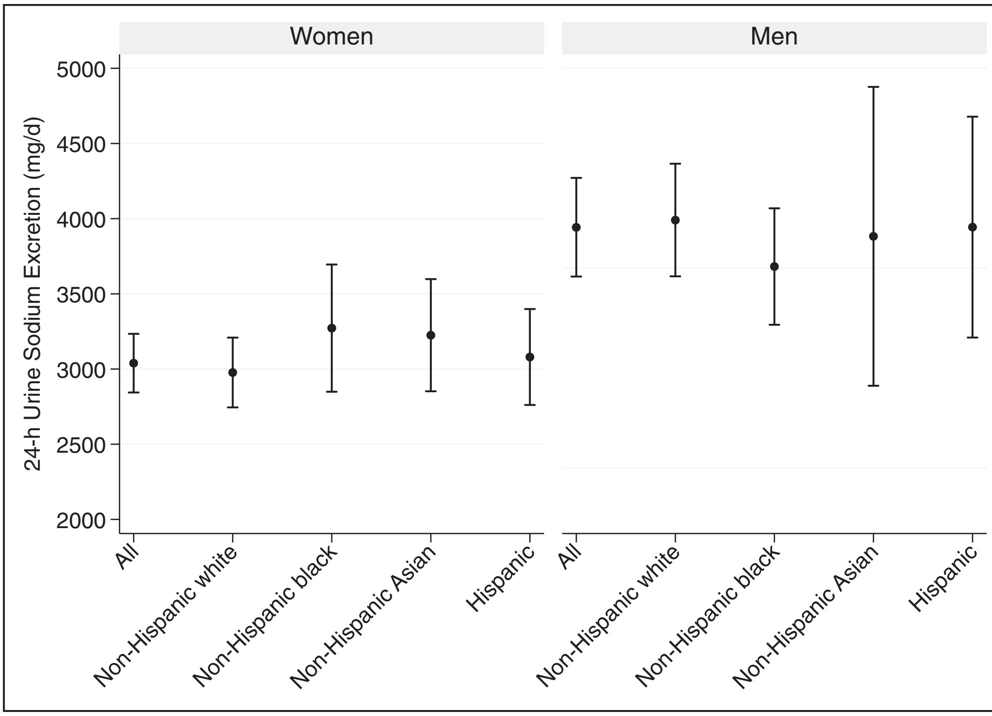
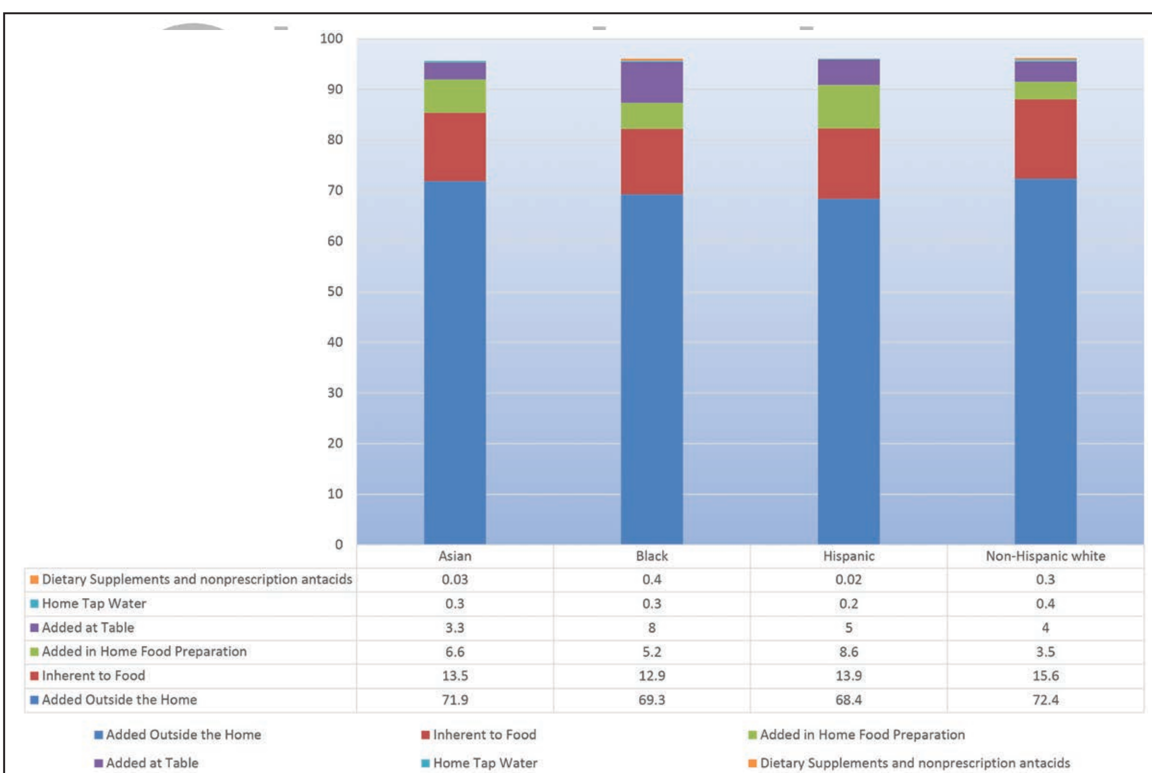


Chart 5-3. Estimated mean sodium intake in the United States by 24-hour urinary excretion.

Estimates based on nationally representative sample of 827 nonpregnant, noninstitutionalized US adults aged 20 to 69 years who completed a 24-hour urine collection in NHANES 2013 to 2014.[14]

NHANES indicates National Health and Nutrition Examination Survey.



	Asian	Black	Hispanic	Non-Hispanic white
Dietary Supplements and nonprescription antacids	0.03	0.4	0.02	0.3
Home Tap Water	0.3	0.3	0.2	0.4
Added at Table	3.3	8	5	4
Added in Home Food Preparation	6.6	5.2	8.6	3.5
Inherent to Food	13.5	12.9	13.9	15.6
Added Outside the Home	71.9	69.3	68.4	72.4

Chart 5-4. Sources of sodium intake in US adults in 3 geographic regions.

Sources of sodium intake determined by four 24-hour dietary recalls with special procedures, in which duplicate samples of salt added to food at the table and in home food preparation were collected in 450 adults recruited in 3 geographic regions (Birmingham, AL, Palo Alto, CA, Minneapolis-St. Paul, MN) with equal numbers of males and females from 4 racial/ethnic groups (Asians, blacks, Hispanics, non-Hispanic whites).[15]

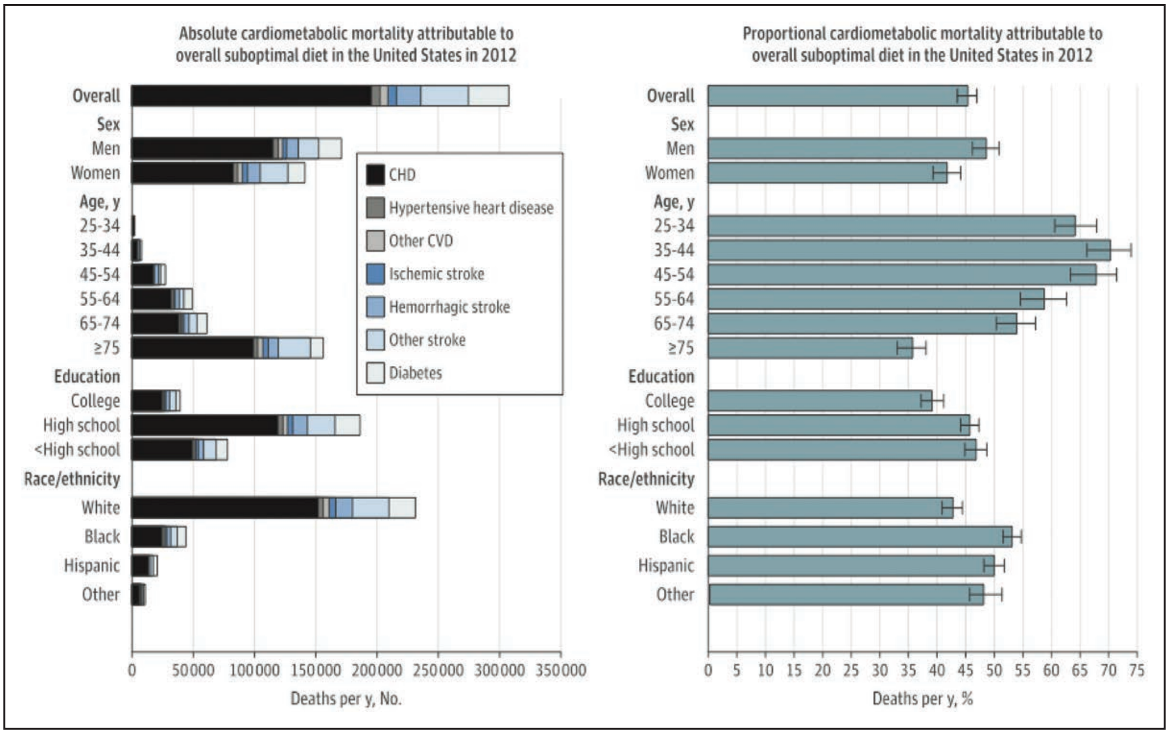


Chart 5-5. Absolute and proportional cardiometabolic disease mortality associated with overall suboptimal diet in the United States in 2012 by population subgroups.

Bars represent absolute number (**left**) and percentage (**right**) of cardiometabolic deaths jointly related to suboptimal intakes of 10 dietary factors. The 10 factors were low intakes of fruits, vegetables, nuts/seeds, whole grains, seafood omega-3 fats, and polyunsaturated fats (replacing saturated fats) and high intakes of sodium, unprocessed red meats, processed meats, and sugar-sweetened beverages. Error bars indicate 95% uncertainty intervals.

CHD indicates coronary heart disease; and CVD, cardiovascular disease.

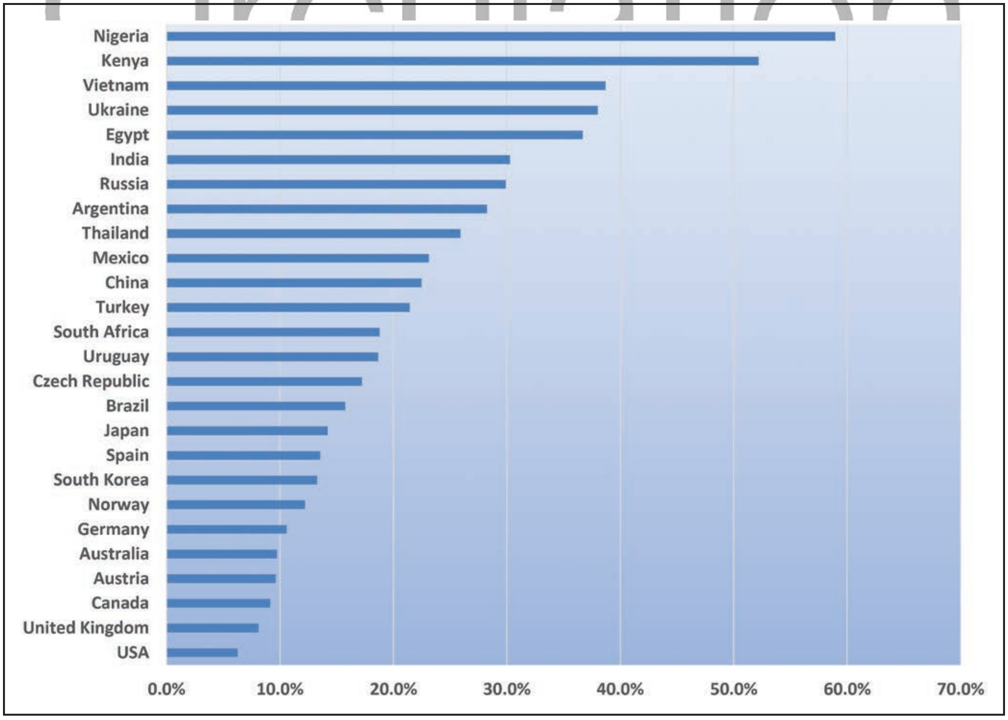


Chart 5-6. Proportion of consumer expenditures spent on food at home in selected countries.

Data computed by the US Department of Agriculture Economic Research Service, August 2017.[120]

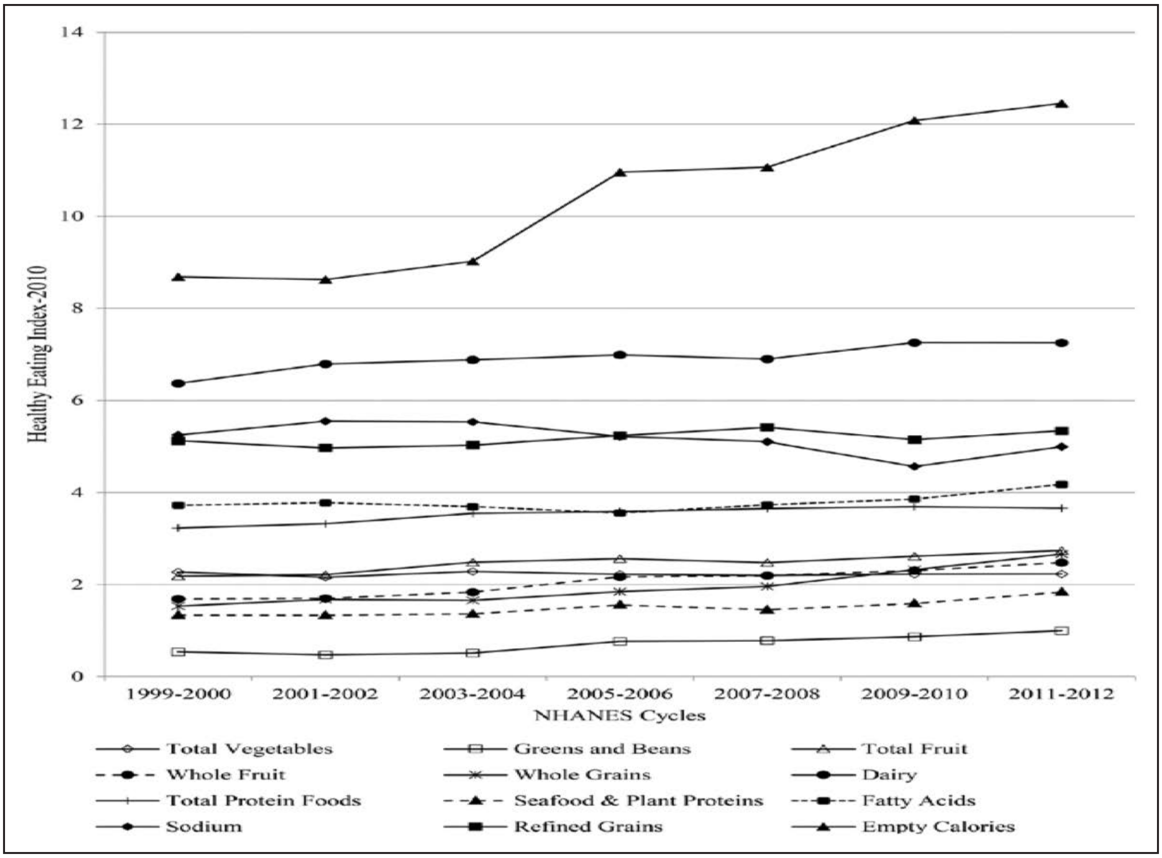


Chart 5-7. Mean Healthy Eating Index (HEI)-2010 component scores in children and adolescents aged 2 to 18 years according to NHANES survey cycles.

Sizes of the study population were as follows: N=3590 for 1999 to 2000, N=4039 for 2001 to 2002, N=6841 for 2003 to 2004, N=7215 for 2005 to 2006, N=5402 for 2007 to 2008, N=5751 for 2009 to 2010, and N=5649 for 2011 to 2012. For total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, and fatty acids, higher scores corresponded to higher intakes. For refined grains, sodium, and empty calories, higher scores corresponded to lower intakes. The HEI-2010 component score increased by 3.8 points for empty calories; 1.1 points for whole grains; 0.9 points for dairy; 0.8 points for whole fruit; 0.6 points for total fruit; 0.5 points for seafood and plant proteins, greens and beans, and fatty acids; 0.4 points for total protein foods (all *P* for linear trend <0.001); and 0.2 points for refined grains (*P* for linear trend=0.01). The HEI-2010 component score decreased by 0.2 points for sodium (*P* for trend <0.001). There was no significant improvement for total vegetable intake over the period.
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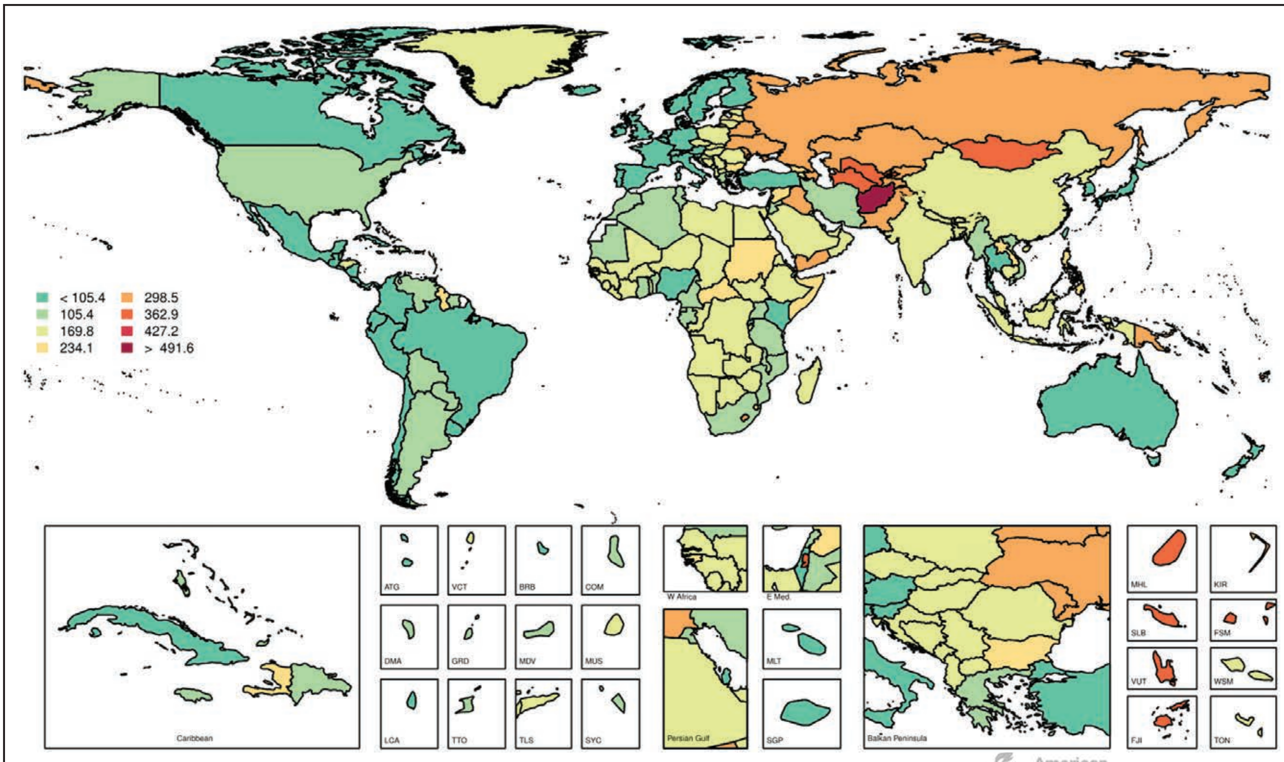

Chart 5-8. Age-standardized global mortality rates attributable to dietary risks per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016 with permission.[121] Copyright © 2017, University of Washington.

REFERENCES

1. American Heart Association. My Life Check – Life's Simple 7. https://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check--lifes-simple-7. Accessed November 9, 2018.
2. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
3. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2018 update: a report from the American Heart Association [published correction appears in *Circulation*. 2018;137:e493]. *Circulation*. 2018;137:e67–e492. doi: 10.1161/CIR.0000000000000558
4. Rehm CD, Peñalvo JL, Afshin A, Mozaffarian D. Dietary intake among US adults, 1999-2012. *JAMA*. 2016;315:2542–2553. doi: 10.1001/jama.2016.7491
5. Singh GM, Micha R, Khatibzadeh S, Shi P, Lim S, Andrews KG, Engell RE, Ezzati M, Mozaffarian D; on behalf of the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NutriCoDE). Global, regional, and national consumption of sugar-sweetened beverages, fruit juices, and milk: a systematic assessment of beverage intake in 187 countries. *PLoS One* 2015;10:e0124845. doi: 10.1371/journal.pone.0124845
6. Popkin BM, Hawkes C. Sweetening of the global diet, particularly beverages: patterns, trends, and policy responses. *Lancet Diabetes Endocrinol*. 2016;4:174–186. doi: 10.1016/S2213-8587(15)00419-2
7. Colchero MA, Rivera-Dommarco J, Popkin BM, Ng SW. In Mexico, evidence of sustained consumer response two years after implementing a sugar-sweetened beverage tax. *Health Aff (Millwood)*. 2017;36:564–571. doi: 10.1377/hlthaff.2016.1231
8. Silver LD, Ng SW, Ryan-Ibarra S, Taillie LS, Induni M, Miles DR, Poti JM, Popkin BM. Changes in prices, sales, consumer spending, and beverage consumption one year after a tax on sugar-sweetened beverages in Berkeley, California, US: a before-and-after study. *PLoS Med*. 2017;14:e1002283. doi: 10.1371/journal.pmed.1002283
9. Powles J, Fahimi S, Micha R, Khatibzadeh S, Shi P, Ezzati M, Engell RE, Lim SS, Danaei G, Mozaffarian D; on behalf of the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NutriCoDE). Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. *BMJ Open*. 2013;3:e003733. doi: 10.1136/bmjopen-2013-003733
10. Barberio AM, Sumar N, Trieu K, Lorenzetti DL, Tarasuk V, Webster J, Campbell NRC, McLaren L. Population-level interventions in government jurisdictions for dietary sodium reduction: a Cochrane Review. *Int J Epidemiol*. 2017;46:1551–1405. doi: 10.1093/ije/dyw361
11. Laatikainen T, Pietinen P, Valsta L, Sundvall J, Reinivuo H, Tuomilehto J. Sodium in the Finnish diet: 20-year trends in urinary sodium excretion among the adult population. *Eur J Clin Nutr*. 2006;60:965–970. doi: 10.1038/sj.ejcn.1602406
12. Kastarinen MJ, Salomaa VV, Vartiainen EA, Jousilahti PJ, Tuomilehto JO, Puska PM, Nissinen AM. Trends in blood pressure levels and control of hypertension in Finland from 1982 to 1997. *J Hypertens*. 1998;16:1379–1387.

13. He FJ, Brinsden HC, MacGregor GA. Salt reduction in the United Kingdom: a successful experiment in public health. *J Hum Hypertens*. 2014;28:345–352. doi: 10.1038/jhh.2013.105
14. Cogswell ME, Loria CM, Terry AL, Zhao L, Wang CY, Chen TC, Wright JD, Pfeiffer CM, Merritt R, Moy CS, Appel LJ. Estimated 24-hour urinary sodium and potassium excretion in US adults. *JAMA*. 2018;319:1209–1220. doi: 10.1001/jama.2018.1156
15. Harnack LJ, Cogswell ME, Shikany JM, Gardner CD, Gillespie C, Loria CM, Zhou X, Yuan K, Steffen LM. Sources of sodium in US adults from 3 Geographic regions. *Circulation*. 2017;135:1775–1783. doi: 10.1161/CIRCULATIONAHA.116.024446
16. Quader ZS, Zhao L, Gillespie C, Cogswell ME, Terry AL, Moshfegh A, Rhodes D. Sodium intake among persons aged ≥2 years: United States, 2013–2014. *MMWR Morb Wkly Rep*. 2017;66:324. doi: 10.15585/mmwr.mm6612a3
17. US Department of Agriculture and US Department of Health and Human Services. *Dietary Guidelines for Americans, 2015–2020*. 8th ed. Washington, DC: US Government Printing Office; December 2015. https://health.gov/dietaryguidelines/2015/guidelines/. Accessed September 19, 2016.
18. Micha R, Peñalvo JL, Cudhea F, Imamura F, Rehm CD, Mozaffarian D. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. *JAMA*. 2017;317:912–924. doi: 10.1001/jama.2017.0947
19. USDA Economic Research Service. Food price outlook: changes in food price indexes, 2015 through 2018. USDA Economic Research Service website. https://www.ers.usda.gov/data-products/food-price-outlook.aspx. Accessed August 30, 2017.
20. USDA Economic Research Service. Food expenditures. USDA Economic Research Service website. https://www.ers.usda.gov/data-products/food-expenditures.aspx. Accessed May 15, 2018.
21. Rao M, Afshin A, Singh G, Mozaffarian D. Do healthier foods and diet patterns cost more than less healthy options? A systematic review and meta-analysis. *BMJ Open*. 2013;3:e004277. doi: 10.1136/bmjopen-2013-004277
22. Mozaffarian RS, Andry A, Lee RM, Wiecha JL, Gortmaker SL. Price and healthfulness of snacks in 32 YMCA after-school programs in 4 US metropolitan areas, 2006-2008. *Prev Chronic Dis*. 2012;9:E38.
23. Beets MW, Weaver RG, Turner-McGrievy G, Huberty J, Ward DS, Freedman D, Hutto B, Moore JB, Beighle A. Making healthy eating policy practice: a group randomized controlled trial on changes in snack quality, costs, and consumption in after-school programs. *Am J Health Promot*. 2016;30:521–531. doi: 10.4278/ajhp.141001-QUAN-486
24. Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, Goldman L. Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med*. 2010;362:590–599. doi: 10.1056/NEJMoa0907355
25. Webb M, Fahimi S, Singh GM, Khatibzadeh S, Micha R, Powles J, Mozaffarian D. Cost effectiveness of a government supported policy strategy to decrease sodium intake: global analysis across 183 nations. *BMJ*. 2017;356:i6699. doi: 10.1136/bmj.i6699
26. Ahluwalia N, Andreeva VA, Kesse-Guyot E, Hercberg S. Dietary patterns, inflammation and the metabolic syndrome. *Diabetes Metab*. 2013;39:99–110. doi: 10.1016/j.diabet.2012.08.007
27. Harmon BE, Boushey CJ, Shvetsov YB, Ettienne R, Reedy J, Wilkens LR, Le Marchand L, Henderson BE, Kolonel LN. Associations of key diet-quality indexes with mortality in the Multiethnic Cohort: the Dietary Patterns Methods Project. *Am J Clin Nutr*. 2015;101:587–597. doi: 10.3945/ajcn.114.090688
28. Wang DD, Leung CW, Li Y, Ding EL, Chiuve SE, Hu FB, Willett WC. Trends in dietary quality among adults in the United States, 1999 through 2010. *JAMA Intern Med*. 2014;174:1587–1595. doi: 10.1001/jamainternmed.2014.3422
29. Gu X, Tucker KL. Dietary quality of the US child and adolescent population: trends from 1999 to 2012 and associations with the use of federal nutrition assistance programs. *Am J Clin Nutr*. 2017;105:194–202. doi: 10.3945/ajcn.116.135095
30. Grummon AH, Taillie LS. Nutritional profile of Supplemental Nutrition Assistance Program household food and beverage purchases. *Am J Clin Nutr*. 2017;105:1433–1442. doi: 10.3945/ajcn.116.147173
31. Tester JM, Leung CW, Crawford PB. Revised WIC food package and children's diet quality. *Pediatrics*. 2016;137:e20153557. doi: 10.1542/peds.2015-3557
32. Imamura F, Micha R, Khatibzadeh S, Fahimi S, Shi P, Powles J, Mozaffarian D; Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NutriCoDE). Dietary quality among men and women in 187 countries in 1990 and 2010: a systematic assessment. *Lancet Glob Health*. 2015;3:e132–e142. doi: 10.1016/S2214-109X(14)70381-X
33. Duffey KJ, Popkin BM. Energy density, portion size, and eating occasions: contributions to increased energy intake in the United States, 1977-2006. *PLoS Med*. 2011;8:e1001050. doi: 10.1371/journal.pmed.1001050
34. Ford ES, Dietz WH. Trends in energy intake among adults in the United States: findings from NHANES. *Am J Clin Nutr*. 2013;97:848–853. doi: 10.3945/ajcn.112.052662
35. Gross LS, Li L, Ford ES, Liu S. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. *Am J Clin Nutr*. 2004;79:774–779. doi: 10.1093/ajcn/79.5.774
36. Piernas C, Popkin BM. Food portion patterns and trends among U.S. children and the relationship to total eating occasion size, 1977–2006. *J Nutr*. 2011;141:1159–1164. doi: 10.3945/jn.111.138727
37. Duffey KJ, Popkin BM. Causes of increased energy intake among children in the U.S., 1977-2010. *Am J Prev Med*. 2013;44:e1–e8. doi: 10.1016/j.amepre.2012.10.011
38. Malik VS, Pan A, Willett WC, Hu FB. Sugar-sweetened beverages and weight gain in children and adults: a systematic review and meta-analysis. *Am J Clin Nutr*. 2013;98:1084–1102. doi: 10.3945/ajcn.113.058362
39. Del Gobbo LC, Falk MC, Feldman R, Lewis K, Mozaffarian D. Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. *Am J Clin Nutr*. 2015;102:1347–1356. doi: 10.3945/ajcn.115.110965
40. Ebbeling CB, Swain JF, Feldman HA, Wong WW, Hachey DL, Garcia-Lago E, Ludwig DS. Effects of dietary composition on energy expenditure during weight-loss maintenance. *JAMA*. 2012;307:2627–2634. doi: 10.1001/jama.2012.6607
41. Gardner CD, Trepanowski JF, Del Gobbo LC, Hauser ME, Rigdon J, Ioannidis JPA, Desai M, King AC. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial [published corrections appear in *JAMA*. 2018;319:1386 and *JAMA*. 2018;319:1728]. *JAMA*. 2018;319:667–679. doi: 10.1001/jama.2018.0245
42. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Martínez-González MA. Retraction and republication: primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279–90 [corrected and republished in *N Engl J Med*. 2018;378:e34]. *N Engl J Med*. 2018;378:2441–2442. doi: 10.1056/NEJMc1806491
43. Sofi F, Dinu M, Pagliai G, Cesari F, Gori AM, Sereni A, Becatti M, Fiorillo C, Marcucci R, Casini A. Low-calorie vegetarian versus Mediterranean diets for reducing body weight and improving cardiovascular risk profile: CARDIVEG Study (Cardiovascular Prevention With Vegetarian Diet). *Circulation*. 2018;137:1103–1113. doi: 10.1161/CIRCULATIONAHA.117.030088
44. He FJ, Li J, Macgregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. *BMJ*. 2013;346:f1325. 10.1136/bmj.f1325
45. Mozaffarian D, Fahimi S, Singh GM, Micha R, Khatibzadeh S, Engell RE, Lim S, Danaei G, Ezzati M, Powles J; for the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group. Global sodium consumption and death from cardiovascular causes. *N Engl J Med*. 2014;371:624–634. doi: 10.1056/NEJMoa1304127
46. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER 3rd, Simons-Morton DG, Karanja N, Lin PH; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med*. 2001;344:3–10. doi: 10.1056/NEJM200101043440101.
47. Juraschek SP, Miller ER 3rd, Weaver CM, Appel LJ. Effects of sodium reduction and the DASH diet in relation to baseline blood pressure. *J Am Coll Cardiol*. 2017;70:2841–2848. doi: 10.1016/j.jacc.2017.10.011
48. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER 3rd, Conlin PR, Erlinger TP, Rosner BA, Laranjo NM, Charleston J, McCarron P, Bishop LM; for the OmniHeart Collaborative Research Group. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA*. 2005;294:2455–2464. doi: 10.1001/jama.294.19.2455

49. Gadgil MD, Appel LJ, Yeung E, Anderson CA, Sacks FM, Miller ER 3rd. The effects of carbohydrate, unsaturated fat, and protein intake on measures of insulin sensitivity: results from the OmniHeart trial. *Diabetes Care*. 2013;36:1132–1137. doi: 10.2337/dc12-0869
50. Gay HC, Rao SG, Vaccarino V, Ali MK. Effects of different dietary interventions on blood pressure: systematic review and meta-analysis of randomized controlled trials. *Hypertension*. 2016;67:733–739. doi: 10.1161/HYPERTENSIONAHA.115.06853
51. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr*. 2003;77:1146–1155. doi: 10.1093/ajcn/77.5.1146
52. Brassard D, Tessier-Grenier M, Allaire J, Rajendiran E, She Y, Ramprasath V, Gigleux I, Talbot D, Levy E, Tremblay A, Jones PJ, Couture P, Lamarche B. Comparison of the impact of SFAs from cheese and butter on cardiometabolic risk factors: a randomized controlled trial. *Am J Clin Nutr*. 2017;105:800–809. doi: 10.3945/ajcn.116.150300
53. Uauy R, Aro A, Clarke R. WHO Scientific Update on trans fatty acids: summary and conclusions. *Eur J Clin Nutr*. 2009;63:S68–S75.
54. Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. *J Hypertens*. 2002;20:1493–1499.
55. Imamura F, Micha R, Wu JH, de Oliveira Otto MC, Otite FO, Abioye AI, Mozaffarian D. Effects of saturated fat, polyunsaturated fat, monounsaturated fat, and carbohydrate on glucose-insulin homeostasis: a systematic review and meta-analysis of randomised controlled feeding trials. *PLoS Med*. 2016;13:e1002087. doi: 10.1371/journal.pmed.1002087
56. Howard BV, Van Horn L, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, Kuller LH, LaCroix AZ, Langer RD, Lasser NL, Lewis CE, Limacher MC, Margolis KL, Mysiw WJ, Ockene JK, Parker LM, Perri MG, Phillips L, Prentice RL, Robbins J, Rossouw JE, Sarto GE, Schatz IJ, Snetselaar LG, Stevens VJ, Tinker LF, Trevisan M, Vitolins MZ, Anderson GL, Assaf AR, Bassford T, Beresford SA, Black HR, Brunner RL, Brzyski RG, Caan B, Chlebowski RT, Gass M, Granek I, Greenland P, Hays J, Heber D, Heiss G, Hendrix SL, Hubbell FA, Johnson KC, Kotchen JM. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295:655–666. doi: 10.1001/jama.295.6.655
57. Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases. Diet, nutrition and the prevention of chronic diseases: report of a joint WHO/FAO expert consultation, Geneva, 28 January – 1 February 2002. WHO Technical Report Series No. 916. 2003. http://www.who.int/dietphysicalactivity/publications/trs916/en/gsfao_introduction.pdf. Accessed June 14, 2016.
58. Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr*. 2010;91:535–546. doi: 10.3945/ajcn.2009.27725
59. Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Bälter K, Fraser GE, Goldbourt U, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. *Am J Clin Nutr*. 2009;89:1425–1432. doi: 10.3945/ajcn.2008.27124
60. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med*. 2010;7:e1000252. doi: 10.1371/journal.pmed.1000252
61. Farvid MS, Ding M, Pan A, Sun Q, Chiuve SE, Steffen LM, Willett WC, Hu FB. Dietary linoleic acid and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies. *Circulation*. 2014;130:1568–1578. doi: 10.1161/CIRCULATIONAHA.114.010236
62. Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Trans fatty acids and cardiovascular disease. *N Engl J Med*. 2006;354:1601–1613. doi: 10.1056/NEJMra054035
63. Barclay AW, Petocz P, McMillan-Price J, Flood VM, Prvan T, Mitchell P, Brand-Miller JC. Glycemic index, glycemic load, and chronic disease risk: a meta-analysis of observational studies. *Am J Clin Nutr*. 2008;87:627–637. doi: 10.1093/ajcn/87.3.627
64. Dong JY, Zhang YH, Wang P, Qin LQ. Meta-analysis of dietary glycemic load and glycemic index in relation to risk of coronary heart disease. *Am J Cardiol*. 2012;109:1608–1613. doi: 10.1016/j.amjcard.2012.01.385
65. Yu D, Zhang X, Shu XO, Cai H, Li H, Ding D, Hong Z, Xiang YB, Gao YT, Zheng W, Yang G. Dietary glycemic index, glycemic load, and refined carbohydrates are associated with risk of stroke: a prospective cohort study in urban Chinese women. *Am J Clin Nutr*. 2016;104:1345–1351. doi: 10.3945/ajcn.115.129379
66. Dauchet L, Amouyel P, Dallongeville J. Fruit and vegetable consumption and risk of stroke: a meta-analysis of cohort studies. *Neurology*. 2005;65:1193–1197. doi: 10.1212/01.wnl.0000180600.09719.53
67. Dauchet L, Amouyel P, Hercberg S, Dallongeville J. Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. *J Nutr*. 2006;136:2588–2593. doi: 10.1093/jn/136.10.2588
68. Wang X, Ouyang Y, Liu J, Zhu M, Zhao G, Bao W, Hu FB. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies [published correction appears in *BMJ*. 2014;349:5472]. *BMJ*. 2014;349:g4490. doi: 10.1136/bmj.g4490
69. Du H, Li L, Bennett D, Guo Y, Key TJ, Bian Z, Sherliker P, Gao H, Chen Y, Yang L, Chen J, Wang S, Du R, Su H, Collins R, Peto R, Chen Z; China Kadoorie Biobank Study. Fresh fruit consumption and major cardiovascular disease in China. *N Engl J Med*. 2016;374:1332–1343. doi: 10.1056/NEJMoa1501451
70. Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, Tonstad S, Vatten LJ, Riboli E, Norat T. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ*. 2016;353:i2716. doi: 10.1136/bmj.i2716
71. Harris WS, Mozaffarian D, Lefevre M, Toner CD, Colombo J, Cunnane SC, Holden JM, Klurfeld DM, Morris MC, Whelan J. Towards establishing dietary reference intakes for eicosapentaenoic and docosahexaenoic acids. *J Nutr*. 2009;139:804S–819S. doi: 10.3945/jn.108.101329
72. Nahab F, Pearson K, Frankel MR, Ard J, Safford MM, Kleindorfer D, Howard VJ, Judd S. Dietary fried fish intake increases risk of CVD: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Public Health Nutr*. 2016;19:3327–3336. doi: 10.1017/S136898001600152X
73. Micha R, Wallace SK, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. *Circulation*. 2010;121:2271–2283. doi: 10.1161/CIRCULATIONAHA.109.924977
74. Guasch-Ferré M, Liu X, Malik VS, Sun Q, Willett WC, Manson JE, Rexrode KM, Li Y, Hu FB, Bhupathiraju SN. Nut consumption and risk of cardiovascular disease. *J Am Coll Cardiol*. 2017;70:2519–2532. doi: 10.1016/j.jacc.2017.09.035
75. Afshin A, Micha R, Khatibzadeh S, Mozaffarian D. Consumption of nuts and legumes and risk of incident ischemic heart disease, stroke, and diabetes: a systematic review and meta-analysis. *Am J Clin Nutr*. 2014;100:278–288. doi: 10.3945/ajcn.113.076901
76. Chen M, Li Y, Sun Q, Pan A, Manson JE, Rexrode KM, Willett WC, Rimm EB, Hu FB. Dairy fat and risk of cardiovascular disease in 3 cohorts of US adults. *Am J Clin Nutr*. 2016;104:1209–1217. doi: 10.3945/ajcn.116.134460
77. Pimpin L, Wu JH, Haskelberg H, Del Gobbo L, Mozaffarian D. Is butter back? A systematic review and meta-analysis of butter consumption and risk of cardiovascular disease, diabetes, and total mortality. *PLoS One*. 2016;11:e0158118. doi: 10.1371/journal.pone.0158118
78. Kalogeropoulos AP, Georgiopoulou VV, Murphy RA, Newman AB, Bauer DC, Harris TB, Yang Z, Applegate WB, Kritchevsky SB. Dietary sodium content, mortality, and risk for cardiovascular events in older adults: the Health, Aging, and Body Composition (Health ABC) Study. *JAMA Intern Med*. 2015;175:410–419. doi: 10.1001/jamainternmed.2014.6278
79. Mente A, O'Donnell M, Rangarajan S, Dagenais G, Lear S, McQueen M, Diaz R, Avezum A, Lopez-Jaramillo P, Lanas F, Li W, Lu Y, Yi S, Rensheng L, Iqbal R, Mony P, Yusuf R, Yusoff K, Szuba A, Oguz A, Rosengren A, Bahonar A, Yusufali A, Schutte AE, Chifamba J, Mann JF, Anand SS, Teo K, Yusuf S; PURE, EPIDREAM and ONTARGET/TRANSCEND Investigators. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. *Lancet*. 2016;388:465–475. doi: 10.1016/S0140-6736(16)30467-6
80. O'Donnell M, Mente A, Rangarajan S, McQueen MJ, Wang X, Liu L, Yan H, Lee SF, Mony P, Devanath A, Rosengren A, Lopez-Jaramillo P, Diaz R, Avezum A, Lanas F, Yusoff K, Iqbal R, Ilow R, Mohammadifard N, Gulec S, Yusufali AH, Kruger L, Yusuf R, Chifamba J, Kabali C, Dagenais G, Lear SA, Teo K, Yusuf S; for the PURE Investigators. Urinary sodium and potassium excretion, mortality, and cardiovascular events [published correction appears in *N Engl J Med*. 2014;371:1267]. *N Engl J Med*. 2014;371:612–623. doi: 10.1056/NEJMoa1311889
81. Whelton PK, Appel LJ, Sacco RL, Anderson CA, Antman EM, Campbell N, Dunbar SB, Frohlich ED, Hall JE, Jessup M, Labarthe DR, MacGregor GA, Sacks FM, Stamler J, Vafiadis DK, Van Horn LV. Sodium, blood pressure,

and cardiovascular disease: further evidence supporting the American Heart Association sodium reduction recommendations [published correction appears in *Circulation*. 2013;127:e263]. *Circulation*. 2012;126:2880–2889. doi: 10.1161/CIR.0b013e318279acbf

82. Cobb LK, Anderson CA, Elliott P, Hu FB, Liu K, Neaton JD, Whelton PK, Woodward M, Appel LJ; on behalf of the American Heart Association Council on Lifestyle and Metabolic Health. Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes: a science advisory from the American Heart Association. *Circulation*. 2014;129:1173–1186. doi: 10.1161/CIR.0000000000000015
83. Cook NR, Obarzanek E, Cutler JA, Buring JE, Rexrode KM, Kumanyika SK, Appel LJ, Whelton PK; Trials of Hypertension Prevention Collaborative Research Group. Joint effects of sodium and potassium intake on subsequent cardiovascular disease: the Trials of Hypertension Prevention follow-up study. *Arch Intern Med*. 2009;169:32–40. doi: 10.1001/archinternmed.2008.523
84. Cook NR, Appel LJ, Whelton PK. Sodium intake and all-cause mortality over 20 years in the Trials of Hypertension Prevention. *J Am Coll Cardiol*. 2016;68:1609–1617. doi: 10.1016/j.jacc.2016.07.745
85. Schwingshackl L, Boeing H, Stelmach-Mardas M, Gottschald M, Dietrich S, Hoffmann G, Chaimani A. Dietary supplements and risk of cause-specific death, cardiovascular disease, and cancer: a systematic review and meta-analysis of primary prevention trials. *Adv Nutr*. 2017;8:27–39. doi: 10.3945/an.116.013516
86. Bailey RL, Gahche JJ, Miller PE, Thomas PR, Dwyer JT. Why US adults use dietary supplements. *JAMA Intern Med*. 2013;173:355–361. doi: 10.1001/jamainternmed.2013.2299
87. Bailey RL, Fulgoni VL 3rd, Keast DR, Dwyer JT. Dietary supplement use is associated with higher intakes of minerals from food sources. *Am J Clin Nutr*. 2011;94:1376–1381. doi: 10.3945/ajcn.111.020289
88. Bailey RL, Fulgoni VL 3rd, Keast DR, Dwyer JT. Examination of vitamin intakes among US adults by dietary supplement use. *J Acad Nutr Diet*. 2012;112:657–663.e4. doi: 10.1016/j.jand.2012.01.026
89. Chung M, Tang AM, Fu Z, Wang DD, Newberry SJ. Calcium intake and cardiovascular disease risk: an updated systematic review and meta-analysis [published correction appears in *Ann Intern Med*. 2017;166:687]. *Ann Intern Med*. 2016;165:856–866. doi: 10.7326/M16-1165
90. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. [published corrections appear in *Lancet*. 2001;357:642 and *Lancet*. 2007;369:106]. *Lancet*. 1999;354:447–455. doi: 10.1016/S0140-6736(99)07072-5
91. Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, Belanger C, LaMotte F, Gaziano JM, Ridker PM, Willett W, Peto R. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med*. 1996;334:1145–1149. doi: 10.1056/NEJM199605023341801
92. Losonczy KG, Harris TB, Havlik RJ. Vitamin E and vitamin C supplement use and risk of all-cause and coronary heart disease mortality in older persons: the Established Populations for Epidemiologic Studies of the Elderly. *Am J Clin Nutr*. 1996;64:190–196. doi: 10.1093/ajcn/64.2.190
93. Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC. Vitamin E consumption and the risk of coronary disease in women. *N Engl J Med*. 1993;328:1444–1449. doi: 10.1056/NEJM199305203282003
94. Vivekananthan DP, Penn MS, Sapp SK, Hsu A, Topol EJ. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials [published correction appears in *Lancet*. 2004;363:662]. *Lancet*. 2003;361:2017–2023. doi: 10.1016/S0140-6736(03)13637-9
95. Ye Y, Li J, Yuan Z. Effect of antioxidant vitamin supplementation on cardiovascular outcomes: a meta-analysis of randomized controlled trials. *PLoS One*. 2013;8:e56803. doi: 10.1371/journal.pone.0056803
96. Siscovick DS, Barringer TA, Fretts AM, Wu JH, Lichtenstein AH, Costello RB, Kris-Etherton PM, Jacobson TA, Engler MB, Alger HM, Appel LJ, Mozaffarian D; on behalf of the American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: a science advisory from the American Heart Association. *Circulation*. 2017;135:e867–e884. doi: 10.1161/CIR.0000000000000482
97. Aung T, Halsey J, Kromhout D, Gerstein HC, Marchioli R, Tavazzi L, Geleijnse JM, Rauch B, Ness A, Galan P, Chew EY, Bosch J, Collins R, Lewington S, Armitage J, Clarke R; Omega-3 Treatment Trialists' Collaboration. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77 917 individuals. *JAMA Cardiol*. 2018;3:225–234. doi: 10.1001/jamacardio.2017.5205
98. Kwok CS, Umar S, Myint PK, Mamas MA, Loke YK. Vegetarian diet, Seventh Day Adventists and risk of cardiovascular mortality: a systematic review and meta-analysis. *Int J Cardiol*. 2014;176:680–686. doi: 10.1016/j.ijcard.2014.07.080
99. Satija A, Bhupathiraju SN, Rimm EB, Spiegelman D, Chiuve SE, Borgi L, Willett WC, Manson JE, Sun Q, Hu FB. Plant-based dietary patterns and incidence of type 2 diabetes in US men and women: results from three prospective cohort studies. *PLoS Med*. 2016;13:e1002039. doi: 10.1371/journal.pmed.1002039
100. Mitrou PN, Kipnis V, Thiébaut AC, Reedy J, Subar AF, Wirfält E, Flood A, Mouw T, Hollenbeck AR, Leitzmann MF, Schatzkin A. Mediterranean dietary pattern and prediction of all-cause mortality in a US population: results from the NIH-AARP Diet and Health Study. *Arch Intern Med*. 2007;167:2461–2468. doi: 10.1001/archinte.167.22.2461
101. Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu FB. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women [published correction appears in *Arch Intern Med*. 2008;168:1276]. *Arch Intern Med*. 2008;168:713–720. doi: 10.1001/archinte.168.7.713
102. Fung TT, Rexrode KM, Mantzoros CS, Manson JAE, Willett WC, Hu FB. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women [published correction appears in *Circulation*. 2009;119:e379] *Circulation*. 2009;119:1093–1100. doi: 10.1161/CIRCULATIONAHA.108.816736
103. Heidemann C, Schulze MB, Franco OH, van Dam RM, Mantzoros CS, Hu FB. Dietary patterns and risk of mortality from cardiovascular disease, cancer, and all causes in a prospective cohort of women. *Circulation*. 2008;118:230–237. doi: 10.1161/CIRCULATIONAHA.108.771881
104. Brunner EJ, Mosdøl A, Witte DR, Martikainen P, Stafford M, Shipley MJ, Marmot MG. Dietary patterns and 15-y risks of major coronary events, diabetes, and mortality. *Am J Clin Nutr*. 2008;87:1414–1421. doi: 10.1093/ajcn/87.5.1414
105. Fitzgerald KC, Chiuve SE, Buring JE, Ridker PM, Glynn RJ. Comparison of associations of adherence to a Dietary Approaches to Stop Hypertension (DASH)-style diet with risks of cardiovascular disease and venous thromboembolism. *J Thromb Haemost*. 2012;10:189–198. doi: 10.1111/j.1538-7836.2011.04588.x
106. Heidemann C, Hoffmann K, Spranger J, Klipstein-Grobusch K, Möhlig M, Pfeiffer AF, Boeing H; European Prospective Investigation into Cancer and Nutrition (EPIC)–Potsdam Study Cohort. A dietary pattern protective against type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)–Potsdam Study cohort. *Diabetologia*. 2005;48:1126–1134. doi: 10.1007/s00125-005-1743-1
107. Joosten MM, Grobbee DE, van der A DL, Verschuren WM, Hendriks HF, Beulens JW. Combined effect of alcohol consumption and lifestyle behaviors on risk of type 2 diabetes. *Am J Clin Nutr*. 2010;91:1777–1783. doi: 10.3945/ajcn.2010.29170
108. Lutsey PL, Steffen LM, Stevens J. Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. *Circulation*. 2008;117:754–761. doi: 10.1161/CIRCULATIONAHA.107.716159
109. Osler M, Heitmann BL, Gerdes LU, Jørgensen LM, Schroll M. Dietary patterns and mortality in Danish men and women: a prospective observational study. *Br J Nutr*. 2001;85:219–225.
110. van Dam RM, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Dietary patterns and risk for type 2 diabetes mellitus in U.S. men. *Ann Intern Med*. 2002;136:201–209.
111. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99:779–785.
112. Ferguson JF, Allayee H, Gerszten RE, Ideraabdullah F, Kris-Etherton PM, Ordovás JM, Rimm EB, Wang TJ, Bennett BJ; on behalf of the American Heart Association Council on Functional Genomics and Translational Biology, Council on Epidemiology and Prevention, and Stroke Council. Nutrigenomics, the microbiome, and gene-environment interactions: new directions in cardiovascular disease research, prevention, and treatment: a scientific statement from the American

Heart Association. *Circ Cardiovasc Genet*. 2016;9:291–313. doi: 10.1161/HCG.0000000000000030
113. Pirastu N, Kooyman M, Traglia M, Robino A, Willems SM, Pistis G, Amin N, Sala C, Karssen LC, Van Duijn C, Toniolo D, Gasparini P. A genome-wide association study in isolated populations reveals new genes associated to common food likings. *Rev Endocr Metab Disord*. 2016;17:209–219. doi: 10.1007/s11154-016-9354-3
114. Kumanyika S, Grier S. Targeting interventions for ethnic minority and low-income populations. *Future Child*. 2006;16:187–207.
115. Li F, Harmer PA, Cardinal BJ, Bosworth M, Acock A, Johnson-Shelton D, Moore JM. Built environment, adiposity, and physical activity in adults aged 50-75. *Am J Prev Med*. 2008;35:38–46. doi: 10.1016/j.amepre.2008.03.021
116. Sallis JF, Glanz K. The role of built environments in physical activity, eating, and obesity in childhood. *Future Child*. 2006;16:89–108.
117. Mozaffarian D, Afshin A, Benowitz NL, Bittner V, Daniels SR, Franch HA, Jacobs DR Jr, Kraus WE, Kris-Etherton PM, Krummel DA, Popkin BM, Whitsel LP, Zakai NA; on behalf of the American Heart Association Council on Epidemiology and Prevention, Council on Nutrition, Physical Activity and Metabolism, Council on Clinical Cardiology, Council on Cardiovascular Disease in the Young, Council on the Kidney in Cardiovascular Disease, Council on Peripheral Vascular Disease, and the Advocacy Coordinating Committee. Population approaches to improve diet, physical activity, and smoking habits: a scientific statement from the American Heart Association. *Circulation*. 2012;126:1514–1563. doi: 10.1161/CIR.0b013e318260a20b
118. Rummo PE, Guilkey DK, Ng SW, Popkin BM, Evenson KR, Gordon-Larsen P. Beyond supermarkets: food outlet location selection in four U.S. cities over time. *Am J Prev Med*. 2017;52:300–310. doi: 10.1016/j.amepre.2016.08.042
119. Ng SW, Poti JM, Popkin BM. Trends in racial/ethnic and income disparities in foods and beverages consumed and purchased from stores among US households with children, 2000-2013. *Am J Clin Nutr*. 2016;104:750–759. doi: 10.3945/ajcn.115.127944
120. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015 [published correction appears in *Lancet*. 2017;389:e1]. *Lancet*. 2016;388:1659–1724. doi: 10.1016/S0140-6736(16)31679-8
121. Global Burden of Disease Study 2016. Global Burden of Disease Study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed May 1, 2018.

6. OVERWEIGHT AND OBESITY

See Table 6-1 and Charts 6-1 through 6-12

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Overweight and obesity are major risk factors for CVD, including CHD, stroke,[1,2] AF,[3] VTE,[4,5] and CHF. According to NHANES 2015 to 2016, the prevalence of obesity was 39.6% of US adults and 18.5% of youths, with 7.7% of adults and 5.6% of youth having severe obesity.[6–8] The AHA has identified BMI <85th percentile in youth (aged 2–19 years) and <25 kg/m^2 in adults (aged ≥20 years) as 1 of the 7 components of ideal cardiovascular health.[9] In 2013 to 2014, 63.1% of youth and 29.6% of adults met these criteria (Chapter 2, Cardiovascular Health).

Abbreviations Used in Chapter 6

ACTION	Acute Coronary Treatment and Intervention Outcomes Network
AF	atrial fibrillation
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
AHA	American Heart Association
APCSC	Asia-Pacific Cohort Studies Collaboration
APPROACH	Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease
ARIC	Atherosclerosis Risk in Communities Study
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
BMI	body mass index
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CABG	coronary artery bypass graft
CAC	coronary artery calcification
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CVD	cardiovascular disease
DBP	diastolic blood pressure
DM	diabetes mellitus
DNA	deoxyribonucleic acid
ERFC	Emerging Risk Factor Collaboration
GBD	Global Burden of Disease
GWAS	genome-wide association study
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HD	heart disease
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
HUNT 2	Nord-Trøndelag Health Study
IHD	ischemic heart disease
IMT	intima-media thickness
IRR	incidence rate ratio
LDL-C	low-density lipoprotein cholesterol
Look AHEAD	Look: Action for Health in Diabetes
MESA	Multi-Ethnic Study of Atherosclerosis
MHO	metabolically healthy obesity
MI	myocardial infarction
NCDR	National Cardiovascular Data Registry
NCHS	National Center for Health Statistics
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHDS	National Hospital Discharge Survey
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute

(*Continued*)

Abbreviations Used in Chapter 6 Continued

OR	odds ratio
PA	physical activity
PCI	percutaneous coronary intervention
PSC	Prospective Studies Collaboration
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	relative risk
SBP	systolic blood pressure
SCD	sudden cardiac death
SD	standard deviation
SES	socioeconomic status
SNP	single-nucleotide polymorphism
SOS	Swedish Obese Subjects
STEMI	ST-segment–elevation myocardial infarction
TC	total cholesterol
UI	uncertainty interval
VTE	venous thromboembolism
WC	waist circumference
WHI	Women's Health Initiative
YRBSS	Youth Risk Behavior Surveillance System

Classification of Overweight and Obesity

- For adults, NHLBI weight categories are as follows: overweight (25.0 ≤ BMI ≤ 29.9 kg/m^2) and obese class I (BMI 30–35 kg/m^2), class II (BMI >35–39.9 kg/m^2), and class III (BMI ≥40 kg/m^2). BMI cutoffs often misclassify obesity in those with muscle mass on the upper and lower tails of the distribution. BMI categories also vary in prognostic value by race/ethnicity; they appear to overestimate risk in African Americans and underestimate risk in Asians.[10] For this reason, lower BMI cutoffs have been recommended to classify obesity and associated health risks for Asian and South Asian populations.[11]
- For youth, sex-specific BMI-for-age 2000 CDC growth charts for the United States are used,[12] and overweight is defined as 85th to <95th percentile and obesity as ≥95th percentile. These categories were previously called "at risk for overweight" and "overweight." The change in terminology reflects the labels used by organizations such as the Health and Medicine Division and the American Academy of Pediatrics. More information is available elsewhere.[13]
- A 2013 AHA scientific statement recommended that the definition of severe obesity for children

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≥2 years old and adolescents be changed to BMI ≥120% of the 95th percentile for age and sex or an absolute BMI ≥35 kg/m^2, whichever is lower.[14] This definition of severe obesity among children could better identify this small but important group compared with the other common definition of BMI ≥99th percentile for age and sex.[14]

- Current obesity guidelines define WC ≥40 inches (102 cm) for males and ≥35 inches (88 cm) for females as being associated with increased cardiovascular risk[15]; however, lower cutoffs have been recommended for various racial/ethnic groups, for example, ≥80 cm for Asian females and ≥90 cm for Asian males.[10,16] WC measurement is recommended for those with BMI of 25 to 34.9 kg/m^2, to provide additional information on CVD risk.[17]

Prevalence

Youth
(See Table 6-1 and Chart 6-1)

- According to 2015 to 2016 data from NHANES (NCHS/CDC), the overall prevalence of obesity (≥95th percentile) was 18.5%. By age group, the prevalence of obesity for children aged 2 to 5 years was 13.9%; for children aged 6 to 11 years, the prevalence was 18.4%; and for adolescents aged 12 to 19 years, the prevalence was 20.6%.[8]
- According to 2013 to 2014 data from NHANES (NCHS/CDC), the overall prevalence of overweight, including obesity, in children and adolescents aged 2 to 19 years was 33.4% based on a BMI-for-age value ≥85th percentile of the 2000 CDC growth charts: 16.2% were overweight, and 17.2% had obesity (≥95th percentile). There were no significant differences in overweight (including obesity) prevalence for boys and girls.[18]
- The prevalence of obesity was lower for NH Asian and NH white children than for NH black and Hispanic children, without significant differences between NH black and Hispanic children (Chart 6-1).[7,19]
- Extreme obesity, defined as BMI ≥120% of the 95th percentile for age and sex, was prevalent in 5.8% of youth aged 2 to 19 years, which was similar for boys (5.7%) and girls (5.9%) but was higher among Hispanic and NH black youth than among NH white youth.[18]
- According to 2013 to 2014 NHANES data, among all children aged 2 to 19 years, the prevalence of obesity was lower for NH Asian boys (12.1%) and girls (5.0%) than for NH white (15.9%, 14.6%), NH black (16.8%, 20.9%), and Hispanic (20.6%, 22.1%) boys and girls, respectively.[18,20]
- The prevalence of childhood obesity varies by SES. According to 2011 to 2014 NHANES data, for children 12 to 19 years old, the prevalence of obesity by percentage of poverty level was 22.4% for those below 100%, 25.7% for 100% to 199%, 19.7% for 200% to 399%, and 13.7% for ≥400% of poverty level.[19]
- In addition, obesity prevalence among adolescents was higher for those whose parents had a high school degree or less education (21.6%) than for adolescents whose parents had a bachelor's degree or higher (9.6%).[21,22]
- According to self-reported height and weight data from the YRBSS 2015,[23] 13.9% of US high school students had obesity and 16.0% were overweight. The percentages of obesity were higher in boys (16.8%) than girls (10.8%) and in blacks (16.8%) and Hispanics (16.4%) than in whites (12.4%). Obesity rates varied by states: The highest rates of obesity in females were observed in Kentucky and Mississippi (16.2%), and in males, West Virginia (23.4%); the lowest rates in females were observed in Nevada (6.3%), whereas for males, the lowest rates were seen in Montana (13.0%).
- A systematic review and meta-analysis of 15 prospective cohort studies with 200 777 participants showed that children and adolescents who had obesity were ≈5 times more likely to have obesity in adulthood than those who did not have obesity. Approximately 55% of children with obesity will remain with obesity in adolescence, 80% of adolescents with obesity will remain with obesity in their adulthood, and 70% of these adolescents will remain with obesity over age 30.

Adults
(See Table 6-1 and Charts 6-2 through 6-8)

- According to NHANES 2015 to 2016, among US adults aged ≥20 years:
  — The age-adjusted prevalence of obesity was 39.6% (37.9% of males and 41.1% of females), and 7.7% had class III obesity (5.6% of males and 9.7% of females).[8]
- According to NHANES 2013 to 2014, among US adults aged ≥20 years[6]:
  — The age-adjusted prevalence of obesity was 37.7% (35.0% of males and 40.4% of females), and 7.7% had class III obesity (5.5% of males and 9.9% of females).
  — Among males, the age-adjusted prevalence of obesity and class III obesity was not significantly different for NH blacks (38.0% and

7.2%), NH Asians (12.6% and data not available for class III obesity), Hispanics (37.9% and 5.4%), and NH whites (34.7% and 5.6%).
    - Among females, the age-adjusted prevalence of obesity and class III obesity, respectively, was greater in NH blacks (57.2% and 16.8%), lower in NH Asians (12.4% and data not available for class III obesity), and similar in Hispanics (46.9% and 8.7%) compared with NH whites (38.2% and 9.7%).
- According to NHANES 2011 to 2014, the age-adjusted prevalence of obesity was higher among middle-aged (40–59 years: 40.2%) and older (≥60 years: 37.0%) adults than younger (20–39 years: 32.3%) adults. This pattern (lower prevalence of obesity among younger adults) was similar for males and females, although the prevalence of obesity was higher among females (Chart 6-2).[7]
- Using NHANES 2011 to 2014 data, obesity prevalence was higher in females than males when stratified by race/ethnicity (Table 6-1 and Chart 6-3). By sex, the only significant differences were higher prevalence of obesity among NH black females than among NH black males and among Hispanic females than among Hispanic males (Table 6-1 and Chart 6-3).[7]
- Females have had a higher prevalence of class III obesity and a lower prevalence of overweight than males in all NHANES surveys from 1999 through 2014 (Chart 6-4).[19]
- In the United States, the prevalence of obesity, as estimated from self-reported height and weight in the BRFSS/CDC (2016),[24] varies by region and state. Self-reported estimates usually underestimate BMI and obesity. In 2016, by state, the prevalence of obesity was highest in Mississippi (37.3%) and West Virginia (37.7%) and lowest in Colorado (22.3%) (Chart 6-5).[24] When BRFSS data from 2014 to 2016 were combined, the prevalence of obesity by state was higher for Hispanic adults and substantially higher for NH black adults than for white adults (Charts 6-6 through 6-8).

Complications

Youth

- According to the National Longitudinal Study of Adolescent Health, compared with those with normal weight or those who were overweight, adolescents who were obese had a 16-fold increased risk of having severe obesity as adults, and 70.5% of adolescents with severe obesity maintained this weight status into adulthood.[25]
- Children and adolescents who are overweight and have obesity are at increased risk for future adverse health effects, including the following[26]:
    - Increased prevalence of traditional cardiovascular risk factors such as hypertension, hyperlipidemia, and DM. Among 8579 youths in the NHANES study, higher BMI was associated with higher SBP and DBP, lower HDL, and high triglyceride and HbA_{1c} levels.[27,28]
    - Poor school performance, tobacco use, alcohol use, premature sexual behavior, and poor diet.
    - Other associated health conditions, such as asthma, hepatic steatosis, sleep apnea, stroke, some cancers (breast, colon, and kidney), renal insufficiency, musculoskeletal disorders, gallbladder disease, and reproductive abnormalities.
- Data from 4 Finnish cohort studies examining childhood and adult BMI with a mean follow-up of 23 years found that children who were overweight or had obesity and had obesity in their adulthood had an increased risk of type 2 DM (RR, 5.4), hypertension (RR, 2.7), dyslipidemia (high LDL-C: RR, 1.8; low HDL-C: RR, 2.1; high triglycerides: RR, 3.0), and carotid atherosclerosis (RR, 1.7), whereas those who achieved normal weight by adulthood had risks comparable to individuals who never had obesity.[29]
- The CARDIA study showed that young adults who were overweight or had obesity had lower self-reported physical health-related quality of life than normal-weight participants 20 years later.[30]

Adults
(See Chart 6-9)

- Obesity is associated with increased lifetime risk of CVD and increased prevalence of type 2 DM, hypertension, dyslipidemia, sleep-disordered breathing, VTE, AF, and dementia.[31,32]
- Analyses of continuous BMI show the risk of type 2 DM increases with increasing BMI.[33]
- Among 68 070 adult participants across multiple NHANES surveys, the decline in BP in recent birth cohorts slowed, mediated by BMI.[34]
- Another systematic review and meta-analysis of 37 studies showed that high childhood BMI was associated with an increased incidence of adult DM (OR, 1.70; 95% CI, 1.30–2.22), CHD (OR, 1.20; 95% CI, 1.10–1.31), and a range of cancers, but not stroke or breast cancer; however, the accuracy of childhood BMI predicting any adult morbidity was low. Only 31% of future DM and 22% of future hypertension and CHD occurred in those who as youth aged ≥12 years had been classified as overweight or who had obesity. Only

20% of future adult cancers occurred in children classified as overweight or who had obesity.[35]

- Another study examining longitudinal data from 2.3 million adolescents (aged 16–19 years) demonstrated increased cardiovascular mortality in adulthood in youth with obesity compared with youth with BMI in the 5th to 24th percentile, with an HR of 4.9 (95% CI, 3.9–6.1) for death attributable to CHD, 2.6 (95% CI, 1.7–4.1) for death attributable to stroke, 2.1 (95% CI, 1.5–2.9) for sudden death, and 3.5 (95% CI, 2.9–4.1) for death attributable to total cardiovascular causes, after adjustment for sex, age, birth year, sociodemographic characteristics, and height.[36]
- A meta-analysis of 123 cohorts with 1.4 million adults and 52 000 CVD events reported that associations of BMI with IHD, hypertensive HD, stroke, and DM declined with advancing age (Chart 6-9) but were largely similar by sex and by region. The RRs for 5-kg/m^2 higher BMI for ages 55 to 64 years ranged from 1.44 (95% CI, 1.40–1.48) for IHD to 2.32 (95% CI, 2.04–2.63) for DM. On the basis of their data, the authors suggested that the theoretical minimum-risk exposure distribution for BMI is 21 to 23 kg/m^2 ± 1.1 to 1.8 kg/m^2 (Chart 6-9).[37]
- Cardiovascular risks might be even higher with class III obesity than with class I or class II obesity.[38] Among 156 775 postmenopausal females in the WHI, for severe obesity versus normal BMI, HRs (95% CIs) for mortality were 1.97 (1.77–2.20) in white females, 1.55 (1.20–2.00) in African American females, and 2.59 (1.55–4.31) in Hispanic females; for CHD, HRs were 2.05 (1.80–2.35), 2.24 (1.57–3.19), and 2.95 (1.60–5.41), respectively; and for CHF, HRs were 5.01 (4.33–5.80), 3.60 (2.30–5.62), and 6.05 (2.49–14.69), respectively. However, CHD risk was strongly related to CVD risk factors across BMI categories, even in class III obesity, and CHD incidence was similar by race/ethnicity with adjustment for differences in BMI and CVD risk factors.[38]
- In a meta-analysis from 58 cohorts representing 221 934 people in 17 developed countries with 14 297 incident CVD outcomes, BMI, WC, and waist-to-hip ratio were strongly associated with intermediate risk factors of DM, higher SBP and TC, and lower HDL-C. The associations of adiposity measures (BMI, WC, waist-to-hip ratio) with CVD outcomes were attenuated after adjustment for intermediate risk factors (DM, SBP, TC, and HDL-C), along with age, sex, and smoking status. Measures of adiposity also did not substantively improve risk discrimination or reclassification when data on intermediate risk factors were included.[39]
- Obesity was cross-sectionally associated with subclinical atherosclerosis, including CAC and carotid IMT, among older adults in MESA, and this association persisted after adjustment for CVD risk factors.[40] In prospective analysis of younger adults through midlife, greater duration of overall and abdominal obesity was associated with presence of and progression of subclinical atherosclerosis in the CARDIA study.[41]
- A systematic review of 25 prospective studies examining overweight and obesity as predictors of major stroke subtypes in >2 million participants with >30 000 events in ≥4 years found an adjusted RR for ischemic stroke of 1.22 (95% CI, 1.05–1.41) in overweight individuals and an RR of 1.64 (95% CI, 1.36–1.99) for individuals with obesity relative to normal-weight individuals. RRs for hemorrhagic stroke were 1.01 (95% CI, 0.88–1.17) and 1.24 (95% CI, 0.99–1.54) for overweight individuals and individuals with obesity, respectively. These risks were graded with increasing BMI and persisted after adjustment for age, lifestyle, and other cardiovascular risk factors.[42]
- A recent mendelian randomization study of participants from 7 prospective cohorts demonstrated that genetic variants associated with higher BMI were significantly associated with incident AF, which supports a causal relationship between obesity and AF.[43]
- A recent meta-analysis of 10 case-referent studies and 4 prospective cohort studies (including ARIC)[5] reported that when individuals with BMI ≥30 kg/m^2 were compared with those with BMI <30 kg/m^2, obesity was associated with a significantly higher prevalence (OR, 2.45; 95% CI, 1.78–3.35) and incidence (RR, 2.39; 95% CI, 1.79–3.17) of VTE, although there was significant heterogeneity in the studies.[4]
- A recent meta-analysis of 15 prospective studies of midlife BMI demonstrated that the increased risk for Alzheimer disease or any dementia was 1.35 and 1.26 for overweight, respectively, and 2.04 and 1.64 for obesity, respectively.[44] The inclusion of obesity in dementia forecast models increased the estimated prevalence of dementia through 2050 by 9% in the United States and 19% in China.[45]
- A BMI paradox is often reported, with higher-BMI patients demonstrating favorable outcomes among adults with prevalent CHF, hypertension, peripheral vascular disease, and CAD; similar findings have been seen for percent body fat. However, recent studies suggest that the obesity paradox might be explained by lead-time bias, because it is not present before the development of CVD.[32,46]

- The ARISTOTLE trial reported that in adjusted analyses, higher BMI was associated with lower all-cause mortality (overweight HR, 0.67 [95% CI, 0.59–0.78]; obesity HR, 0.63 [95% CI, 0.54–0.74]), similar to an earlier study from the AFFIRM trial.[47]
- In a study of 2625 participants with new-onset DM pooled from 5 longitudinal cohort studies, rates of total, CVD, and non-CVD mortality were higher among normal-weight people than among overweight participants and participants with obesity, with adjusted HRs of 2.08 (95% CI, 1.52–2.85), 1.52 (95% CI, 0.89–2.58), and 2.32 (95% CI, 1.55–3.48), respectively.[48]
- In a study of 189 672 participants from 10 US longitudinal cohort studies, obesity was associated with a shorter total longevity and greater proportion of life lived with CVD, and higher BMI was associated with significantly higher risk of death attributable to CVD.[32]
- Recent studies have evaluated risks for MHO versus "metabolically unhealthy" or "metabolically abnormal" obesity. The definition of MHO has varied across studies, but it has often comprised 0 or 1 metabolic abnormality by metabolic syndrome criteria, sometimes excluding WC.
  - Using strict criteria of 0 metabolic syndrome components and no previous CVD diagnosis, a recent report of 10 European cohort studies (N=163 517 people) reported that the prevalence of MHO varied from 7% to 28% in females and from 2% to 19% in males.[49]
  - MHO appears to be unstable over time, with 1 study showing that 44.5% of MHO individuals transitioned to metabolically unhealthy obesity over 8 years of follow-up.[50]
  - Among younger adults in the CARDIA study, after 20 years of follow-up, 47% of people were defined as being metabolically healthy overweight (presence of 0 or 1 metabolic risk factor).[51] Among older adults in MESA, approximately half of participants with MHO developed metabolic syndrome and had increased odds of CVD (OR, 1.60; 95% CI, 1.14–2.25) compared with those with stable MHO or healthy normal weight.[52]
  - A recent meta-analysis of 22 prospective studies suggested that CVD risk was higher in MHO than metabolically healthy normal-weight participants (RR, 1.45; 95% CI, 1.20–1.70); however, the risk in MHO individuals was lower than in individuals who were metabolically unhealthy and normal weight (RR, 2.07; 95% CI, 1.62–2.65) or obese (RR, 2.31; 95% CI, 1.99–2.69).[31]
  - Other reports suggest that obesity, especially long-lasting or severe obesity, without metabolic abnormalities might not increase risk for MI but does increase risk for HF.[53,54]

Mortality

- Childhood BMIs in the highest quartile were associated with premature death as an adult in a cohort of 4857 American Indian children during a median follow-up of 23.9 years (BMI for quartile 4 versus quartile 1: IRR, 2.30; 95% CI, 1.46–3.62).[55]
- According to NHIS-linked mortality data, among young adults aged 18 to 39 years, the HR for all-cause mortality was 1.07 (95% CI, 0.91–1.26) for self-reported overweight (not including obesity), 1.41 (95% CI, 1.16–1.73) for obesity, and 2.46 (95% CI, 1.91–3.16) for extreme obesity.[56]
- On the basis of NHANES I and II data, among adults, obesity was associated with nearly 112 000 excess deaths (95% CI, 53 754–170 064) relative to normal weight in 2000. Class I obesity was associated with almost 30 000 of these excess deaths (95% CI, 8534–68 220) and class II and III obesity with >82 000 deaths (95% CI, 44 843–119 289). Underweight was associated with nearly 34 000 excess deaths (95% CI, 15 726–51 766).[57] As other studies have found,[58] being overweight but not obese was not associated with excess deaths.[57]
- A systematic review (2.88 million people and >270 000 deaths) showed that relative to normal BMI (18.5 to <25 kg/m^2), all-cause mortality was lower for overweight individuals (BMI 18.5 to <25 kg/m^2: HR, 0.94; 95% CI, 0.91–0.96) and was not elevated for class I obesity (HR, 0.95; 95% CI, 0.88–1.01). All-cause mortality was higher for obesity overall (HR, 1.18; 95% CI, 1.12–1.25) and for the subset of class II and III obesity (HR, 1.29; 95% CI, 1.18–1.41).[59]
- Fluctuation of weight is associated with cardiovascular events and death. In 9509 participants of the Treating to New Targets trial, those in the quintile of highest body weight fluctuation had the highest rates of cardiovascular events, MI, stroke, and death.[60]
- Recent meta-analysis of 3.74 million deaths among 30.3 million participants found that overweight and obesity were associated with higher risk of all-cause mortality, with lowest risks at BMI 22 to 23 kg/m^2 in healthy never-smokers and 20 to 22 kg/m^2 in never-smokers with ≥20 years of follow-up.[61]
- In a collaborative analysis of data from almost 900 000 adults in 57 prospective studies, mostly in Western Europe and North America, overall

mortality was lowest at a BMI of ≈22.5 to 25 kg/m² in both sexes and at all ages, after exclusion of early follow-up and adjustment for smoking status. Above this range, each 5-kg/m²-higher BMI was associated with ≈30% higher all-cause mortality, and no specific cause of death was inversely associated with BMI. Below 22.5 to 25 kg/m², the overall inverse association with BMI was predominantly related to strong inverse associations for smoking-related respiratory disease, and the only clearly positive association was for IHD.[62]

- In a meta-analysis of 1.46 million white adults, over a mean follow-up period of 10 years, all-cause mortality was lowest at BMI levels of 20.0 to 24.9 kg/m². Among females, compared with a BMI of 22.5 to 24.9 kg/m², the HRs for death were as follows: BMI 15.0 to 18.4 kg/m², 1.47; 18.5 to 19.9 kg/m², 1.14; 20.0 to 22.4 kg/m², 1.00; 25.0 to 29.9 kg/m², 1.13; 30.0 to 34.9 kg/m², 1.44; 35.0 to 39.9 kg/m², 1.88; and 40.0 to 49.9 kg/m², 2.51. Similar estimates were observed in males.[63]
- In 10 large population cohorts in the United States, individual-level data from adults aged 20 to 79 years with 3.2 million person-years of follow-up (1964–2015) demonstrated that overweight and obesity were associated with early development of CVD and reinforced the greater mortality associated with obesity.[32]
- According to data from the NCDR ACTION Registry–Get With The Guidelines, among patients presenting with STEMI and a BMI ≥40 kg/m², in-hospital mortality rates were higher for patients with class III obesity (OR, 1.64; 95% CI, 1.32–2.03) when class I obesity was used as the referent.[64] In the APPROACH registry of individuals after CABG and PCI, overweight and class 1 obesity (BMI 20–24.9 kg/m²) were associated with lower mortality, whereas BMI ≥40 kg/m² was associated with elevated mortality.[65] Similar results in the National Adult Cardiac Surgery registry from 2002 to 2013 showed lower mortality in overweight and obesity class I and II (OR, 0.81 [95% CI, 0.76–0.86] and 0.83 [95% CI, 0.74–0.94], respectively) relative to normal-weight individuals and greater mortality risk with underweight (OR, 1.51; 95% CI, 1.41–1.62), with these results persisting after adjustment for residual confounding and reverse causation.[66]
- In a study of 22 203 females and males from England and Scotland, metabolically unhealthy obese individuals were at an increased risk of all-cause mortality compared with MHO individuals (HR, 1.72; 95% CI, 1.23–2.41).[67]
- Relation of various anthropometric measures to mortality:
  — In a comparison of 5 different anthropometric variables (BMI, WC, hip circumference, waist-to-hip ratio, and waist-to-height ratio) in 62 223 individuals from Norway with 12 years of follow-up from the HUNT 2 study, the risk of death per SD increase in each measure was 1.02 (95% CI, 0.99–1.06) for BMI, 1.10 (95% CI, 1.06–1.14) for WC, 1.01 (95% CI, 0.97–1.05) for hip circumference, 1.15 (95% CI, 1.11–1.19) for waist-to-hip ratio, and 1.12 (95% CI, 1.08–1.16) for waist-to-height ratio. For CVD mortality, the risk of death per SD increase was 1.12 (95% CI, 1.06–1.20) for BMI, 1.19 (95% CI, 1.12–1.26) for WC, 1.06 (95% CI, 1.00–1.13) for hip circumference, 1.23 (95% CI, 1.16–1.30) for waist-to-hip ratio, and 1.24 (95% CI, 1.16–1.31) for waist-to-height ratio.[68]
- However, because BMI and WC are strongly correlated, large samples are needed to evaluate their independent contributions to risk.[15,69]
  — A recent pooled analysis of WC and mortality in 650 386 adults followed up for a median of 9 years revealed that a 5-cm increment in WC was associated with an increase in all-cause mortality at all BMI categories examined from 20 to 50 kg/m².[70]
  — Similarly, in an analysis of postmenopausal females in the WHI limited to those with BMI ≥40 kg/m², mortality, CHD, and CHF incidence all increased with WC >115 and >122 cm compared with ≤108.4 cm.[38]
  — Finally, among 14 941 males and females in ARIC, the risk of SCD was associated with higher BMI and WC, with traditional risk factors mediating the association with BMI but not with WC.[71]

Cost

Obesity costs the healthcare system, healthcare payers, and individuals with obesity.

- In the United States, the estimated annual medical cost of obesity in 2008 was $147 billion; the annual medical costs for individuals with obesity were $1429 higher than for normal-weight individuals.[72] A more recent study estimated mean annual per capita healthcare expenses associated with obesity were $1160 for males and $1525 for females.[73]
- According to NHANES I data linked to Medicare and mortality records, 45-year-old individuals with obesity had lifetime Medicare costs of $163 000 compared with $117 000 for those who were at normal weight at 65 years of age.[74]

- According to data from the Medicare Current Beneficiary Survey from 1997 to 2006, in 1997, expenditures for Part A and Part B services per beneficiary were $6832 for a normal-weight person, which was more than for overweight people ($5473) or people with obesity ($5790); however, over time, expenses increased more rapidly for overweight people and people with obesity.[75]
- The costs of obesity are high: People with obesity paid on average $1429 (42%) more for health-care costs than normal-weight people in 2006. For beneficiaries who are obese, Medicare pays $1723 more, Medicaid pays $1021 more, and private insurers pay $1140 more annually than for beneficiaries who are at normal weight. Similarly, people with obesity have 46% higher inpatient costs and 27% more outpatient visits and spend 80% more on prescription drugs.[72]
- Using 4 waves of NHANES data (through 2000), the total excess cost in 2007 US dollars related to the current prevalence of adolescent overweight and obesity was estimated to be $254 billion ($208 billion in lost productivity secondary to premature morbidity and mortality and $46 billion in direct medical costs).[76]
- A recent study recommended the use of $19 000 (2012 US dollars) as the incremental lifetime medical cost of a child with obesity relative to a normal-weight child who maintains normal weight throughout adulthood.[77]
- According to the 2006 NHDS, the incidence of bariatric surgery was estimated at 113 000 cases per year, with costs of nearly $1.5 billion annually.[78]
- A recent cost-effectiveness study of laparoscopic adjustable gastric banding showed that after 5 years, $4970 was saved in medical expenses; if indirect costs were included (absenteeism and presenteeism), savings increased to $6180 and $10 960, respectively.[79] However, when expressed per QALY, only $6600 was gained for laparoscopic gastric bypass, $6200 for laparoscopic adjustable gastric band, and $17 300 for open Roux-en-Y gastric bypass, none of which exceeded the standard $50 000 per QALY gained.[80] Two other recent large studies failed to demonstrate a cost benefit for bariatric surgery versus matched patients over 6 years of follow-up.[81,82]
- The cost effectiveness of bariatric surgery among individuals with DM is unclear, with 2 studies showing cost savings[83,84] but a recent study demonstrating no improvement compared with intensive lifestyle and medical interventions.[85]
- Bariatric surgery appears to be cost-effective for the treatment of nonalcoholic steatohepatitis, with increasing degree of obesity associated with decreasing cost per QALY ($19 222/QALY in the severely obese), which suggests that subsets of indications for bariatric surgery may be more cost-effective.[86]

Secular Trends (See Charts 6-10 and 6-11)

Youth

- According to NHANES data, overall prevalence of obesity and severe obesity in youth (aged 2–19 years old) did not increase significantly between 2007 to 2008 and 2015 to 2016. Among children 2 to 5 years old, a quadratic trend was seen, with obesity decreasing from 10.1% in 2007 to 2008 to 8.4% in 2011 to 2012 and increasing to 13.9% in 2015 to 2016.[8]
- According to NHANES 2011 to 2014 data, prevalence of obesity in youth (aged 2–19 years) increased from 1988 to 1994 until 2003 to 2004 but did not change significantly afterward. The prevalence of severe obesity increased between 1988 to 1994 and 2013 to 2014.[18]
- According to NCHS/CDC and NHANES surveys, the prevalence of obesity among children and adolescents increased substantially from 1963 to 1965 through 2009 to 2010, but this increase has slowed (Chart 6-10).
- Specifically, according to NHANES data, from 1988 to 1994, 2003 to 2006, and 2011 to 2014, the percentage of children 12 to 19 years of age with obesity increased from 10.5% to 17.6% to 20.5%, respectively[19]; however, during the same time periods, among children aged 2 to 5 years, the prevalence of obesity changed from 7.2% in 1988 to 1994 to 12.5% in 2003 to 2006 to 8.9% in 2011 to 2014.[18,19] Another analysis of NHANES data showed that between 1988 to 1994 and 2013 to 2014, extreme obesity increased among children aged 6 to 11 years (from 3.6% to 4.3%) and among adolescents aged 12 to 19 years (from 2.6% to 9.1%).[18]
- Among infants and children from birth to >2 years old, the prevalence of high weight for recumbent length (ie, ≥95th percentile of sex-specific CDC 2000 growth charts) was 9.5% in 2003 to 2004 and 8.1% in 2011 to 2014. The decrease of 1.4% was not statistically significant.[87]
- According to the YRBSS, among US high school students between 1999 and 2015, there was a significant linear increase in the prevalence of obesity (from 10.6% to 13.9%) and in the prevalence of overweight (from 14.1% to 16.0%). Between 1991 and 2015, there was a corresponding significant linear increase of students who reported

they were trying to lose weight, from 41.8% to 45.6%.[23]

Adults

- In the United States, the age-standardized prevalence of obesity and severe obesity increased significantly in the past decade (from 2007–2008 to 2015–2016) among adults.[8]
- In the United States, the prevalence of obesity among adults, estimated using NHANES data, increased from 1999 to 2000 through 2013 to 2014 from 30.5% to 37.7%[6] (Chart 6-11); however, from 2005 to 2006 through 2013 to 2014, there was a significant linear trend for the increase in obesity and class III obesity for females (from 35.6% to 41.1% and from 7.5% to 10.0%, respectively) but not males (from 33.4% to 35.1% and from 7.5% to 10.0%, respectively).[6]
- From NHANES 1999 to 2002 to NHANES 2007 to 2010, the prevalence of total and undiagnosed DM, total hypertension, total dyslipidemia, and smoking did not change significantly within any of the BMI categories, but there was a lower prevalence of dyslipidemia (−3.4%; 95% CI, −6.3% to −0.5%) among overweight adults. However, the prevalence of untreated hypertension decreased among adults with overweight or obesity, and the prevalence of untreated dyslipidemia decreased for all BMI categories (normal, overweight, obesity, and BMI ≥35 kg/m^2).[88]
- Another study reported that for females, but not males, the increase in WC from NHANES 1999 to 2000 to NHANES 2010 to 2011 was greater than expected based on the increase in BMI.[89]

Prevention

- In adults, 2 prevention targets are the built environment and the workplace. The built environment plays a role in promoting healthy lifestyles and preventing obesity.[90] Similar to schools for children, the workplace can provide an opportunity to educate adults on methods to reduce weight and can also motivate individuals to lose weight through group participation.[91]
- 70% of adults with obesity did not have obesity in childhood or adolescence, so reducing the overall burden of adult obesity might require interventions beyond targeting obesity reduction solely at overweight children and children with obesity.[92]
- The CDC Prevention Status Reports highlight the status of public health policies and practices to address public health problems, including obesity, by state. Reports rate the extent to which the state has implemented the policies or practices identified from systemic reviews, national strategies or action plans, or expert bodies.[93] Obesity reduction policies and programs implemented by country are also provided online.[94]

Awareness

- According to NHANES 2003 to 2006 data, ≈23% of adults who were overweight and with obesity misperceived themselves to be at a healthier weight status, and those people were less likely to have tried to lose weight in the prior year.[95]
- Recent studies show that parents' perceptions of overweight and obesity differ according to the child's race and sex. Boys 6 to 15 years of age with obesity were more likely than girls to be misperceived as being "about the right weight" by their parents (OR, 1.40; 95% CI, 1.12–1.76; *P*=0.004). Obesity was significantly less likely to be misperceived among girls 11 to 15 years of age than among girls 6 to 10 years of age (OR, 0.46; 95% CI, 0.29–0.74; *P*=0.002) and among Hispanic males than among white males (OR, 0.58; 95% CI, 0.36–0.93; *P*=0.02).[95] Notification of a child's unhealthy weight by healthcare practitioners increased from 22% in 1999 to 34% in 2014.[96]

Treatment and Control

- The randomized trial Look AHEAD showed that among adults who were overweight, had obesity, and had type 2 DM, an intensive lifestyle intervention produced a greater percentage of weight loss at 4 years than DM support education.[97]
  - After 8 years of intervention, the percentage of weight loss ≥5% and ≥10% was greater in the intensive lifestyle intervention than in DM support education groups (50.3% and 26.9% versus 35.7% and 17.2%, respectively).[98]
  - Look AHEAD was stopped early with a median 9.6 years of follow-up for failure to show a significant difference in CVD events between the intensive lifestyle intervention and control group.[97]
  - Intensive lifestyle interventions produce greater weight loss than education alone among those with class III obesity[99] and childhood obesity.[100]
- A comprehensive review and meta-analysis of 54 RCTs suggests that dietary weight loss interventions reduce all-cause mortality (34 trials, 685 events; RR, 0.82; 95% CI, 0.71–0.95), but the benefit on lowering cardiovascular mortality is less clear.[101]

- Ten-year follow-up data from the nonrandomized SOS bariatric intervention study (see Bariatric Surgery) suggested that to maintain a favorable effect on cardiovascular risk factors, more than the short-term goal of 5% weight loss is needed to overcome secular trends and aging effects.[102] Long-term follow-up might be necessary to show reductions in CVD risk.
- Lifestyle and surgical interventions are both beneficial: After gastric bypass, individuals with regular PA had improved fat mass, insulin sensitivity, and HDL-C.[103]

Bariatric Surgery

- Lifestyle interventions often do not provide sustained significant weight loss for people with obesity. Among adults with obesity, bariatric surgery produces greater weight loss and maintenance of lost weight than lifestyle intervention, with some variations depending on the type of procedure and the patient's initial weight.[33] Gastric bypass surgery is typically performed as a Roux-en-Y gastric bypass, vertical sleeve gastrectomy, adjustable gastric banding, or biliopancreatic diversion with duodenal switch.
- Benefits reported for bariatric surgery include substantial weight loss; remission of DM, hypertension, and dyslipidemia; reduced incidence of mortality; reduction in microvascular disease; and fewer CVD events.[104] Reported risks with bariatric surgery include not only perioperative mortality and adverse events but also weight regain, DM recurrence (particularly for those with longer DM duration before surgery), bone loss, increases in substance use disorders, suicide, and nutritional deficiencies. Outcomes vary by bariatric surgery technique.[105]
- Outcomes must be assessed cautiously, because most bariatric surgery data come from nonrandomized observational studies, with only a few RCTs comparing bariatric surgery to medical treatment for patients with DM. Furthermore, studies have not always reported their definition of remission or partial remission for comorbidities such as DM, hypertension, and dyslipidemia, and many have not reported laboratory values or medication use.[105,106]
- In a large bariatric surgery cohort, the prevalence of high 10-year predicted CVD risk was 36.5%,[91] but 76% of those with low 10-year risk had high lifetime predicted CVD risk. The corresponding prevalence in US adults is 18% and 56%, respectively.[107]
- A meta-analysis of RCTs also showed substantially higher weight loss and DM remission for bariatric surgery than for conventional medical therapy, with follow-up of ≤2 years.[108]
- The longest follow-up to date of 12 years in 1156 patients with severe obesity, including 418 individuals who underwent gastric bypass, demonstrated sustained weight loss and both remission and prevention of incident type 2 DM, hypertension, and dyslipidemia.[109]
- An RCT demonstrated that weight loss from laparoscopic sleeve gastrectomy was similar to that achieved by traditional gastric bypass surgery, although the latter achieved greater improvement in lipid levels.[110,111]
- According to retrospective data, among 9949 patients who underwent gastric bypass surgery, after a mean of 7 years, long-term mortality was 40% lower among the surgically treated patients than among control subjects with obesity. Specifically, cancer mortality was reduced by 60%, DM mortality by 92%, and CAD mortality by 56%. Nondisease death rates (eg, accidents, suicide) were 58% higher in the surgery group.[112]
- A recent DM consensus statement recommended bariatric surgery to treat type 2 DM among adults with class III obesity and recommended it be considered to treat type 2 DM among adults with class I obesity.[99]
- The role of bariatric surgery to treat type 2 DM in adolescence is controversial.[113] Although bariatric surgery improves insulin requirements and comorbidities in type 1 DM, there was minimal sustained effect in glycemic control in long-term follow-up in a small series.[114]

Family History and Genetics

- Overweight and obesity have considerable genetic components, with heritability estimates ranging from ≈40% to 75%.[115] However, only ≈1.5% of interindividual variation of BMI is explained by commonly occurring SNPs, which suggests a role for DNA methylation variants.[116]
- Monogenic or mendelian causes of obesity include mutations with strong effects in genes that control appetite and energy balance (eg, *LEP, MC4R*), as well as obesity that occurs in the context of syndromes.[117]
- Most cases of obesity are determined by the interaction of genetic and epigenetic factors with an obesogenic environment, including diet, PA, and the microbiome. Although BMI is most commonly used to define obesity at the population level, measures of visceral adiposity more closely approximate the pathogenic form of excess body weight.

- GWASs in diverse populations have implicated multiple loci for obesity, mostly defined by BMI, WC, or waist-hip ratio. The FTO locus is the most well-established obesity locus, first reported in 2007[118,119] and replicated in many studies with diverse populations and age groups since then.[120–124] The mechanisms underlying the association remain incompletely elucidated but could be related to mitochondrial thermogenesis[11] or food intake.[125]
- Other GWASs have reported numerous additional loci,[126] with >300 putative loci, most of which explain only a small proportion of the variance in obesity, have not been mechanistically defined, and have unclear clinical significance. Fine mapping of loci, including recent efforts focused on GWASs in African ancestry, in addition to mechanistic studies, is required to define functionality of obesity-associated loci.[127]
- A large GWAS of obesity in >240 000 individuals of predominately European ancestry revealed an interaction with smoking, which highlights the need to consider gene-environment interactions in genetic studies of obesity.[128]
- Epigenetic modifications such as DNA methylation have both genetic and environmental contributors and may contribute to risk of and adverse consequences of obesity. An epigenome-wide association study in 479 people demonstrated that increased methylation at the HIF3A locus in circulating white blood cells and in adipose tissue was associated with increased BMI.[129]

Global Burden (See Chart 6-12)

- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories.[130] The Pacific Island countries, Eastern Europe, Central Asia, and the North Africa/Middle East region have the highest mortality rates attributable to high BMI (Chart 6-12).[130]
- Although there is considerable variability in overweight and obesity data methodology and quality worldwide, cross-country comparisons can help reveal different patterns. Worldwide, from 1975 to 2014, the prevalence of obesity increased from 3.2% in 1975 to 10.8% in 2014 in males and from 6.4% to 14.9% in females, and mean age-standardized BMI increased from 21.7 to 24.2 kg/m^2 in males and from 22.1 to 24.4 kg/m^2 in females.[131] Worldwide, between 1980 and 2013, the proportion of adults with overweight or obesity increased from 28.8% (95% UI, 28.4%–29.3%) to 36.9% (95% UI, 36.3%–37.4%) among males and from 29.8% (95% UI, 29.3%–30.2%) to 38.0% (95% UI, 37.5%–38.5%) among females. Since 2006, the increase in adult obesity in developed countries has slowed. The estimated prevalence of adult obesity exceeded 50% of males in Tonga and females in Kuwait, Kiribati, the Federated States of Micronesia, Libya, Qatar, Tonga, and Samoa. In the sub-Saharan African country of Malawi, representative of rural but developing countries, the prevalence of overweight or obesity was 18% and 44% of urban males and females, respectively, and 9% and 27% of rural males and females, respectively. Associated hypertension and DM are highly prevalent and underdiagnosed.[132] As of 2013, around the world, obesity rates are higher for females than males and in developed countries than in developing countries. Higher obesity rates for females than for males occur for age ≥45 years in developed countries but for age ≥25 years in developing countries.[133]
- Between 1980 and 2013, the prevalence of overweight and obesity rose by 27.5% for adults.[133] Over this same period, no declines in obesity prevalence were detected. In 2008, an estimated 1.46 billion adults were overweight or obese. The prevalence of obesity was estimated at 205 million males and 297 million females in 2013. The highest prevalence of male obesity is in the United States, southern and central Latin America, Australasia, and Central and Western Europe, and the lowest prevalence is in South and Southeast Asia and East, Central, and West Africa. For females, the highest prevalence of obesity is in Southern and North Africa, the Middle East, central and southern Latin America, and the United States, and the lowest is in South, East, and Southeast Asia, the high-income Asia-Pacific subregion, and East, Central, and West Africa.[134]
- An appraisal of the prevalence of obesity in sub-Saharan Africa from 2009 to 2012 suggests an increase in BMI and WC, associated with hypertension. In 2726 university students in Cameroon, the prevalence of obesity, overweight and obesity (combined), and hypertension was 3.5%, 21%, and 6.3%, respectively. There was an increase over time in overweight and obesity in males and an increase in prevalence of abdominal obesity in females, which were both associated with incident hypertension.[135]
- In 2015, a total of 107.7 million youth and 603.7 million adults had obesity, with an overall obesity

prevalence of 5.0% among children and 12.0% among adults. High BMI contributed to 4.0 million deaths globally, with the leading cause of death and disability being attributable to CVD.[136]

Future Research

The dramatic increase in prevalence and disease burden of obesity over the past several decades highlights the ongoing need to focus on the development of and dissemination and implementation of evidence-based interventions focusing on primordial prevention. In recent years, the rate of decline of CVD mortality has decelerated substantially, which might be attributable to the obesity epidemic, and there are concerns about the increasing future burden of CVD. Identification of evidence-based strategies to maintain and achieve a healthy body weight is necessary to reverse the slowing progress in cardiovascular mortality rates and reduce the overall burden of obesity.

Table 6-1. Overweight and Obesity

	Prevalence of Overweight and Obesity, 2011–2014, Age ≥20 y		Prevalence of Obesity, 2011–2014, Age ≥20 y		Prevalence of Overweight and Obesity, 2011–2014, Ages 2–19 y		Prevalence of Obesity, 2011–2014, Ages 2–19 y		
	n	%	n	%	n	%	n	%	Cost, 2008*
Total	157 232 115	69.4	82 241 005	36.3	24 036 573	32.1	12 339 701	16.5	$147 billion
Males	78 854 444	72.5	37 306 309	34.3	12 326 869	32.3	6 231 683	16.3	…
Females	78 215 543	66.4	45 115 291	38.3	11 709 947	32.0	6 107 613	16.7	…
NH white									
Males	53 310 267	73.0	24 537 328	33.6	5 962 553	29.3	2 848 504	14.0	…
Females	49 632 907	63.7	27 660 411	35.5	5 419 620	28.0	2 847 989	14.7	…
NH black									
Males	7 968 039	69.1	4 324 189	37.5	1 734 453	32.8	924 000	17.5	…
Females	11 782 661	82.2	8 156 124	56.9	1 929 861	37.6	1 026 805	20.0	…
NH Asian									
Males	2 504 566	46.6	601 956	11.2	416 430	24.9	190 805	11.4	…
Females	2 165 586	34.6	744 811	11.9	245 206	15.0	86 088	5.3	…
Hispanic									
Males	13 015 852	79.6	6 377 113	39.0	3 601 223	40.4	1 939 812	21.7	…
Females	12 721 527	77.1	7 540 516	45.7	3 400 898	39.8	1 798 951	21.0	…

Overweight and obesity in adults is defined as body mass index (BMI) ≥25 kg/m². Obesity in adults is defined as BMI ≥30 kg/m². In children, overweight and obesity are based on BMI-for-age values at or above the 85th percentile of the 2000 Centers for Disease Control and Prevention (CDC) growth charts. In children, obesity is based on BMI-for-age values at or above the 95th percentile of the CDC growth charts. In January 2007, the American Medical Association's Expert Task Force on Childhood Obesity recommended new definitions for overweight and obesity in children and adolescents[137]; however, statistics based on this new definition are not yet available. Estimates for the total include those of "other" racial/ethnic groups.

Ellipses (…) indicate data not available; and NH, non-Hispanic.

*Data from Finkelstein et al.[79]

Sources: NHANES (National Health and Nutrition Examination Survey) 2011 to 2014 (adults), unpublished CDC tabulation; NHANES 2011 to 2014 (ages 2–19 years) from Ogden et al.[7] Population count extrapolations calculated using the average of the 2011 and 2013 American Community Survey Summary File data.[138]

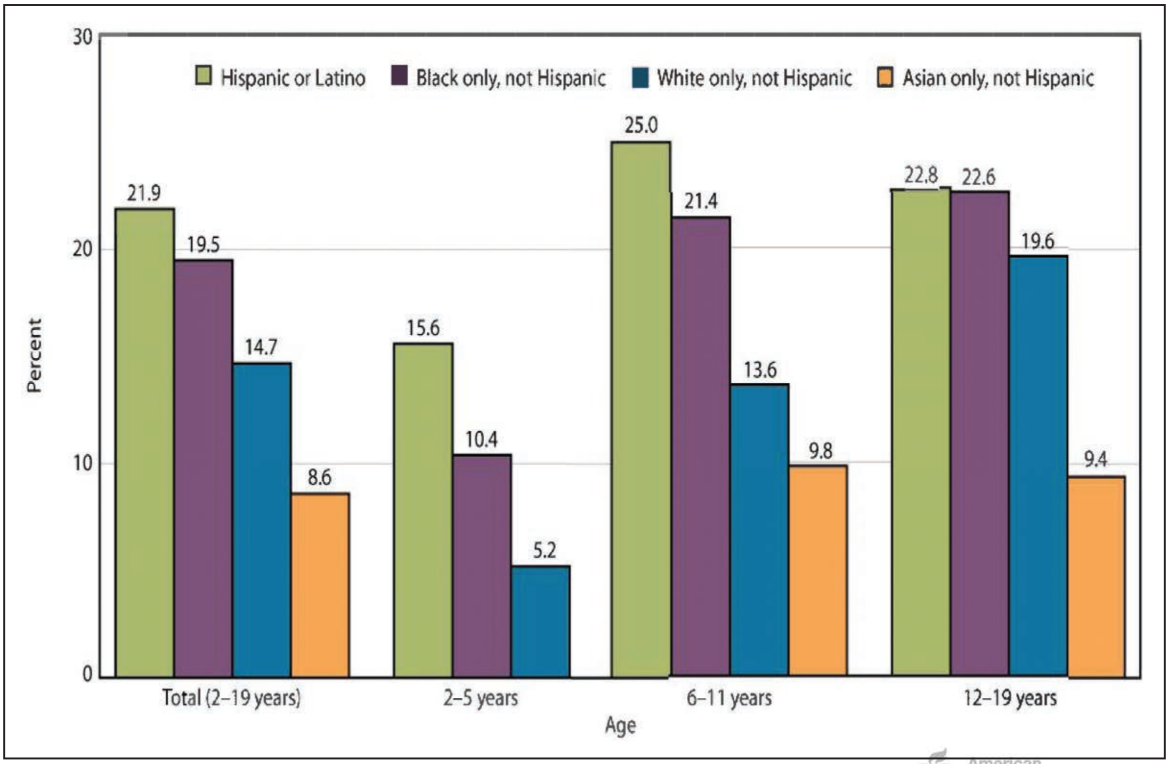

Chart 6-1. US children and adolescents with obesity by race/ethnicity, 2011 to 2014.
Obesity is body mass index (BMI) at or above the sex-and age-specific 95th percentile BMI cutoff points from the 2000 CDC growth charts.
CDC indicates Centers for Disease Control and Prevention.
Source: CDC and National Center for Health Statistics. Data derived from the National Health and Nutrition Examination Survey, Table 59.[7]

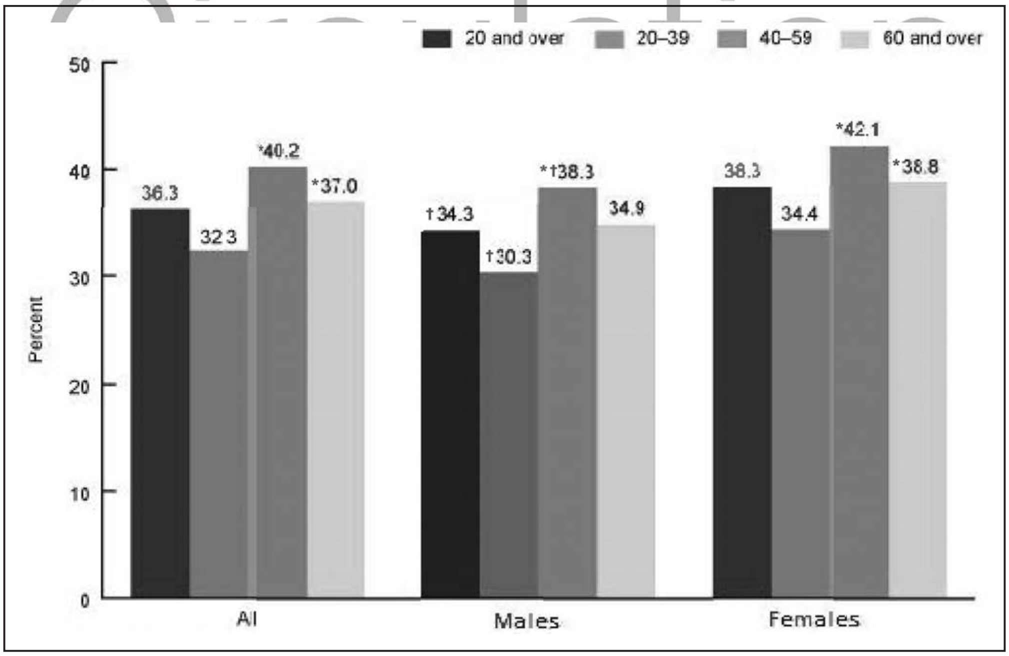

Chart 6-2. Age-adjusted prevalence of obesity in adults ≥20 years of age by sex and age group (NHANES, 2011–2014).
Totals were age-adjusted by the direct method to the 2000 US census population using the age groups 20 to 39, 40 to 59, and ≥60 years old. Crude estimates are 36.5% for all, 34.5% for males, and 38.5% for females.
NHANES indicates National Health and Nutrition Examination Survey.
*Significantly different from those aged 20 to 39 years.
†Significantly different from females of the same age group.
Source: Centers for Disease Control and Prevention/National Center for Health Statistics, NHANES, 2011 to 2014.

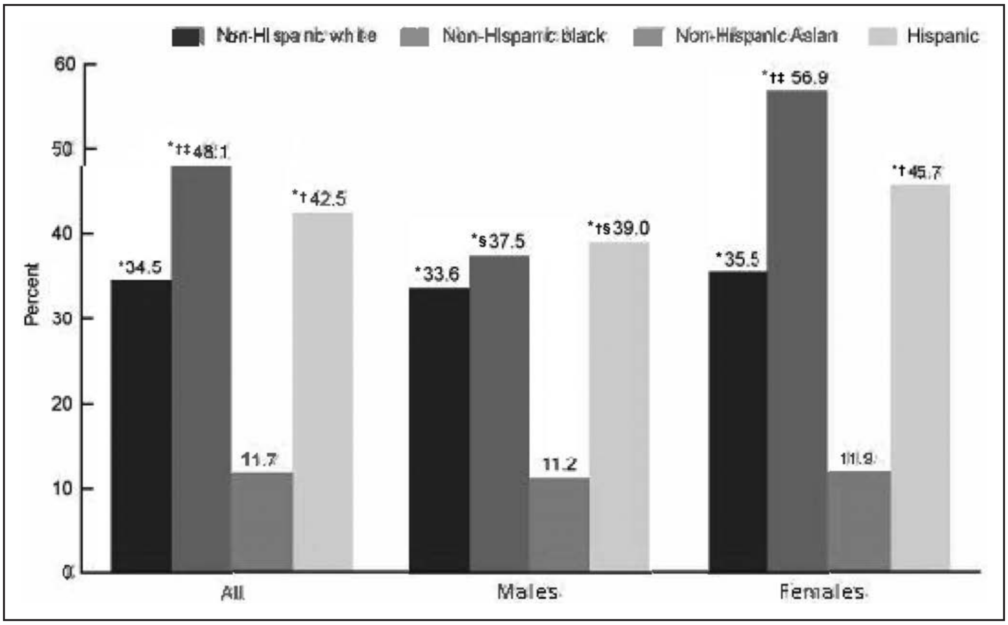

Chart 6-3. Age-adjusted prevalence of obesity in adults ≥20 years of age by sex and race/ethnicity (NHANES, 2011–2014).
NHANES indicates National Health and Nutrition Examination Survey.
*Significantly different from non-Hispanic Asian people.
†Significantly different from non-Hispanic white people.
‡Significantly different from females of the same race and Hispanic origin.
§Significantly different from non-Hispanic black people.
Source: Centers for Disease Control and Prevention/National Center for Health Statistics, NHANES, 2011 to 2014.

American Heart Association

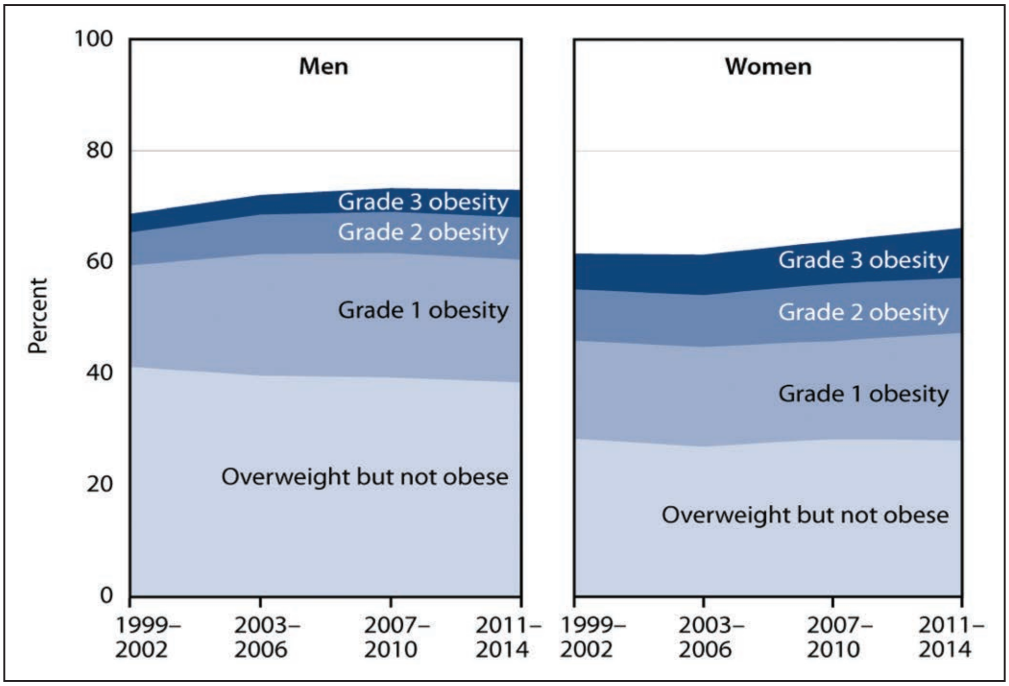

Chart 6-4. Trends in overweight and obesity between 1999 to 2002 and 2011 to 2014 among US adults aged ≥20 years, by sex.
Overweight but not obese (25 ≤ body mass index [BMI] <30 kg/m²); grade 1 obesity (30 ≤ BMI <35 kg/m²); grade 2 obesity (35 ≤ BMI <40 kg/m²); grade 3 obesity (BMI ≥40 kg/m²).
Source: Centers for Disease Control and Prevention/National Center for Health Statistics, Health, United States, 2015, Figure 9 and Table 58. Data from National Health and Nutrition Examination Survey.[19]

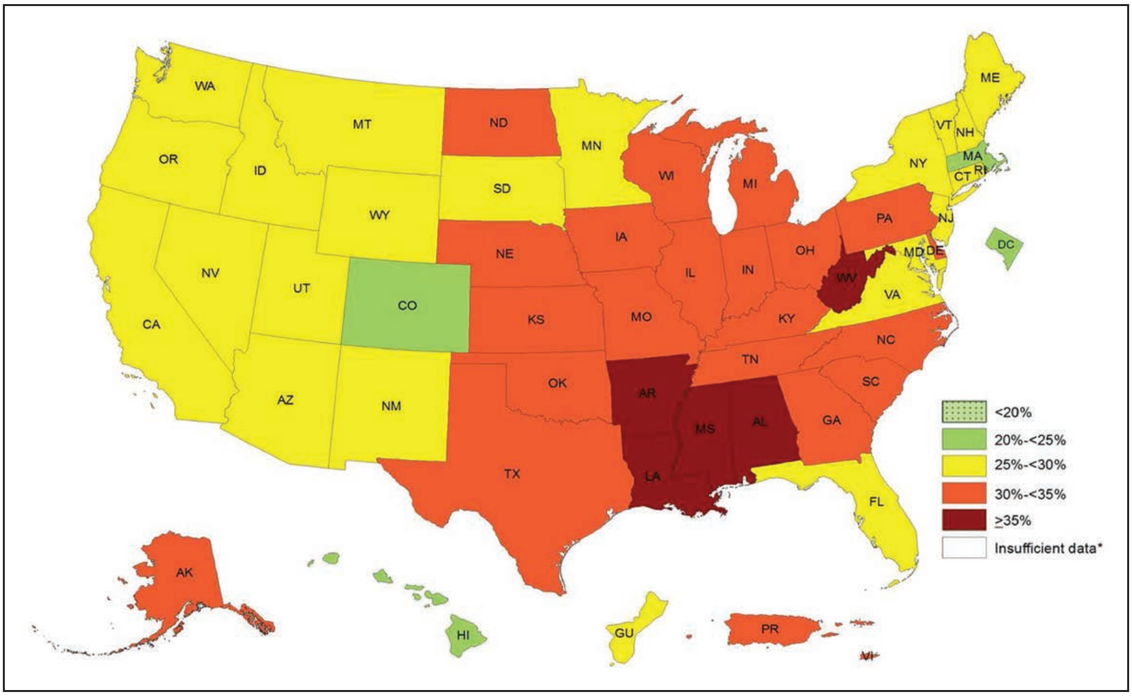

Chart 6-5. Prevalence† of self-reported obesity among US adults aged ≥20 years by state and territory, BRFSS, 2016.
BRFSS indicates Behavioral Risk Factor Surveillance System; GU, Guam; PR, Puerto Rico; and VI, Virgin Islands.
*Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥30%.
†Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.
Source: Centers for Disease Control and Prevention, Obesity Prevalence Map, 2016.[24]

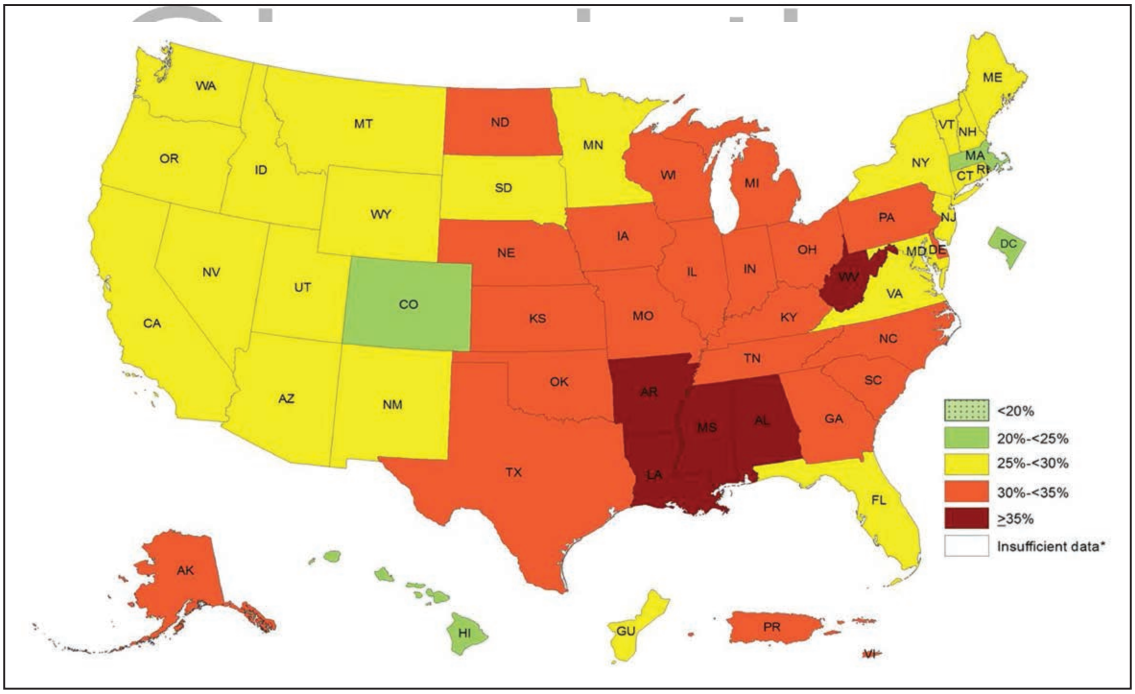

Chart 6-6. Prevalence of self-reported obesity among non-Hispanic white adults aged ≥20 years, by state and territory, BRFSS, 2014 to 2016.
BRFSS indicates Behavioral Risk Factor Surveillance System; GU, Guam; PR, Puerto Rico; and VI, Virgin Islands.
*Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥30%.
Source: Centers for Disease Control and Prevention, Obesity Prevalence Map, 2014 to 2016.[24]

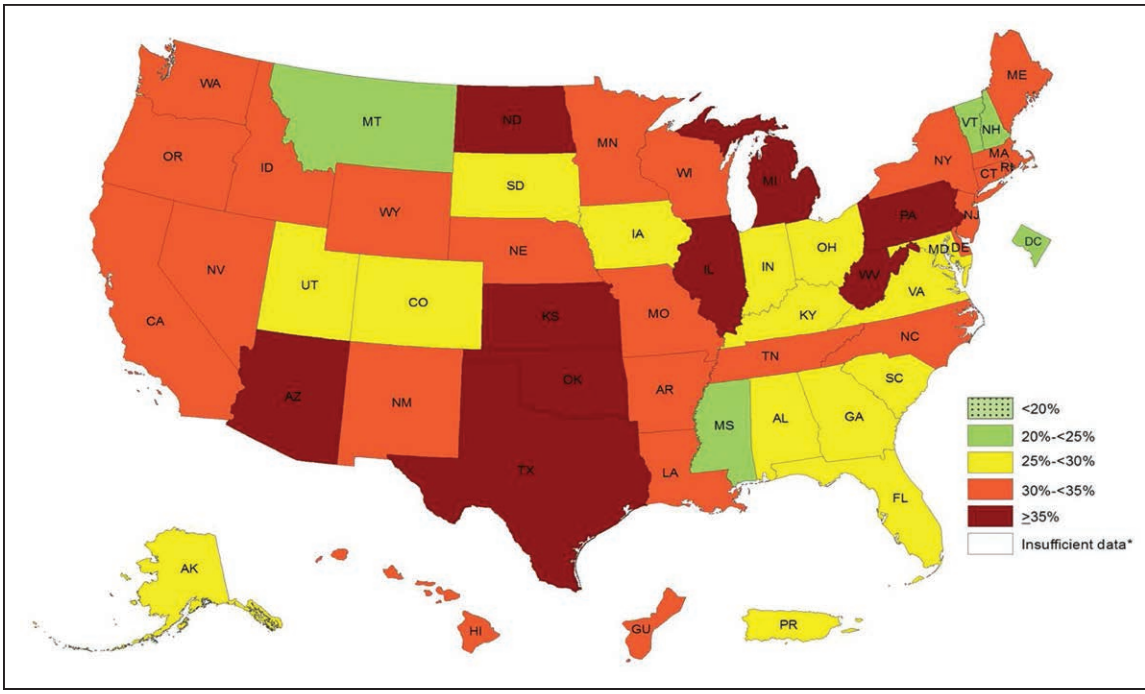

Chart 6-7. Prevalence of self-reported obesity among Hispanic adults aged ≥20 years, by state and territory, BRFSS, 2014 to 2016.
BRFSS indicates Behavioral Risk Factor Surveillance System; GU, Guam; and PR, Puerto Rico.
*Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥30%.
Source: Centers for Disease Control and Prevention, Obesity Prevalence Map, 2014 to 2016.[24]

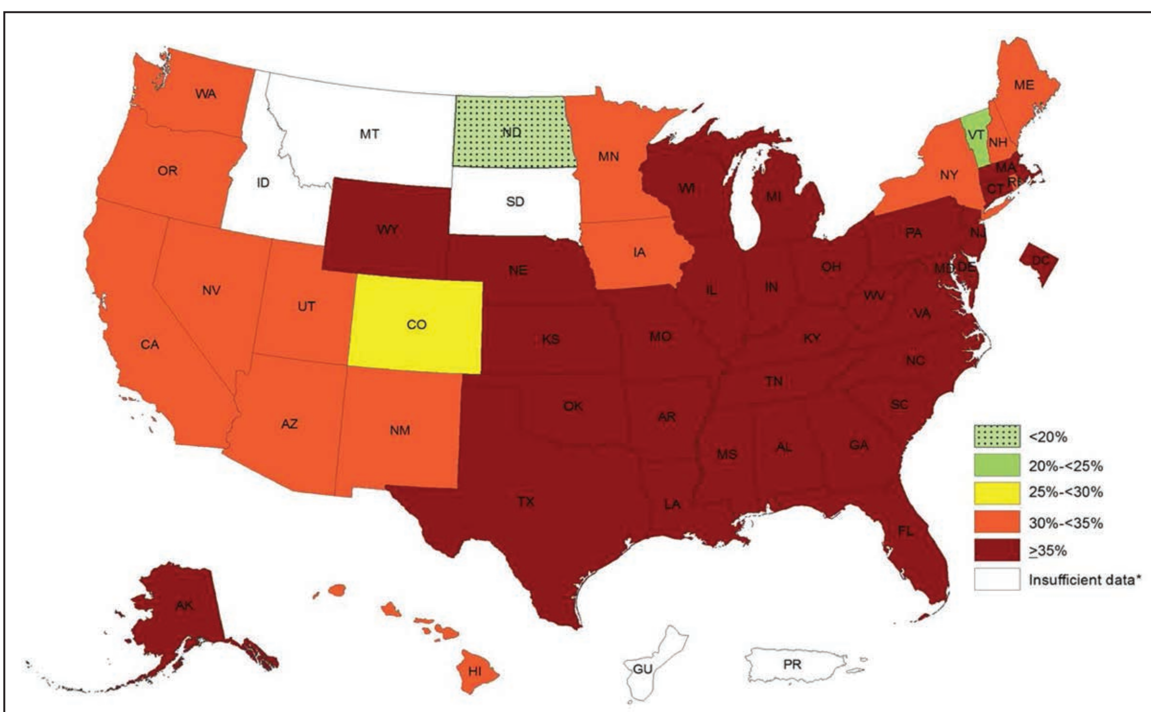

Chart 6-8. Prevalence of self-reported obesity among non-Hispanic black adults aged ≥20 years, by state and territory, BRFSS, 2014 to 2016.
BRFSS indicates Behavioral Risk Factor Surveillance System; GU, Guam; and PR, Puerto Rico.
*Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥30%.
Source: Centers for Disease Control and Prevention, Obesity Prevalence Map, 2014 to 2016.[24]

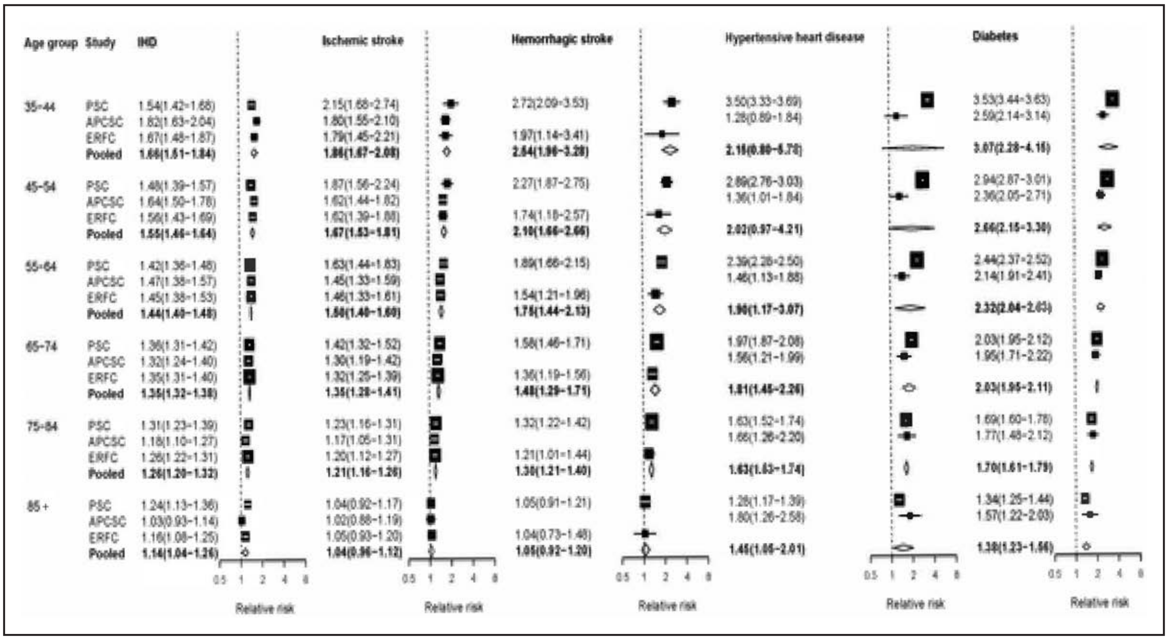

Chart 6-9. Relative risks for diseases associated with body mass index by age group.

APCSC indicates Asia-Pacific Cohort Studies Collaboration; ERFC, Emerging Risk Factor Collaboration; IHD, ischemic heart disease; and PSC, Prospective Studies Collaboration.

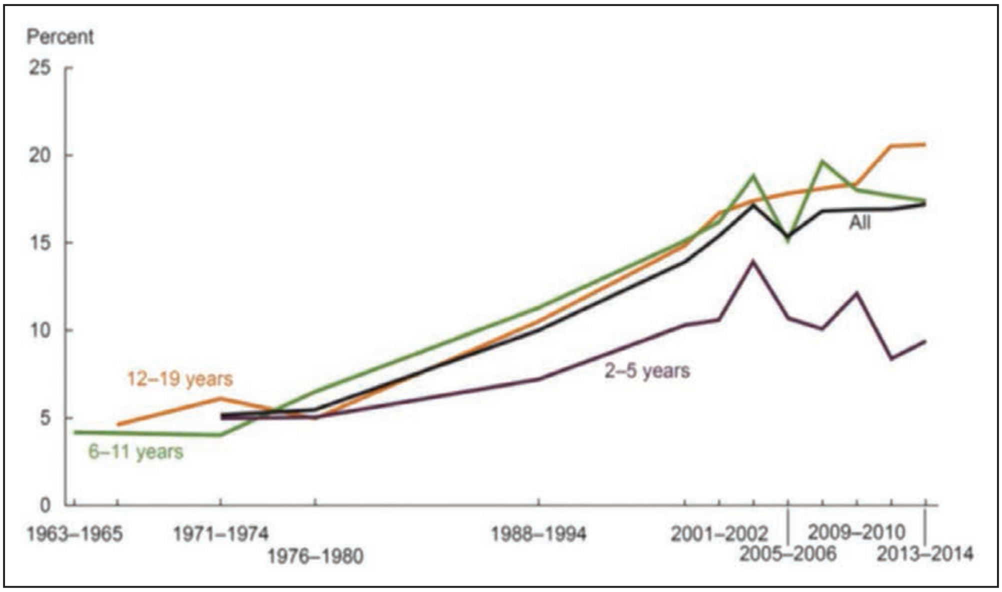

Chart 6-10. US children and adolescents with obesity, 1963 to 2014.

Obesity is body mass index (BMI) at or above the sex- and age-specific 95th percentile BMI cutoff points from the 2000 CDC growth charts.

CDC indicates Centers for Disease Control and Prevention.

Source: CDC/National Center for Health Statistics, Health, United States, 2015, Figure 8 and Table 59. Data from the National Health and Nutrition Examination Survey.[19]

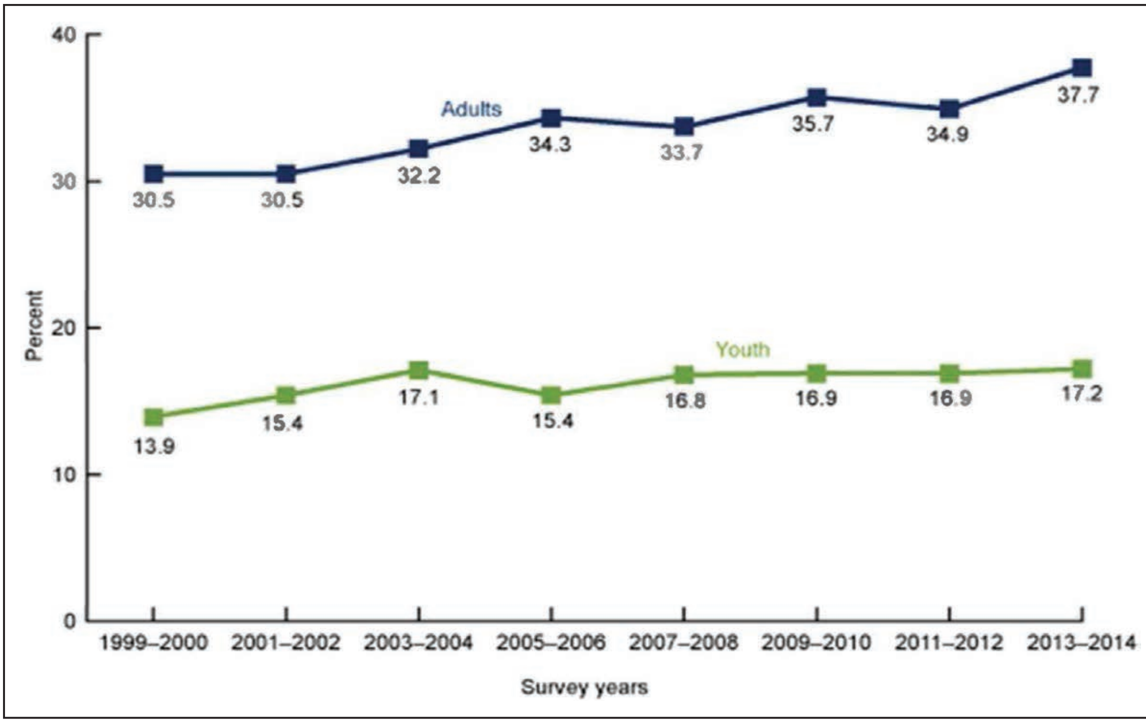

Chart 6-11. **Trends in obesity prevalence among adults aged ≥20 years (age adjusted) and youth aged 2 to 19 years, United States, 1999 to 2000 through 2013 to 2014.**
Data from the National Center for Health Statistics.[19]

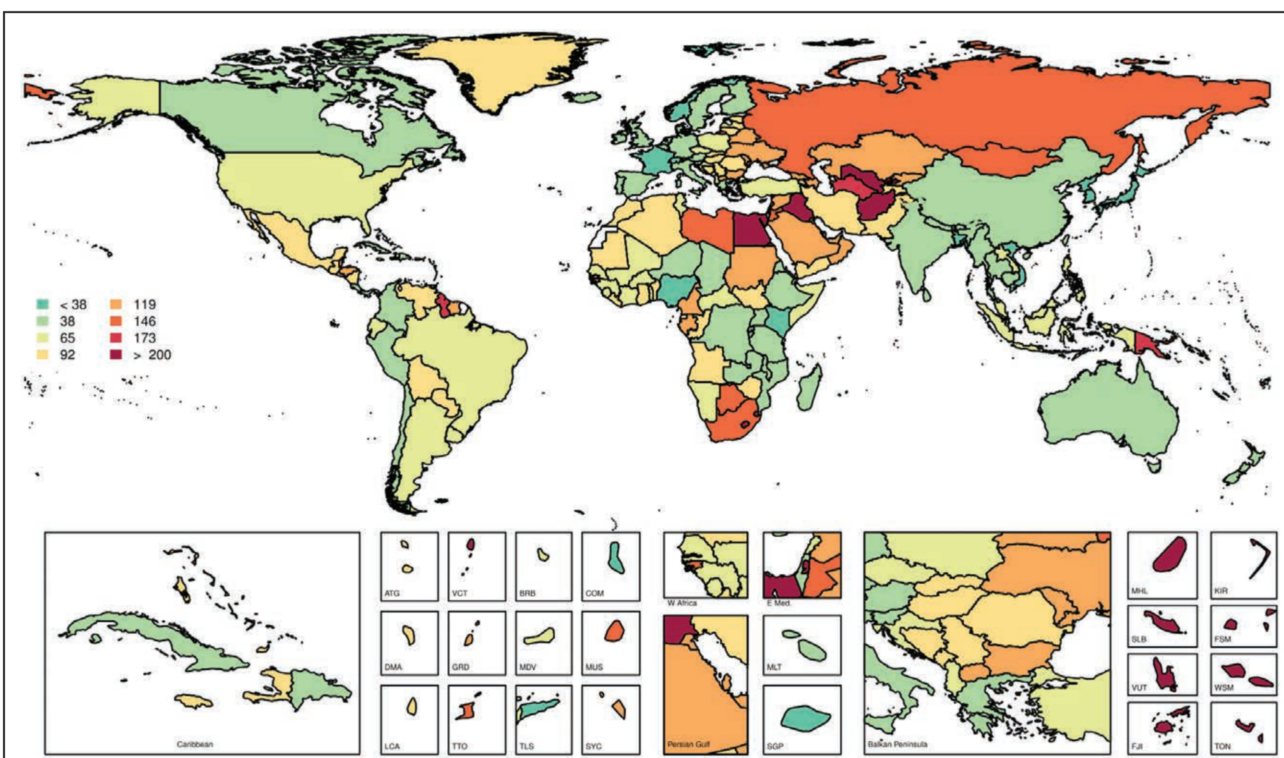

Chart 6-12. **Age-standardized global mortality rates attributable to high body mass index per 100 000, both sexes 2016.**
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Data derived from Global Burden of Disease Study 2016 with permission.[130] Copyright © 2017, University of Washington

REFERENCES

1. Klein S, Burke LE, Bray GA, Blair S, Allison DB, Pi-Sunyer X, Hong Y, Eckel RH; on behalf of the American Heart Association Council on Nutrition, Physical Activity, and Metabolism. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2004;110:2952–2967. doi: 10.1161/01.CIR.0000145546.97738.1E
2. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, Eckel RH; on behalf of the American Heart Association; Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2006;113:898–918. doi: 10.1161/CIRCULATIONAHA.106.171016
3. Aune D, Sen A, Schlesinger S, Norat T, Janszky I, Romundstad P, Tonstad S, Riboli E, Vatten LJ. Body mass index, abdominal fatness, fat mass and the risk of atrial fibrillation: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol*. 2017;32:181–192. doi: 10.1007/s10654-017-0232-4
4. Mi Y, Yan S, Lu Y, Liang Y, Li C. Venous thromboembolism has the same risk factors as atherosclerosis: a PRISMA-compliant systemic review and meta-analysis. *Medicine (Baltimore)*. 2016;95:e4495. doi: 10.1097/MD.0000000000004495
5. Wattanakit K, Lutsey PL, Bell EJ, Gornik H, Cushman M, Heckbert SR, Rosamond WD, Folsom AR. Association between cardiovascular disease risk factors and occurrence of venous thromboembolism: a time-dependent analysis. *Thromb Haemost*. 2012;108:508–515. doi: 10.1160/TH11-10-0726
6. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA*. 2016;315:2284–2291. doi: 10.1001/jama.2016.6458
7. Ogden CL, Carroll MD, Fryar CD, Flegal KM. Prevalence of obesity among adults and youth: United States, 2011–2014. *NCHS Data Brief*. 2015;(219):1–8.
8. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007–2008 to 2015–2016. *JAMA*. 2018;319:1723–1725. doi: 10.1001/jama.2018.3060
9. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
10. Rao G, Powell-Wiley TM, Ancheta I, Hairston K, Kirley K, Lear SA, North KE, Palaniappan L, Rosal MC; on behalf of the American Heart Association Obesity Committee of the Council on Lifestyle and Cardiometabolic Health. Identification of Obesity and Cardiovascular Risk in Ethnically and Racially Diverse Populations: A Scientific Statement From the American Heart Association [published correction appears in *Circulation*. 2015;132:e130]. *Circulation*. 2015;132:457–472. doi: 10.1161/CIR.0000000000000223
11. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies [published correction appears in *Lancet*. 2004;363:902]. *Lancet*. 2004;363:157–163.
12. CDC growth charts. Centers for Disease Control and Prevention website. http://www.cdc.gov/growthcharts/cdc_charts.htm. Accessed July 13, 2016.
13. Ogden CL, Flegal KM. Changes in terminology for childhood overweight and obesity. *Natl Health Stat Report*. 2010;(25):1–5.
14. Kelly AS, Barlow SE, Rao G, Inge TH, Hayman LL, Steinberger J, Urbina EM, Ewing LJ, Daniels SR; on behalf of the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young, Council on Nutrition, Physical Activity and Metabolism, and Council on Clinical Cardiology. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. *Circulation*. 2013;128:1689–1712. doi: 10.1161/CIR.0b013e3182a5cfb3
15. Cornier MA, Després JP, Davis N, Grossniklaus DA, Klein S, Lamarche B, Lopez-Jimenez F, Rao G, St-Onge MP, Towfighi A, Poirier P; on behalf of the American Heart Association Obesity Committee of the Council on Nutrition; Physical Activity and Metabolism; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing, Council on Epidemiology and Prevention; Council on the Kidney in Cardiovascular Disease, and Stroke Council. Assessing adiposity: a scientific statement from the American Heart Association. *Circulation*. 2011;124:1996–2019. doi: 10.1161/CIR.0b013e318233bc6a
16. World Health Organization. Waist Circumference and Waist–Hip Ratio: Report of a WHO Expert Consultation, Geneva, 8–11 December 2008. Geneva, Switzerland: World Health Organization; 2011.
17. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society [published correction appears in *Circulation*. 2014;129(suppl 2):S139–140]. *Circulation*. 2014;129(suppl 2):S102–S138. doi: 10.1161/01.cir.0000437739.71477.ee
18. Ogden CL, Carroll MD, Lawman HG, Fryar CD, Kruszon-Moran D, Kit BK, Flegal KM. Trends in obesity prevalence among children and adolescents in the United States, 1988-1994 through 2013-2014. *JAMA*. 2016;315:2292–2299. doi: 10.1001/jama.2016.6361
19. National Center for Health Statistics. *Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities.* Hyattsville, MD: National Center for Health Statistics; 2016. http://www.cdc.gov/nchs/data/hus/hus15.pdf. Accessed August 24, 2016.
20. Fryar CD, Carroll MD, Ogden CL. Prevalence of overweight and obesity among children and adolescents aged 2–19 years: United States, 1963–1965 through 2013–2014. National Center for Health Statistics: Health E-Stats. Centers for Disease Control and Prevention website. July 2016. https://www.cdc.gov/nchs/data/hestat/obesity_child_13_14/obesity_child_13_14.htm. Accessed September 1, 2018.
21. Frederick CB, Snellman K, Putnam RD. Increasing socioeconomic disparities in adolescent obesity. *Proc Natl Acad Sci U S A*. 2014;111:1338–1342. doi: 10.1073/pnas.1321355110
22. Ogden CL, Carroll MD, Fakhouri TH, Hales CM, Fryar CD, Li X, Freedman DS. Prevalence of obesity among youths by household income and education level of head of household: United States 2011-2014. *MMWR Morb Mortal Wkly Rep*. 2018;67:186–189. doi: 10.15585/mmwr.mm6706a3
23. Kann L, McManus T, Harris WA, Shanklin SL, Flint KH, Hawkins J, Queen B, Lowry R, Olsen EO, Chyen D, Whittle L, Thornton J, Lim C, Yamakawa Y, Brener N, Zaza S. Youth Risk Behavior Surveillance: United States, 2015. *MMWR Surveill Summ*. 2016;65:1–174. doi: 10.15585/mmwr.ss6506a1
24. BRFSS Prevalence & Trends Data. Centers for Disease Control and Prevention website. https://www.cdc.gov/brfss/brfssprevalence/index.html. Accessed June 30, 2018.
25. The NS, Suchindran C, North KE, Popkin BM, Gordon-Larsen P. Association of adolescent obesity with risk of severe obesity in adulthood. *JAMA*. 2010;304:2042–2047. doi: 10.1001/jama.2010.1635
26. Daniels SR, Jacobson MS, McCrindle BW, Eckel RH, Sanner BM. American Heart Association Childhood Obesity Research Summit: executive summary. *Circulation*. 2009;119:2114–2123. doi: 10.1161/CIRCULATIONAHA.109.192215
27. Skinner AC, Perrin EM, Moss LA, Skelton JA. Cardiometabolic risks and severity of obesity in children and young adults. *N Engl J Med*. 2015;373:1307–1317. doi: 10.1056/NEJMoa1502821
28. Umer A, Kelley GA, Cottrell LE, Giacobbi P Jr, Innes KE, Lilly CL. Childhood obesity and adult cardiovascular disease risk factors: a systematic review with meta-analysis. *BMC Public Health*. 2017;17:683. doi: 10.1186/s12889-017-4691-z
29. Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, Srinivasan SR, Daniels SR, Davis PH, Chen W, Sun C, Cheung M, Viikari JS, Dwyer T, Raitakari OT. Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med*. 2011;365:1876–1885. doi: 10.1056/NEJMoa1010112
30. Kozak AT, Daviglus ML, Chan C, Kiefe CI, Jacobs DR Jr, Liu K. Relationship of body mass index in young adulthood and health-related quality of life two decades later: the Coronary Artery Risk Development in Young Adults study. *Int J Obes (Lond)*. 2011;35:134–141. doi: 10.1038/ijo.2010.120

31. Eckel N, Meidtner K, Kalle-Uhlmann T, Stefan N, Schulze MB. Metabolically healthy obesity and cardiovascular events: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2016;23:956–966. doi: 10.1177/2047487315623884
32. Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, Sweis RN, Lloyd-Jones DM. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. *JAMA Cardiol*. 2018;3:280–287. doi: 10.1001/jamacardio.2018.0022
33. Guidelines (2013) for managing overweight and obesity in adults. Preface to the Expert Panel Report (comprehensive version which includes systematic evidence review, evidence statements, and recommendations). *Obesity (Silver Spring)*. 2014;22(suppl 2):S40. doi: 10.1002/oby.20822
34. Goff DC Jr, Gillespie C, Howard G, Labarthe DR. Is the obesity epidemic reversing favorable trends in blood pressure? Evidence from cohorts born between 1890 and 1990 in the United States. *Ann Epidemiol*. 2012;22:554–561. doi: 10.1016/j.annepidem.2012.04.021
35. Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. *Obes Rev*. 2016;17:56–67. doi: 10.1111/obr.12316
36. Twig G, Yaniv G, Levine H, Leiba A, Goldberger N, Derazne E, Ben-Ami Shor D, Tzur D, Afek A, Shamiss A, Haklai Z, Kark JD. Body-mass index in 2.3 million adolescents and cardiovascular death in adulthood. *N Engl J Med*. 2016;374:2430–2440. doi: 10.1056/NEJMoa1503840
37. Singh GM, Danaei G, Farzadfar F, Stevens GA, Woodward M, Wormser D, Kaptoge S, Whitlock G, Qiao Q, Lewington S, Di Angelantonio E, Vander Hoorn S, Lawes CM, Ali MK, Mozaffarian D, Ezzati M; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group; Asia-Pacific Cohort Studies Collaboration (APCSC); Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe (DECODE); Emerging Risk Factor Collaboration (ERFC); Prospective Studies Collaboration (PSC). The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. *PLoS One*. 2013;8:e65174. doi: 10.1371/journal.pone.0065174
38. McTigue KM, Chang YF, Eaton C, Garcia L, Johnson KC, Lewis CE, Liu S, Mackey RH, Robinson J, Rosal MC, Snetselaar L, Valoski A, Kuller LH. Severe obesity, heart disease, and death among white, African American, and Hispanic postmenopausal women. *Obesity (Silver Spring)*. 2014;22:801–810. doi: 10.1002/oby.20224
39. Emerging Risk Factors Collaboration. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet*. 2011;377:1085–1095. doi: 10.1016/S0140-6736(11)60105-0
40. Burke GL, Bertoni AG, Shea S, Tracy R, Watson KE, Blumenthal RS, Chung H, Carnethon MR. The impact of obesity on cardiovascular disease risk factors and subclinical vascular disease: the Multi-Ethnic Study of Atherosclerosis. *Arch Intern Med*. 2008;168:928–935. doi: 10.1001/archinte.168.9.928
41. Reis JP, Loria CM, Lewis CE, Powell-Wiley TM, Wei GS, Carr JJ, Terry JG, Liu K. Association between duration of overall and abdominal obesity beginning in young adulthood and coronary artery calcification in middle age. *JAMA*. 2013;310:280–288. doi: 10.1001/jama.2013.7833
42. Strazzullo P, D'Elia L, Cairella G, Garbagnati F, Cappuccio FP, Scalfi L. Excess body weight and incidence of stroke: meta-analysis of prospective studies with 2 million participants. *Stroke*. 2010;41:e418–e426. doi: 10.1161/STROKEAHA.109.576967
43. Chatterjee NA, Giulianini F, Geelhoed B, Lunetta KL, Misialek JR, Niemeijer MN, Rienstra M, Rose LM, Smith AV, Arking DE, Ellinor PT, Heeringa J, Lin H, Lubitz SA, Soliman EZ, Verweij N, Alonso A, Benjamin EJ, Gudnason V, Stricker BHC, Van Der Harst P, Chasman DI, Albert CM. Genetic obesity and the risk of atrial fibrillation: causal estimates from mendelian randomization. *Circulation*. 2017;135:741–754. doi: 10.1161/CIRCULATIONAHA.116.024921
44. Anstey KJ, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. *Obes Rev*. 2011;12:e426–e437. doi: 10.1111/j.1467-789X.2010.00825.x
45. Loef M, Walach H. Midlife obesity and dementia: meta-analysis and adjusted forecast of dementia prevalence in the United States and China. *Obesity (Silver Spring)*. 2013;21:E51–E55. doi: 10.1002/oby.20037
46. Chang VW, Langa KM, Weir D, Iwashyna TJ. The obesity paradox and incident cardiovascular disease: A population-based study. *PLoS One*. 2017;12:e0188636. doi: 10.1371/journal.pone.0188636
47. Badheka AO, Rathod A, Kizilbash MA, Garg N, Mohamad T, Afonso L, Jacob S. Influence of obesity on outcomes in atrial fibrillation: yet another obesity paradox. *Am J Med*. 2010;123:646–651. doi: 10.1016/j.amjmed.2009.11.026
48. Carnethon MR, De Chavez PJ, Biggs ML, Lewis CE, Pankow JS, Bertoni AG, Golden SH, Liu K, Mukamal KJ, Campbell-Jenkins B, Dyer AR. Association of weight status with mortality in adults with incident diabetes [published correction appears in *JAMA*. 2012;308:2085]. *JAMA*. 2012;308:581–590. doi: 10.1001/jama.2012.9282
49. van Vliet-Ostaptchouk JV, Nuotio ML, Slagter SN, Doiron D, Fischer K, Foco L, Gaye A, Gögele M, Heier M, Hiekkalinna T, Joensuu A, Newby C, Pang C, Partinen E, Reischl E, Schwienbacher C, Tammesoo ML, Swertz MA, Burton P, Ferretti V, Fortier I, Giepmans L, Harris JR, Hillege HL, Holmen J, Jula A, Kootstra-Ros JE, Kvaløy K, Holmen TL, Männistö S, Metspalu A, Midthjell K, Murtagh MJ, Peters A, Pramstaller PP, Saaristo T, Salomaa V, Stolk RP, Uusitupa M, van der Harst P, van der Klauw MM, Waldenberger M, Perola M, Wolffenbuttel BH. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. *BMC Endocr Disord*. 2014;14:9. doi: 10.1186/1472-6823-14-9
50. Hamer M, Bell JA, Sabia S, Batty GD, Kivimäki M. Stability of metabolically healthy obesity over 8 years: the English Longitudinal Study of Ageing. *Eur J Endocrinol*. 2015;173:703–708. doi: 10.1530/EJE-15-0449
51. Fung MD, Canning KL, Mirdamadi P, Ardern CI, Kuk JL. Lifestyle and weight predictors of a healthy overweight profile over a 20-year follow-up. *Obesity (Silver Spring)*. 2015;23:1320–1325. doi: 10.1002/oby.21087
52. Mongraw-Chaffin M, Foster MC, Anderson CAM, Burke GL, Haq N, Kalyani RR, Ouyang P, Sibley CT, Tracy R, Woodward M, Vaidya D. Metabolically healthy obesity, transition to metabolic syndrome, and cardiovascular risk. *J Am Coll Cardiol*. 2018;71:1857–1865. doi: 10.1016/j.jacc.2018.02.055
53. Mørkedal B, Vatten LJ, Romundstad PR, Laugsand LE, Janszky I. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trøndelag Health Study), Norway. *J Am Coll Cardiol*. 2014;63:1071–1078. doi: 10.1016/j.jacc.2013.11.035
54. Janszky I, Romundstad P, Laugsand LE, Vatten LJ, Mukamal KJ, Mørkedal B. Weight and weight change and risk of acute myocardial infarction and heart failure: the HUNT Study. *J Intern Med*. 2016;280:312–322. doi: 10.1111/joim.12494
55. Franks PW, Hanson RL, Knowler WC, Sievers ML, Bennett PH, Looker HC. Childhood obesity, other cardiovascular risk factors, and premature death. *N Engl J Med*. 2010;362:485–493. doi: 10.1056/NEJMoa0904130
56. Ma J, Flanders WD, Ward EM, Jemal A. Body mass index in young adulthood and premature death: analyses of the US National Health Interview Survey linked mortality files. *Am J Epidemiol*. 2011;174:934–944. doi: 10.1093/aje/kwr169
57. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. *JAMA*. 2005;293:1861–1867. doi: 10.1001/jama.293.15.1861
58. McGee DL; Diverse Populations Collaboration. Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. *Ann Epidemiol*. 2005;15:87–97. doi: 10.1016/j.annepidem.2004.05.012
59. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA*. 2013;309:71–82. doi: 10.1001/jama.2012.113905
60. Bangalore S, Fayyad R, Laskey R, DeMicco DA, Messerli FH, Waters DD. Body-weight fluctuations and outcomes in coronary disease. *N Engl J Med*. 2017;376:1332–1340. doi: 10.1056/NEJMoa1606148
61. Aune D, Sen A, Prasad M, Norat T, Janszky I, Tonstad S, Romundstad P, Vatten LJ. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. *BMJ*. 2016;353:i2156. doi: 10.1136/bmj.i2156
62. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009;373:1083–1096. doi: 10.1016/S0140-6736(09)60318-4
63. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, Moore SC, Tobias GS, Anton-Culver H, Freeman LB, Beeson WL, Clipp SL, English DR, Folsom AR, Freedman DM, Giles G, Hakansson N, Henderson KD, Hoffman-Bolton J, Hoppin JA, Koenig KL, Lee IM, Linet MS, Park Y, Pocobelli G, Schatzkin A, Sesso HD, Weiderpass E, Willcox BJ, Wolk A, Zeleniuch-Jacquotte A, Willett WC, Thun MJ. Body-mass index and mortality among 1.46 million white adults [published correction

appears in *N Engl J Med*. 2011;365:869]. *N Engl J Med*. 2010;363:2211–2219. doi: 10.1056/NEJMoa1000367
64. Das SR, Alexander KP, Chen AY, Powell-Wiley TM, Diercks DB, Peterson ED, Roe MT, de Lemos JA. Impact of body weight and extreme obesity on the presentation, treatment, and in-hospital outcomes of 50,149 patients with ST-segment elevation myocardial infarction: results from the NCDR (National Cardiovascular Data Registry). *J Am Coll Cardiol*. 2011;58:2642–2650. doi: 10.1016/j.jacc.2011.09.030
65. Terada T, Forhan M, Norris CM, Qiu W, Padwal R, Sharma AM, Nagendran J, Johnson JA. Differences in short- and long-term mortality associated with BMI following coronary revascularization. *J Am Heart Assoc*. 2017;6:e005335. doi: 10.1161/JAHA.116.005335
66. Mariscalco G, Wozniak MJ, Dawson AG, Serraino GF, Porter R, Nath M, Klersy C, Kumar T, Murphy GJ. Body mass index and mortality among adults undergoing cardiac surgery: a nationwide study with a systematic review and meta-analysis. *Circulation*. 2017;135:850–863. doi: 10.1161/CIRCULATIONAHA.116.022840
67. Hamer M, Stamatakis E. Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. *J Clin Endocrinol Metab*. 2012;97:2482–2488. doi: 10.1210/jc.2011-3475
68. Petursson H, Sigurdsson JA, Bengtsson C, Nilsen TI, Getz L. Body configuration as a predictor of mortality: comparison of five anthropometric measures in a 12 year follow-up of the Norwegian HUNT 2 study. *PLoS One*. 2011;6:e26621. doi: 10.1371/journal.pone.0026621
69. Després JP. Excess visceral adipose tissue/ectopic fat the missing link in the obesity paradox? *J Am Coll Cardiol*. 2011;57:1887–1889. doi: 10.1016/j.jacc.2010.10.063
70. Cerhan JR, Moore SC, Jacobs EJ, Kitahara CM, Rosenberg PS, Adami HO, Ebbert JO, English DR, Gapstur SM, Giles GG, Horn-Ross PL, Park Y, Patel AV, Robien K, Weiderpass E, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Hartge P, Bernstein L, Berrington de Gonzalez A. A pooled analysis of waist circumference and mortality in 650,000 adults. *Mayo Clin Proc*. 2014;89:335–345. doi: 10.1016/j.mayocp.2013.11.011
71. Adabag S, Huxley RR, Lopez FL, Chen LY, Sotoodehnia N, Siscovick D, Deo R, Konety S, Alonso A, Folsom AR. Obesity related risk of sudden cardiac death in the atherosclerosis risk in communities study. *Heart*. 2015;101:215–221. doi: 10.1136/heartjnl-2014-306238
72. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. *Health Aff (Millwood)*. 2009;28:w822–w831. doi: 10.1377/hlthaff.28.5.w822
73. An R. Health care expenses in relation to obesity and smoking among U.S. adults by gender, race/ethnicity, and age group: 1998-2011. *Public Health*. 2015;129:29–36. doi: 10.1016/j.puhe.2014.11.003
74. Cai L, Lubitz J, Flegal KM, Pamuk ER. The predicted effects of chronic obesity in middle age on Medicare costs and mortality. *Med Care*. 2010;48:510–517. doi: 10.1097/MLR.0b013e3181dbdb20
75. Alley D, Lloyd J, Shaffer T, Stuart B. Changes in the association between body mass index and Medicare costs, 1997-2006. *Arch Intern Med*. 2012;172:277–278. doi: 10.1001/archinternmed.2011.702
76. Lightwood J, Bibbins-Domingo K, Coxson P, Wang YC, Williams L, Goldman L. Forecasting the future economic burden of current adolescent overweight: an estimate of the coronary heart disease policy model. *Am J Public Health*. 2009;99:2230–2237. doi: 10.2105/AJPH.2008.152595
77. Finkelstein EA, Graham WC, Malhotra R. Lifetime direct medical costs of childhood obesity. *Pediatrics*. 2014;133:854–862. doi: 10.1542/peds.2014-0063
78. Livingston EH. The incidence of bariatric surgery has plateaued in the U.S. *Am J Surg*. 2010;200:378–385. doi: 10.1016/j.amjsurg.2009.11.007
79. Finkelstein EA, Allaire BT, Dibonaventura MD, Burgess SM. Incorporating indirect costs into a cost-benefit analysis of laparoscopic adjustable gastric banding. *Value Health*. 2012;15:299–304. doi: 10.1016/j.jval.2011.12.004
80. Wang BC, Wong ES, Alfonso-Cristancho R, He H, Flum DR, Arterburn DE, Garrison LP, Sullivan SD. Cost-effectiveness of bariatric surgical procedures for the treatment of severe obesity. *Eur J Health Econ*. 2014;15:253–263. doi: 10.1007/s10198-013-0472-5
81. Maciejewski ML, Livingston EH, Smith VA, Kahwati LC, Henderson WG, Arterburn DE. Health expenditures among high-risk patients after gastric bypass and matched controls. *Arch Surg*. 2012;147:633–640. doi: 10.1001/archsurg.2012.818
82. Weiner JP, Goodwin SM, Chang HY, Bolen SD, Richards TM, Johns RA, Momin SR, Clark JM. Impact of bariatric surgery on health care costs of obese persons: a 6-year follow-up of surgical and comparison cohorts using health plan data. *JAMA Surg*. 2013;148:555–562. doi: 10.1001/jamasurg.2013.1504
83. Makary MA, Clark JM, Shore AD, Magnuson TH, Richards T, Bass EB, Dominici F, Weiner JP, Wu AW, Segal JB. Medication utilization and annual health care costs in patients with type 2 diabetes mellitus before and after bariatric surgery [published correction appears in *Arch Surg*. 2011;146:659]. *Arch Surg*. 2010;145:726–731. doi: 10.1001/archsurg.2010.150
84. Keating C, Neovius M, Sjöholm K, Peltonen M, Narbro K, Eriksson JK, Sjöström L, Carlsson LM. Health-care costs over 15 years after bariatric surgery for patients with different baseline glucose status: results from the Swedish Obese Subjects study [published correction appears in *Lancet Diabetes Endocrinol*. 2015;3:e11]. *Lancet Diabetes Endocrinol*. 2015;3:855–865. doi: 10.1016/S2213-8587(15)00290-9
85. Banerjee S, Garrison LP Jr, Flum DR, Arterburn DE. Cost and health care utilization implications of bariatric surgery versus intensive lifestyle and medical intervention for type 2 diabetes. *Obesity (Silver Spring)*. 2017;25:1499–1508. doi: 10.1002/oby.21927
86. Klebanoff MJ, Corey KE, Chhatwal J, Kaplan LM, Chung RT, Hur C. Bariatric surgery for nonalcoholic steatohepatitis: a clinical and cost-effectiveness analysis. *Hepatology*. 2017;65:1156–1164. doi: 10.1002/hep.28958
87. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA*. 2014;311:806–814. doi: 10.1001/jama.2014.732
88. Saydah S, Bullard KM, Cheng Y, Ali MK, Gregg EW, Geiss L, Imperatore G. Trends in cardiovascular disease risk factors by obesity level in adults in the United States, NHANES 1999-2010. *Obesity (Silver Spring)*. 2014;22:1888–1895. doi: 10.1002/oby.20761
89. Freedman DS, Ford ES. Are the recent secular increases in the waist circumference of adults independent of changes in BMI? *Am J Clin Nutr*. 2015;101:425–431. doi: 10.3945/ajcn.114.094672
90. Feng J, Glass TA, Curriero FC, Stewart WF, Schwartz BS. The built environment and obesity: a systematic review of the epidemiologic evidence. *Health Place*. 2010;16:175–190. doi: 10.1016/j.healthplace.2009.09.008
91. Cooklin A, Joss N, Husser E, Oldenburg B. Integrated approaches to occupational health and safety: a systematic review. *Am J Health Promot*. 2017;31:401–412. doi: 10.4278/ajhp.141027-LIT-542
92. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. *Obes Rev*. 2016;17:95–107. doi: 10.1111/obr.12334
93. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention website. Prevention Status Reports. 2016. http://www.cdc.gov/psr/. Accessed June 8, 2016.
94. World Obesity Federation. Policies and interventions. World Obesity Federation website. 2015. http://www.worldobesity.org/resources/policies-and-interventions/. Accessed June 8, 2016.
95. Duncan DT, Wolin KY, Scharoun-Lee M, Ding EL, Warner ET, Bennett GG. Does perception equal reality? Weight misperception in relation to weight-related attitudes and behaviors among overweight and obese US adults. *Int J Behav Nutr Phys Act*. 2011;8:20. doi: 10.1186/1479-5868-8-20
96. Hansen AR, Duncan DT, Baidal JA, Hill A, Turner SC, Zhang J. An increasing trend in health care professionals notifying children of unhealthy weight status: NHANES 1999–2014. *Int J Obes (Lond)*. 2016;40:1480–1485. doi: 10.1038/ijo.2016.85
97. The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes [published correction appears in *N Engl J Med*. 2014;370:1866]. *N Engl J Med*. 2013;369:145–154. doi: 10.1056/NEJMoa1212914
98. Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: the Look AHEAD study. *Obesity (Silver Spring)*. 2014;22:5–13. doi: 10.1002/oby.20662
99. Rubino F, Nathan DM, Eckel RH, Schauer PR, Alberti KG, Zimmet PZ, Del Prato S, Ji L, Sadikot SM, Herman WH, Amiel SA, Kaplan LM, Taroncher-Oldenburg G, Cummings DE; Delegates of the 2nd Diabetes Surgery Summit. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. *Diabetes Care*. 2016;39:861–877. doi: 10.2337/dc16-0236
100. Ho M, Garnett SP, Baur L, Burrows T, Stewart L, Neve M, Collins C. Effectiveness of lifestyle interventions in child obesity: systematic review with meta-analysis. *Pediatrics*. 2012;130:e1647–e1671. doi: 10.1542/peds.2012-1176
101. Ma C, Avenell A, Bolland M, Hudson J, Stewart F, Robertson C, Sharma P, Fraser C, MacLennan G. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and

cancer: systematic review and meta-analysis. *BMJ*. 2017;359:j4849. doi: 10.1136/bmj.j4849
102. Sjöström CD, Lystig T, Lindroos AK. Impact of weight change, secular trends and ageing on cardiovascular risk factors: 10-year experiences from the SOS study. *Int J Obes (Lond)*. 2011;35:1413–1420. doi: 10.1038/ijo.2010.282
103. Wefers JF, Woodlief TL, Carnero EA, Helbling NL, Anthony SJ, Dubis GS, Jakicic JM, Houmard JA, Goodpaster BH, Coen PM. Relationship among physical activity, sedentary behaviors, and cardiometabolic risk factors during gastric bypass surgery-induced weight loss. *Surg Obes Relat Dis*. 2017;13:210–219. doi: 10.1016/j.soard.2016.08.493
104. Shubeck S, Dimick JB, Telem DA. Long-term outcomes following bariatric surgery. *JAMA*. 2018;319:302–303. doi: 10.1001/jama.2017.20521
105. Arterburn DE, Courcoulas AP. Bariatric surgery for obesity and metabolic conditions in adults. *BMJ*. 2014;349:g3961. doi: 10.1136/bmj.g3961
106. Puzziferri N, Roshek TB 3rd, Mayo HG, Gallagher R, Belle SH, Livingston EH. Long-term follow-up after bariatric surgery: a systematic review. *JAMA*. 2014;312:934–942. doi: 10.1001/jama.2014.10706
107. Marma AK, Berry JD, Ning H, Persell SD, Lloyd-Jones DM. Distribution of 10-year and lifetime predicted risks for cardiovascular disease in US adults: findings from the National Health and Nutrition Examination Survey 2003 to 2006. *Circ Cardiovasc Qual Outcomes*. 2010;3:8–14. doi: 10.1161/CIRCOUTCOMES.109.869727
108. Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, Bucher HC, Nordmann AJ. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2013;347:f5934. doi: 10.1136/bmj.f5934
109. Adams TD, Davidson LE, Litwin SE, Kim J, Kolotkin RL, Nanjee MN, Gutierrez JM, Frogley SJ, Ibele AR, Brinton EA, Hopkins PN, McKinlay R, Simper SC, Hunt SC. Weight and metabolic outcomes 12 years after gastric bypass. *N Engl J Med*. 2017;377:1143–1155. doi: 10.1056/NEJMoa1700459
110. Salminen P, Helmiö M, Ovaska J, Juuti A, Leivonen M, Peromaa-Haavisto P, Hurme S, Soinio M, Nuutila P, Victorzon M. Effect of laparoscopic sleeve gastrectomy vs laparoscopic Roux-en-Y gastric bypass on weight loss at 5 years among patients with morbid obesity: the SLEEVEPASS randomized clinical trial. *JAMA*. 2018;319:241–254. doi: 10.1001/jama.2017.20313
111. Van Osdol AD, Grover BT, Borgert AJ, Kallies KJ, Kothari SN. Impact of laparoscopic Roux-en-Y Gastric bypass versus sleeve gastrectomy on postoperative lipid values. *Surg Obes Relat Dis*. 2017;13:399–403. doi: 10.1016/j.soard.2016.09.031
112. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, Lamonte MJ, Stroup AM, Hunt SC. Long-term mortality after gastric bypass surgery. *N Engl J Med*. 2007;357:753–761. doi: 10.1056/NEJMoa066603
113. Viner R, White B, Christie D. Type 2 diabetes in adolescents: a severe phenotype posing major clinical challenges and public health burden. *Lancet*. 2017;389:2252–2260. doi: 10.1016/S0140-6736(17)31371-5
114. Vilarrasa N, Rubio MA, Miñambres I, Flores L, Caixàs A, Ciudin A, Bueno M, García-Luna PP, Ballesteros-Pomar MD, Ruiz-Adana M, Lecube A. Long-term outcomes in patients with morbid obesity and type 1 diabetes undergoing bariatric surgery. *Obes Surg*. 2017;27:856–863. doi: 10.1007/s11695-016-2390-y
115. Wardle J, Carnell S, Haworth CM, Plomin R. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. *Am J Clin Nutr*. 2008;87:398–404. doi: 10.1093/ajcn/87.2.398
116. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, Lango Allen H, Lindgren CM, Luan J, Mägi R, Randall JC, Vedantam S, Winkler TW, Qi L, Workalemahu T, Heid IM, Steinthorsdottir V, Stringham HM, Weedon MN, Wheeler E, Wood AR, Ferreira T, Weyant RJ, Segrè AV, Estrada K, Liang L, Nemesh J, Park JH, Gustafsson S, Kilpeläinen TO, Yang J, Bouatia-Naji N, Esko T, Feitosa MF, Kutalik Z, Mangino M, Raychaudhuri S, Scherag A, Smith AV, Welch R, Zhao JH, Aben KK, Absher DM, Amin N, Dixon AL, Fisher E, Glazer NL, Goddard ME, Heard-Costa NL, Hoesel V, Hottenga JJ, Johansson A, Johnson T, Ketkar S, Lamina C, Li S, Moffatt MF, Myers RH, Narisu N, Perry JR, Peters MJ, Preuss M, Ripatti S, Rivadeneira F, Sandholt C, Scott LJ, Timpson NJ, Tyrer JP, van Wingerden S, Watanabe RM, White CC, Wiklund F, Barlassina C, Chasman DI, Cooper MN, Jansson JO, Lawrence RW, Pellikka N, Prokopenko I, Shi J, Thiering E, Alavere H, Alibrandi MT, Almgren P, Arnold AM, Aspelund T, Atwood LD, Balkau B, Balmforth AJ, Bennett AJ, Ben-Shlomo Y, Bergman RN, Bergmann S, Biebermann H, Blakemore AI, Boes T, Bonnycastle LL, Bornstein SR, Brown MJ, Buchanan TA, Busonero F, Campbell H, Cappuccio FP, Cavalcanti-Proença C, Chen YD, Chen CM, Chines PS, Clarke R, Coin L, Connell J, Day IN, den Heijer M, Duan J, Ebrahim S, Elliott P, Elosua R, Eiriksdottir G, Erdos MR, Eriksson JG, Facheris MF, Felix SB, Fischer-Posovszky P, Folsom AR, Friedrich N, Freimer NB, Fu M, Gaget S, Gejman PV, Geus EJ, Gieger C, Gjesing AP, Goel A, Goyette P, Grallert H, Grässler J, Greenawalt DM, Groves CJ, Gudnason V, Guiducci C, Hartikainen AL, Hassanali N, Hall AS, Havulinna AS, Hayward C, Heath AC, Hengstenberg C, Hicks AA, Hinney A, Hofman A, Homuth G, Hui J, Igl W, Iribarren C, Isomaa B, Jacobs KB, Jarick I, Jewell E, John U, Jørgensen T, Jousilahti P, Jula A, Kaakinen M, Kajantie E, Kaplan LM, Kathiresan S, Kettunen J, Kinnunen L, Knowles JW, Kolcic I, König IR, Koskinen S, Kovacs P, Kuusisto J, Kraft P, Kvaløy K, Laitinen J, Lantieri O, Lanzani C, Launer LJ, Lecoeur C, Lehtimäki T, Lettre G, Liu J, Lokki ML, Lorentzon M, Luben RN, Ludwig B, Manunta P, Marek D, Marre M, Martin NG, McArdle WL, McCarthy A, McKnight B, Meitinger T, Melander O, Meyre D, Midthjell K, Montgomery GW, Morken MA, Morris AP, Mulic R, Ngwa JS, Nelis M, Neville MJ, Nyholt DR, O'Donnell CJ, O'Rahilly S, Ong KK, Oostra B, Paré G, Parker AN, Perola M, Pichler I, Pietiläinen KH, Platou CG, Polasek O, Pouta A, Rafelt S, Raitakari O, Rayner NW, Ridderstråle M, Rief W, Ruokonen A, Robertson NR, Rzehak P, Salomaa V, Sanders AR, Sandhu MS, Sanna S, Saramies J, Savolainen MJ, Scherag S, Schipf S, Schreiber S, Schunkert H, Silander K, Sinisalo J, Siscovick DS, Smit JH, Soranzo N, Sovio U, Stephens J, Surakka I, Swift AJ, Tammesoo ML, Tardif JC, Teder-Laving M, Teslovich TM, Thompson JR, Thomson B, Tönjes A, Tuomi T, van Meurs JB, van Ommen GJ, Vatin V, Viikari J, Visvikis-Siest S, Vitart V, Vogel CI, Voight BF, Waite LL, Wallaschofski H, Walters GB, Widen E, Wiegand S, Wild SH, Willemsen G, Witte DR, Witteman JC, Xu J, Zhang Q, Zgaga L, Ziegler A, Zitting P, Beilby JP, Farooqi IS, Hebebrand J, Huikuri HV, James AL, Kähönen M, Levinson DF, Macciardi F, Nieminen MS, Ohlsson C, Palmer LJ, Ridker PM, Stumvoll M, Beckmann JS, Boeing H, Boerwinkle E, Boomsma DI, Caulfield MJ, Chanock SJ, Collins FS, Cupples LA, Smith GD, Erdmann J, Froguel P, Grönberg H, Gyllensten U, Hall P, Hansen T, Harris TB, Hattersley AT, Hayes RB, Heinrich J, Hu FB, Hveem K, Illig T, Jarvelin MR, Kaprio J, Karpe F, Khaw KT, Kiemeney LA, Krude H, Laakso M, Lawlor DA, Metspalu A, Munroe PB, Ouwehand WH, Pedersen O, Penninx BW, Peters A, Pramstaller PP, Quertermous T, Reinehr T, Rissanen A, Rudan I, Samani NJ, Schwarz PE, Shuldiner AR, Spector TD, Tuomilehto J, Uda M, Uitterlinden A, Valle TT, Wabitsch M, Waeber G, Wareham NJ, Watkins H, Wilson JF, Wright AF, Zillikens MC, Chatterjee N, McCarroll SA, Purcell S, Schadt EE, Visscher PM, Assimes TL, Borecki IB, Deloukas P, Fox CS, Groop LC, Haritunians T, Hunter DJ, Kaplan RC, Mohlke KL, O'Connell JR, Peltonen L, Schlessinger D, Strachan DP, van Duijn CM, Wichmann HE, Frayling TM, Thorsteinsdottir U, Abecasis GR, Barroso I, Boehnke M, Stefansson K, North KE, McCarthy MI, Hirschhorn JN, Ingelsson E, Loos RJ; MAGIC; Procardis Consortium. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010;42:937–948. doi: 10.1038/ng.686
117. Kaur Y, de Souza RJ, Gibson WT, Meyre D. A systematic review of genetic syndromes with obesity. *Obes Rev*. 2017;18:603–634. doi: 10.1111/obr.12531.
118. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Smith GD, Hattersley AT, McCarthy MI. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science*. 2007;316:889–894. doi: 10.1126/science.1141634
119. Scuteri A, Sanna S, Chen WM, Uda M, Albai G, Strait J, Najjar S, Nagaraja R, Orrú M, Usala G, Dei M, Lai S, Maschio A, Busonero F, Mulas A, Ehret GB, Fink AA, Weder AB, Cooper RS, Galan P, Chakravarti A, Schlessinger D, Cao A, Lakatta E, Abecasis GR. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. *PLoS Genet*. 2007;3:e115. doi: 10.1371/journal.pgen.0030115
120. Cho YS, Go MJ, Kim YJ, Heo JY, Oh JH, Ban HJ, Yoon D, Lee MH, Kim DJ, Park M, Cha SH, Kim JW, Han BG, Min H, Ahn Y, Park MS, Han HR, Jang HY, Cho EY, Lee JE, Cho NH, Shin C, Park T, Park JW, Lee JK, Cardon L, Clarke G, McCarthy MI, Lee JY, Lee JK, Oh B, Kim HL. A large-scale genome-wide association study of Asian populations uncovers genetic factors influencing eight quantitative traits. *Nat Genet*. 2009;41:527–534. doi: 10.1038/ng.357
121. Wen W, Cho YS, Zheng W, Dorajoo R, Kato N, Qi L, Chen CH, Delahanty RJ, Okada Y, Tabara Y, Gu D, Zhu D, Haiman CA, Mo Z, Gao YT, Saw SM,

Go MJ, Takeuchi F, Chang LC, Kokubo Y, Liang J, Hao M, Le Marchand L, Zhang Y, Hu Y, Wong TY, Long J, Han BG, Kubo M, Yamamoto K, Su MH, Miki T, Henderson BE, Song H, Tan A, He J, Ng DP, Cai Q, Tsunoda T, Tsai FJ, Iwai N, Chen GK, Shi J, Xu J, Sim X, Xiang YB, Maeda S, Ong RT, Li C, Nakamura Y, Aung T, Kamatani N, Liu JJ, Lu W, Yokota M, Seielstad M, Fann CS, Wu JY, Lee JY, Hu FB, Tanaka T, Tai ES, Shu XO; Genetic Investigation of ANthropometric Traits (GIANT) Consortium. Meta-analysis identifies common variants associated with body mass index in east Asians. *Nat Genet*. 2012;44:307–311. doi: 10.1038/ng.1087

122. Okada Y, Kubo M, Ohmiya H, Takahashi A, Kumasaka N, Hosono N, Maeda S, Wen W, Dorajoo R, Go MJ, Zheng W, Kato N, GIANT Consortium,Wu JY, Lu Q, Tsunoda T, Yamamoto K, Nakamura Y, Kamatani N, Tanaka T. Common variants at CDKAL1 and KLF9 are associated with body mass index in east Asian populations. *Nat Genet*. 2012;44:302–306. doi: 10.1038/ng.1086

123. Monda KL, Chen GK, Taylor KC, Palmer C, Edwards TL, Lange LA, Ng MC, Adeyemo AA, Allison MA, Bielak LF, Chen G, Graff M, Irvin MR, Rhie SK, Li G, Liu Y, Liu Y, Lu Y, Nalls MA, Sun YV, Wojczynski MK, Yanek LR, Aldrich MC, Ademola A, Amos CI, Bandera EV, Bock CH, Britton A, Broeckel U, Cai Q, Caporaso NE, Carlson CS, Carpten J, Casey G, Chen WM, Chen F, Chen YD, Chiang CW, Coetzee GA, Demerath E, Deming-Halverson SL, Driver RW, Dubbert P, Feitosa MF, Feng Y, Freedman BI, Gillanders EM, Gottesman O, Guo X, Haritunians T, Harris T, Harris CC, Hennis AJ, Hernandez DG, McNeill LH, Howard TD, Howard BV, Howard VJ, Johnson KC, Kang SJ, Keating BJ, Kolb S, Kuller LH, Kutlar A, Langefeld CD, Lettre G, Lohman K, Lotay V, Lyon H, Manson JE, Maixner W, Meng YA, Monroe KR, Morhason-Bello I, Murphy AB, Mychaleckyj JC, Nadukuru R, Nathanson KL, Nayak U, N'diaye A, Nemesure B, Wu SY, Leske MC, Neslund-Dudas C, Neuhouser M, Nyante S, Ochs-Balcom H, Ogunniyi A, Ogundiran TO, Ojengbede O, Olopade OI, Palmer JR, Ruiz-Narvaez EA, Palmer ND, Press MF, Rampersaud E, Rasmussen-Torvik LJ, Rodriguez-Gil JL, Salako B, Schadt EE, Schwartz AG, Shriner DA, Siscovick D, Smith SB, Wassertheil-Smoller S, Speliotes EK, Spitz MR, Sucheston L, Taylor H, Tayo BO, Tucker MA, Van Den Berg DJ, Edwards DR, Wang Z, Wiencke JK, Winkler TW, Witte JS, Wrensch M, Wu X, Yang JJ, Levin AM, Young TR, Zakai NA, Cushman M, Zanetti KA, Zhao JH, Zhao W, Zheng Y, Zhou J, Ziegler RG, Zmuda JM, Fernandes JK, Gilkeson GS, Kamen DL, Hunt KJ, Spruill IJ, Ambrosone CB, Ambs S, Arnett DK, Atwood L, Becker DM, Berndt SI, Bernstein L, Blot WJ, Borecki IB, Bottinger EP, Bowden DW, Burke G, Chanock SJ, Cooper RS, Ding J, Duggan D, Evans MK, Fox C, Garvey WT, Bradfield JP, Hakonarson H, Grant SF, Hsing A, Chu L, Hu JJ, Huo D, Ingles SA, John EM, Jordan JM, Kabagambe EK, Kardia SL, Kittles RA, Goodman PJ, Klein EA, Kolonel LN, Le Marchand L, Liu S, McKnight B, Millikan RC, Mosley TH, Padhukasahasram B, Williams LK, Patel SR, Peters U, Pettaway CA, Peyser PA, Psaty BM, Redline S, Rotimi CN, Rybicki BA, Sale MM, Schreiner PJ, Signorello LB, Singleton AB, Stanford JL, Strom SS, Thun MJ, Vitolins M, Zheng W, Moore JH, Williams SM, Ketkar S, Zhu X, Zonderman AB, Kooperberg C, Papanicolaou GJ, Henderson BE, Reiner AP, Hirschhorn JN, Loos RJ, North KE, Haiman CA; NABEC Consortium; UKBEC Consortium; BioBank Japan Project; AGEN Consortium. A meta-analysis identifies new loci associated with body mass index in individuals of African ancestry. *Nat Genet*. 2013;45:690–696. doi: 10.1038/ng.2608

124. Loos RJ, Yeo GS. The bigger picture of FTO: the first GWAS-identified obesity gene. *Nat Rev Endocrinol*. 2014;10:51–61. doi: 10.1038/nrendo.2013.227

125. Speakman JR. The "fat mass and obesity related" (FTO) gene: mechanisms of impact on obesity and energy balance. *Curr Obes Rep*. 2015;4:73–91. doi: 10.1007/s13679-015-0143-1

126. Fall T, Ingelsson E. Genome-wide association studies of obesity and metabolic syndrome. *Mol Cell Endocrinol*. 2014;382:740–757. doi: 10.1016/j.mce.2012.08.018

127. Ng MCY, Graff M, Lu Y, Justice AE, Mudgal P, Liu CT, Young K, Yanek LR, Feitosa MF, Wojczynski MK, Rand K, Brody JA, Cade BE, Dimitrov L, Duan Q, Guo X, Lange LA, Nalls MA, Okut H, Tajuddin SM, Tayo BO, Vedantam S, Bradfield JP, Chen G, Chen WM, Chesi A, Irvin MR, Padhukasahasram B, Smith JA, Zheng W, Allison MA, Ambrosone CB, Bandera EV, Bartz TM, Berndt SI, Bernstein L, Blot WJ, Bottinger EP, Carpten J, Chanock SJ, Chen YI, Conti DV, Cooper RS, Fornage M, Freedman BI, Garcia M, Goodman PJ, Hsu YH, Hu J, Huff CD, Ingles SA, John EM, Kittles R, Klein E, Li J, McKnight B, Nayak U, Nemesure B, Ogunniyi A, Olshan A, Press MF, Rohde R, Rybicki BA, Salako B, Sanderson M, Shao Y, Siscovick DS, Stanford JL, Stevens VL, Stram A, Strom SS, Vaidya D, Witte JS, Yao J, Zhu X, Ziegler RG, Zonderman AB, Adeyemo A, Ambs S, Cushman M, Faul JD, Hakonarson H, Levin AM, Nathanson KL, Ware EB, Weir DR, Zhao W, Zhi D, Arnett DK, Grant SFA, Kardia SLR, Oloapde OI, Rao DC, Rotimi CN, Sale MM, Williams LK, Zemel BS, Becker DM, Borecki IB, Evans MK, Harris TB, Hirschhorn JN, Li Y, Patel SR, Psaty BM, Rotter JI, Wilson JG, Bowden DW, Cupples LA, Haiman CA, Loos RJF, North KE; Bone Mineral Density in Childhood Study (BMDCS) Group. Discovery and fine-mapping of adiposity loci using high density imputation of genome-wide association studies in individuals of African ancestry: African Ancestry Anthropometry Genetics Consortium. *PLoS Genet*. 2017;13:e1006719. doi: 10.1371/journal.pgen.1006719

128. Justice AE, Winkler TW, Feitosa MF, Graff M, Fisher VA, Young K, Barata L, Deng X, Czajkowski J, Hadley D, Ngwa JS, Ahluwalia TS, Chu AY, Heard-Costa NL, Lim E, Perez J, Eicher JD, Kutalik Z, Xue L, Mahajan A, Renström F, Wu J, Qi Q, Ahmad S, Alfred T, Amin N, Bielak LF, Bonnefond A, Bragg J, Cadby G, Chittani M, Coggeshall S, Corre T, Direk N, Eriksson J, Fischer K, Gorski M, Neergaard Harder M, Horikoshi M, Huang T, Huffman JE, Jackson AU, Justesen JM, Kanoni S, Kinnunen L, Kleber ME, Komulainen P, Kumari M, Lim U, Luan J, Lyytikäinen LP, Mangino M, Manichaikul A, Marten J, Middelberg RPS, Müller-Nurasyid M, Navarro P, Pérusse L, Pervjakova N, Sarti C, Smith AV, Smith JA, Stančáková A, Strawbridge RJ, Stringham HM, Sung YJ, Tanaka T, Teumer A, Trompet S, van der Laan SW, van der Most PJ, Van Vliet-Ostaptchouk JV, Vedantam SL, Verweij N, Vink JM, Vitart V, Wu Y, Yengo L, Zhang W, Hua Zhao J, Zimmermann ME, Zubair N, Abecasis GR, Adair LS, Afaq S, Afzal U, Bakker SJL, Bartz TM, Beilby J, Bergman RN, Bergmann S, Biffar R, Blangero J, Boerwinkle E, Bonnycastle LL, Bottinger E, Braga D, Buckley BM, Buyske S, Campbell H, Chambers JC, Collins FS, Curran JE, de Borst GJ, de Craen AJM, de Geus EJC, Dedoussis G, Delgado GE, den Ruijter HM, Eiriksdottir G, Eriksson AL, Esko T, Faul JD, Ford I, Forrester T, Gertow K, Gigante B, Glorioso N, Gong J, Grallert H, Grammer TB, Grarup N, Haitjema S, Hallmans G, Hamsten A, Hansen T, Harris TB, Hartman CA, Hassinen M, Hastie ND, Heath AC, Hernandez D, Hindorff L, Hocking LJ, Hollensted M, Holmen OL, Homuth G, Jan Hottenga J, Huang J, Hung J, Hutri-Kähönen N, Ingelsson E, James AL, Jansson JO, Jarvelin MR, Jhun MA, Jørgensen ME, Juonala M, Kähönen M, Karlsson M, Koistinen HA, Kolcic I, Kolovou G, Kooperberg C, Krämer BK, Kuusisto J, Kvaløy K, Lakka TA, Langenberg C, Launer LJ, Leander K, Lee NR, Lind L, Lindgren CM, Linneberg A, Lobbens S, Loh M, Lorentzon M, Luben R, Lubke G, Ludolph-Donislawski A, Lupoli S, Madden PAF, Männikkö R, Marques-Vidal P, Martin NG, McKenzie CA, McKnight B, Mellström D, Menni C, Montgomery GW, Musk AB, Narisu N, Nauck M, Nolte IM, Oldehinkel AJ, Olden M, Ong KK, Padmanabhan S, Peyser PA, Pisinger C, Porteous DJ, Raitakari OT, Rankinen T, Rao DC, Rasmussen-Torvik LJ, Rawal R, Rice T, Ridker PM, Rose LM, Bien SA, Rudan I, Sanna S, Sarzynski MA, Sattar N, Savonen K, Schlessinger D, Scholtens S, Schurmann C, Scott RA, Sennblad B, Siemelink MA, Silbernagel G, Slagboom PE, Snieder H, Staessen JA, Stott DJ, Swertz MA, Swift AJ, Taylor KD, Tayo BO, Thorand B, Thuillier D, Tuomilehto J, Uitterlinden AG, Vandenput L, Vohl MC, Völzke H, Vonk JM, Waeber G, Waldenberger M, Westendorp RGJ, Wild S, Willemsen G, Wolffenbuttel BHR, Wong A, Wright AF, Zhao W, Zillikens MC, Baldassarre D, Balkau B, Bandinelli S, Böger CA, Boomsma DI, Bouchard C, Bruinenberg M, Chasman DI, Chen YD, Chines PS, Cooper RS, Cucca F, Cusi D, Faire U, Ferrucci L, Franks PW, Froguel P, Gordon-Larsen P, Grabe HJ, Gudnason V, Haiman CA, Hayward C, Hveem K, Johnson AD, Wouter Jukema J, Kardia SLR, Kivimaki M, Kooner JS, Kuh D, Laakso M, Lehtimäki T, Marchand LL, März W, McCarthy MI, Metspalu A, Morris AP, Ohlsson C, Palmer LJ, Pasterkamp G, Pedersen O, Peters A, Peters U, Polasek O, Psaty BM, Qi L, Rauramaa R, Smith BH, Sørensen TIA, Strauch K, Tiemeier H, Tremoli E, van der Harst P, Vestergaard H, Vollenweider P, Wareham NJ, Weir DR, Whitfield JB, Wilson JF, Tyrrell J, Frayling TM, Barroso I, Boehnke M, Deloukas P, Fox CS, Hirschhorn JN, Hunter DJ, Spector TD, Strachan DP, van Duijn CM, Heid IM, Mohlke KL, Marchini J, Loos RJF, Kilpeläinen TO, Liu CT, Borecki IB, North KE, Cupples LA. Genome-wide meta-analysis of 241,258 adults accounting for smoking behaviour identifies novel loci for obesity traits. *Nat Commun*. 2017;8:14977. doi: 10.1038/ncomms14977

129. Dick KJ, Nelson CP, Tsaprouni L, Sandling JK, Aïssi D, Wahl S, Meduri E, Morange PE, Gagnon F, Grallert H, Waldenberger M, Peters A, Erdmann J, Hengstenberg C, Cambien F, Goodall AH, Ouwehand WH, Schunkert H, Thompson JR, Spector TD, Gieger C, Trégouët DA, Deloukas P, Samani NJ. DNA methylation and body-mass index: a genome-wide analysis. *Lancet*. 2014;383:1990–1998. doi: 10.1016/S0140-6736(13)62674-4

130. Global Burden of Disease Study 2016. Global Burden of Disease Study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and

Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed May 1, 2018.
131. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants [published correction appears in *Lancet*. 2016;387:1998]. *Lancet*. 2016;387:1377–1396. doi: 10.1016/S0140-6736(16)30054-X
132. Price AJ, Crampin AC, Amberbir A, Kayuni-Chihana N, Musicha C, Tafatatha T, Branson K, Lawlor DA, Mwaiyeghele E, Nkhwazi L, Smeeth L, Pearce N, Munthali E, Mwagomba BM, Mwansambo C, Glynn JR, Jaffar S, Nyirenda M. Prevalence of obesity, hypertension, and diabetes, and cascade of care in sub-Saharan Africa: a cross-sectional, population-based study in rural and urban Malawi. *Lancet Diabetes Endocrinol*. 2018;6:208–222. doi: 10.1016/S2213-8587(17)30432-1
133. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, Abraham JP, Abu-Rmeileh NM, Achoki T, AlBuhairan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Guzman NA, Ammar W, Anwari P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J, Cabral N, Nonato IC, Chang JC, Chowdhury R, Courville KJ, Criqui MH, Cundiff DK, Dabhadkar KC, Dandona L, Davis A, Dayama A, Dharmaratne SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DF, Feigin VL, Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hafezi-Nejad N, Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A, Idrisov BT, Ikeda N, Islami F, Jahangir E, Jassal SK, Jee SH, Jeffreys M, Jonas JB, Kabagambe EK, Khalifa SE, Kengne AP, Khader YS, Khang YH, Kim D, Kimokoti RW, Kinge JM, Kokubo Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand D, Narayan KM, Nelson EL, Neuhouser ML, Nisar MI, Ohkubo T, Oti SO, Pedroza A, Prabhakaran D, Roy N, Sampson U, Seo H, Sepanlou SG, Shibuya K, Shiri R, Shiue I, Singh GM, Singh JA, Skirbekk V, Stapelberg NJ, Sturua L, Sykes BL, Tobias M, Tran BX, Trasande L, Toyoshima H, van de Vijver S, Vasankari TJ, Veerman JL, Velasquez-Melendez G, Vlassov VV, Vollset SE, Vos T, Wang C, Wang X, Weiderpass E, Werdecker A, Wright JL, Yang YC, Yatsuya H, Yoon J, Yoon SJ, Zhao Y, Zhou M, Zhu S, Lopez AD, Murray CJ, Gakidou E. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013 [published correction appears in *Lancet*. 2014;384:746]. *Lancet*. 2014;384:766–781. doi: 10.1016/S0140-6736(14)60460-8
134. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, Singh GM, Gutierrez HR, Lu Y, Bahalim AN, Farzadfar F, Riley LM, Ezzati M; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet*. 2011;377(9765):557–567. doi: 10.1016/S0140-6736(10)62037-5
135. Choukem SP, Kengne AP, Nguefack ML, Mboue-Djieka Y, Nebongo D, Guimezap JT, Mbanya JC. Four-year trends in adiposity and its association with hypertension in serial groups of young adult university students in urban Cameroon: a time-series study. *BMC Public Health*. 2017;17:499. doi: 10.1186/s12889-017-4449-7
136. The GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years *N Engl J Med*. 2017;377:13–27. doi: 10.1056/NEJMoa1614362
137. Barlow SE; Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics*. 2007;120(suppl 4):S164–S192. doi: 10.1542/peds.2007-2329C
138. United States Census Bureau. American Community Survey (ACS): summary file. https://www.census.gov/programs-surveys/acs/data/summary-file.html. Accessed August 22, 2016.

7. HIGH BLOOD CHOLESTEROL AND OTHER LIPIDS

See Table 7-1 and Charts 7-1 through 7-5

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Cholesterol is one of the primary causal risk factors for the development of atherosclerotic CVD. The AHA has defined untreated TC levels <200 mg/dL as one of the 7 components of ideal cardiovascular health.[1] Thus, there is substantial interest in lowering average cholesterol levels in populations and in identifying individuals likely to benefit from targeted cholesterol-lowering interventions.

US-based population estimates of prevalence reported in this chapter are from unpublished NHLBI summary statistics that are derived from 2013 to 2016 NHANES data for youth and adults for TC and HDL-C. Data are from 2011 to 2014 for LDL-C and triglycerides. For statistics pertaining to dietary cholesterol, fats, and other lifestyle factors that affect cholesterol concentrations, see Chapter 4 (Physical Inactivity), Chapter 5 (Nutrition), and Chapter 6 (Overweight and Obesity).

Abbreviations Used in Chapter 7

ACC	American College of Cardiology
AHA	American Heart Association
ASCVD	atherosclerotic cardiovascular disease
BRFSS	Behavioral Risk Factor Surveillance System
CAD	coronary artery disease
CETP	cholesteryl ester transfer protein
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
DALY	disability-adjusted life-year
DM	diabetes mellitus
FH	familial hypercholesterolemia
GBD	Global Burden of Disease
GWAS	genome wide association studies
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular events
Mex. Am.	Mexican American
NCHS	National Center for Health Statistics
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
PCSK9	proprotein convertase subtilisin kexin 9
QALY	quality-adjusted life-year
RCT	randomized controlled trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SES	socioeconomic status
SOL	Studies of Latinos
TC	total cholesterol
WHO	World Health Organization

Prevalence of High TC

Youth

Ages 6 to 11 years:

- Among children 6 to 11 years of age, the mean TC level is 157.8 mg/dL. For boys, it is 157.9 mg/dL; for girls, it is 157.7 mg/dL. The racial/ethnic breakdown in NHANES 2013 to 2016 is as follows (unpublished NHLBI tabulation):
  - — For NH whites, 157.1 mg/dL for boys and 159.1 mg/dL for girls
  - — For NH blacks, 158.8 mg/dL for boys and 158.2 mg/dL for girls
  - — For Hispanics, 158.7 mg/dL for boys and 153.9 mg/dL for girls
  - — For NH Asians, 160.1 mg/dL for boys and 161.5 mg/dL for girls

Adolescents, ages 12 to 19 years:

- Among adolescents 12 to 19 years of age in NHANES 2013 to 2016, the mean TC level was 154.4 mg/dL; for boys, it was 151.6 mg/dL; for girls, it was 157.5 mg/dL. The racial/ethnic breakdown is as follows (unpublished NHLBI tabulation):
  - — For NH whites, 150.6 mg/dL for boys and 157.2 mg/dL for girls
  - — For NH blacks, 150.8 mg/dL for boys and 156.0 mg/dL for girls
  - — For Hispanics, 152.7 mg/dL for boys and 156.0 mg/dL for girls
  - — For NH Asians, 155.4 mg/dL for boys and 170.2 mg/dL for girls
- From 1999 to 2016, mean serum TC for adolescents 12 to 19 years of age decreased across all subgroups of race and sex (Chart 7-1).
- Fewer than 1% of adolescents are potentially eligible for pharmacological treatment on the basis of guidelines from the American Academy of Pediatrics.[2,3]

Adults (Aged ≥20 Years) (See Table 7-1 and Charts 7-2 through 7-4)

- An estimated 28.5 million adults ≥20 years of age have serum TC levels ≥240 mg/dL (extrapolated for 2016 by use of NCHS/NHANES 2013–2016 data), with a prevalence of 11.7%. From 1999 to 2016, mean serum TC for adults ≥20 years of age decreased across all subgroups of race (Chart 7-2).
- During the period from 2013 to 2016 (unpublished NHLBI tabulation):
  - — The percentage of adults with high TC (≥240 mg/dL) was lower for NH black than for NH white and Hispanic adults; the same patterns were seen in males and females.
  - — NH black males ≥20 years of age had the lowest age-adjusted prevalence of serum TC ≥240 mg/dL (Chart 7-4).

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   — Females had a higher prevalence of high TC ≥240 mg/dL (12.4%) than males (10.7%) (Table 7-1).
- The prevalence of high TC has decreased over time, from 18.3% of adults in 1999 to 2000 to 11.0% of adults in 2013 to 2014.[4]
- During 2013 to 2016, increases in the prevalence rates of high TC (≥240 mg/dL) were seen in NH white and black males and females (Chart 7-4).
- However, the age-adjusted mean TC level for NH white adults ≥20 years of age declined linearly from 1999 to 2016. Similar trends were seen for NH white, NH black, and Mexican American males and females (Chart 7-2).
- The Healthy People 2010 guideline of an age-adjusted mean TC level of ≤200 mg/dL has been achieved in adults, in males, in females, and in all race/ethnicity and sex subgroups.[5] The Healthy People 2020 target is a mean total blood cholesterol of 177.9 mg/dL for adults, which had not been achieved in males or females as of 2011 to 2014 NHANES data[6] (Chart 7-2).
- Overall, the decline in mean cholesterol levels in recent years likely reflects greater uptake of cholesterol-lowering medications rather than changes in dietary patterns.[7]

Lipid Subfractions

LDL Cholesterol

Youth

- There are limited data available on LDL-C for children 6 to 11 years of age.
- Among adolescents 12 to 19 years of age in NHANES (2011–2014), the mean LDL-C level was 87.7 mg/dL (boys, 85.7 mg/dL; girls, 89.8 mg/dL). The racial/ethnic breakdown was as follows (unpublished NHLBI tabulation):
   — For NH whites, 86.5 mg/dL for boys and 89.9 mg/dL for girls
   — For NH blacks, 86.6 mg/dL for boys and 90.9 mg/dL for girls
   — For Hispanic Americans, 85.9 mg/dL for boys and 87.8 mg/dL for girls
   — For NH Asians, 84.5 mg/dL for boys and 96.9 mg/dL for girls
- High levels of LDL-C occurred in 5.5% of male adolescents and 7.5% of female adolescents during 2011 to 2014 (unpublished NHLBI tabulation).

Adults

- The mean level of LDL-C for American adults ≥20 years of age was 113.4 mg/dL in 2011 to 2014 (unpublished NHLBI tabulation).
- According to NHANES 2013 to 2014 (unpublished NHLBI tabulation):
   — Among NH whites, mean LDL-C levels were 112.1 mg/dL for males and 114.9 mg/dL for females.
   — Among NH blacks, mean LDL-C levels were 110.4 mg/dL for males and 111.4 mg/dL for females.
   — Among Hispanics, mean LDL-C levels were 119.2 mg/dL for males and 112.6 mg/dL for females.
   — Among NH Asians, mean LDL-C levels were 112.4 mg/dL for males and 110.3 mg/dL for females.
- Mean levels of LDL-C decreased from 126.2 mg/dL during 1999 to 2000 to 111.3 mg/dL during 2013 to 2014. The age-adjusted prevalence of high LDL-C (≥130 mg/dL) decreased from 42.9% during 1999 to 2000 to 28.5% during 2013 to 2014 (unpublished NHLBI tabulation).

HDL Cholesterol

Youth

- Among children 6 to 11 years of age in NHANES 2013 to 2016, the mean HDL-C level was 56.0 mg/dL. For boys, it was 57.4 mg/dL, and for girls, it was 54.5 mg/dL. The racial/ethnic breakdown was as follows (unpublished NHLBI tabulation):
   — For NH whites, 56.6 mg/dL for boys and 54.7 mg/dL for girls
   — For NH blacks, 62.5 mg/dL for boys and 58.1 mg/dL for girls
   — For Hispanics, 55.9 mg/dL for boys and 52.2 mg/dL for girls
   — For NH Asians, 58.1 mg/dL for boys and 54.4 mg/dL for girls
- Among adolescents 12 to 19 years of age, the mean HDL-C level was 51.8 mg/dL. For boys, it was 49.9 mg/dL, and for girls, it was 53.8 mg/dL. The racial/ethnic breakdown was as follows (NHANES 2013–2016, unpublished NHLBI tabulation):
   — For NH whites, 49.2 mg/dL for boys and 53.5 mg/dL for girls
   — For NH blacks, 54.4 mg/dL for boys and 56.9 mg/dL for girls
   — For Hispanics, 49.6 mg/dL for boys and 52.2 mg/dL for girls
   — For NH Asians, 52.8 mg/dL for boys and 56.6 mg/dL for girls
- Low levels of HDL-C occurred in 20.4% of male adolescents and 10.4% of female adolescents in NHANES 2013 to 2016 (unpublished NHLBI tabulation).

Adults

- According to NHANES 2013 to 2016 (unpublished NHLBI tabulation), the mean level of

HDL-C for American adults ≥20 years of age is 54.2 mg/dL.
  - Among NH whites, mean HDL-C levels were 48.4 mg/dL for males and 60.9 mg/dL for females.
  - Among NH blacks, mean HDL-C levels were 52.8 mg/dL for males and 60.1 mg/dL for females.
  - Among Hispanics, mean HDL-C levels were 45.8 mg/dL for males and 54.4 mg/dL for females.
  - Among NH Asians, mean HDL-C levels were 47.7 mg/dL for males and 60.2 mg/dL for females.
- The prevalence of low HDL-C (<40 mg/dL) was higher (24%) in those with lower education (<12 years) than in those with higher education (>12 years; 17%). Approximately 17% of adults (just over one-quarter of males and <10% of females) had low HDL-C during 2011 to 2012. The percentage of adults with low HDL-C has decreased 20% since 2009 to 2010.[8]
- According to NHANES 2013 to 2016 (unpublished NHLBI tabulations), the age-adjusted prevalence rates for HDL-C <40mg/dL were:
  - 29.0% in males and 9.9% in females
  - 29.7% in NH white males and 9.3% in NH white females
  - 19.8% in NH black males and 8.1% in NH black females
  - 32.6 % in Hispanic males and 13.1% in Hispanic females
  - 25.9% in NH Asian males and 7.9% in NH Asian females

Triglycerides

Youth

- There are limited data available on triglycerides for children 6 to 11 years of age.
- Among adolescents 12 to 19 years of age in NHANES 2011 to 2014, the geometric mean triglyceride level was 79.4 mg/dL. For boys, it was 81.9 mg/dL, and for girls, it was 76.8 mg/dL. The racial/ethnic breakdown was as follows (unpublished NHLBI tabulation):
  - Among NH whites, 82.3 mg/dL for boys and 77.3 mg/dL for girls
  - Among NH blacks, 62.8 mg/dL for boys and 62.7 mg/dL for girls
  - Among Hispanics, 89.0 mg/dL for boys and 85.2 mg/dL for girls
  - Among NH Asians, 78.3 mg/dL for boys and 88.0 mg/dL for girls
- High levels of triglycerides (≥150 mg/dL) occurred in 8.7% of male adolescents and 6.3% of female adolescents during 2011 to 2014 (unpublished NHLBI tabulation).

Adults

- The geometric mean of triglyceride levels for American adults ≥20 years of age was 103.5 mg/dL in NHANES 2011 to 2014 (unpublished NHLBI tabulation).
- Approximately 24.2% of adults had high triglyceride levels (≥150 mg/dL) in NHANES 2011 to 2014 (unpublished NHLBI tabulation).
- Among males, the age-adjusted geometric mean triglyceride level was 111.6 mg/dL in NHANES 2011 to 2014 (unpublished NHLBI tabulation), with the following racial/ethnic breakdown:
  - 113.2 mg/dL for NH white males
  - 86.7 mg/dL for NH black males
  - 124.1 mg/dL for Hispanic males
  - 115.3 mg/dL for NH Asian males
- Among females, the age-adjusted geometric mean triglyceride level was 96.4 mg/dL in NHANES 2011 to 2014 (unpublished NHLBI tabulation), with the following racial/ethnic breakdown:
  - 99.8 mg/dL for NH white females
  - 75.1 mg/dL for NH black females
  - 105.3 mg/dL for Hispanic females
  - 91.5 mg/dL for NH Asian females
- The prevalence of high triglycerides (≥150 mg/dL) was higher (27%) in those with lower education (<12 years) than in those with higher education (>12 years; 23%) (unpublished NHLBI tabulation).

Screening

- The percentage of adults who reported having had a cholesterol check increased from 68.6% during 1999 to 2000 to 74.8% during 2005 to 2006.[9]
- Nearly 70% of adults (67% of males and nearly 72% of females) had been screened for cholesterol (defined as being told by a doctor their cholesterol was high and indicating they had their blood cholesterol checked <5 years ago) according to data from NHANES 2011 to 2012, which was unchanged since 2009 to 2010.[8]
  - Among NH whites, 71.8% were screened (70.6% of males and 72.9% of females).
  - Among NH blacks, 71.9% were screened (66.8% of males and 75.9% of females).
  - Among NH Asians, 70.8% were screened (70.6% of males and 70.9% of females).
  - Among Hispanic adults, 59.3% were screened (54.6% of males and 64.2% of females).

- The percentage of adults screened for cholesterol in the past 5 years was lower for Hispanic adults than for NH white, NH black, and NH Asian adults.

Awareness

- Awareness of high LDL-C increased from 48.9% in 1999 to 2000 to 62.8% in 2003 to 2004; however, awareness did not increase further through 2009 to 2010 (61.5%). Treatment among those aware of having high LDL-C increased from 41.3% in 1999 to 2000 to 72.6% in 2007 to 2008. In 2009 to 2010, it was 70.0%.[10]
- According to 2015 BRFSS data[11]:
  - 36.4% of US adults have been told they have high cholesterol.
  - The percentage of adults told they had high cholesterol was highest in Alabama (42%) and lowest in Colorado (31.5%).
- Almost half (49.6%) of Hispanic participants with high cholesterol (LDL-C >130 mg/dL, TC >240 mg/dL, or taking cholesterol-lowering medications) in the SOL baseline examination (2008–2011) were not aware of their condition.

Treatment

- In high-risk patients, the nonstatin medications ezetimibe, PCSK-9 inhibitors, and a CETP inhibitor, anacetrapib, demonstrated reductions in LDL-C and ASCVD risk in randomized, controlled clinical trials. The PCSK-9 inhibitors evolocumab and alirocumab reduced LDL-C by 40% to 50%, were safe, and reduced the RR for ASCVD events by 15% in high-risk patients on maximum tolerated doses of statins.[12,13] Despite the promising efficacy results, the substantial cost of PCSK9 inhibitors (≈$14 000/year) remains a barrier to their widespread use in the US population. The AHA/ACC guideline committee issued an addendum to the 2013 recommendations (outlined below) on how nonstatin medications can be incorporated into clinic care.[14]
- In 2013, the ACC/AHA released recommendations for statin treatment.[15] AHA 2013 guidelines recommend lipid measurement at baseline, at 1 to 3 months after statin initiation, and then annually to check for the expected percentage decrease of LDL-C levels (30% to <50% with a moderate-intensity statin and ≥50% with a high-intensity statin). Unlike previous recommendations, which had LDL-C and non–HDL-C goals based on the patient's risk category, the 2013 ACC/AHA guideline recommended a discussion regarding statin therapy in 4 identified groups in whom it has been clearly shown to reduce ASCVD risk. The 4 statin benefit groups are (1) people with clinical ASCVD, (2) those with primary elevations of LDL-C >190 mg/dL, (3) people aged 40 to 75 years who have DM with LDL-C 70 to 189 mg/dL and without clinical ASCVD, and (4) those without clinical ASCVD or DM with LDL-C 70 to 189 mg/dL and estimated 10-year ASCVD risk ≥7.5%. Approximately 31.9% of the ASCVD-free, nonpregnant US population between 40 and 79 years of age has a 10-year risk of a first hard CHD event of ≥10% or has DM.[16]
- According to a recent analysis of NHANES data from 2005 to 2010, the number of people eligible for statin therapy would rise from 43.2 million US adults (37.5%) to 56.0 million (48.6%) based on the 2013 ACC/AHA guidelines for the management of blood cholesterol.[17] Most of the increase comes from adults 60 to 75 years old without CVD who have a 10-year ASCVD risk ≥7.5%; the net number of new statin prescriptions could potentially increase by 12.8 million, including 10.4 million for primary prevention.[17] Individuals eligible for treatment under Adult Treatment Panel III but not ACC/AHA guidelines had higher LDL-C levels but were otherwise at lower risk than individuals eligible under both guidelines or only under ACC/AHA guidelines.[18]
- Data from NHANES 1999 to 2012 show that the use of cholesterol-lowering treatment has increased substantially among adults, from 8% in 1999 to 2000 to 18% in 2011 to 2012.[19] During this period, the use of statins increased from 7% to 17%.[19]
- Lower socioeconomic, nonwhite populations typically have a higher prevalence of elevated risk; thus, the 2013 guidelines will be particularly beneficial in terms of reducing ASCVD events in these groups. However, improving access to healthcare for lower SES populations is necessary to realize this potential expansion of statin use in primary prevention as recommended by these guidelines.[20,21]
- Recent data from the REGARDS study indicate that even after accounting for access to medical care, there are disparities in the use of statins in individuals with DM; white males with DM and LDL-C >100 mg/dL were more likely to be prescribed statins (66.0% versus 57.8% for black males, 55.0% for white females, and 53.6% for black females) and were more likely to have LDL-C at goal than were African American males and females and white females.[22]

Adherence

Youth

- In 2011, the NHLBI Expert Panel recommended universal dyslipidemia screening for all children between 9 and 11 years of age and again between 17 and 21 years of age.[23]
- A 2015 study based on NCHS data found that 21% of youths aged 6 to 19 years had at least 1 abnormal cholesterol measure during 2011 to 2014.[24]

Adults

- From 2005 to 2010, among adults with high LDL-C, age-adjusted control of LDL-C increased from 22.3% to 29.5%.[25] The prevalence of LDL-C control was lowest among people who reported receiving medical care less than twice in the previous year (11.7%), being uninsured (13.5%), being Mexican American (20.3%), or having income below the poverty level (21.9%).[26]

CVD Health Impact

- CHD risk can accumulate at normative cholesterol levels with or without the presence of other traditional risk factors.[27]
- Long-term exposure to even modestly elevated cholesterol levels can lead to CHD later in life.[1,28]

HDL Cholesterol

- Low levels of HDL-C and apolipoprotein A1 are strongly associated with increased ASCVD risk in young and middle-aged adults.[29] The association between CHD risk and HDL-C appears to be inverse and linear until HDL-C values exceed 70 to 80 mg/dL, at which point there may be a slight increase in CHD risk in some people.[30,31]
- Negative RCTs and mendelian randomization studies have suggested that HDL-C content is not in the causal pathway of atheroprotection.[32–34]
- Metrics of HDL particle function, notably HDL efflux capacity, have been shown to have strong, independent associations with ASCVD risk in several cohort studies.[35,36]
- HDL efflux capacity may predict residual risk in statin-treated patients.[37]

Triglycerides

- Triglyceride concentration has strong associations with ASCVD risk; however, in most studies the association is attenuated after adjustment for other traditional risk factors.[29]
- Triglyceride levels are biologically linked to other causal factors for ASCVD, notably LDL-C, LDL particle concentration, insulin resistance, low HDL-C, central adiposity, and poor diet, among others. The interconnectedness of triglycerides with other risk factors makes it challenging to determine the isolated effect of serum triglyceride concentration on ASCVD risk.
- Although multiple clinical trials do not suggest added benefit of triglyceride lowering with fibrate medications in statin-treated patients, several mendelian randomization studies suggest a causal association between pathways that lead to high triglycerides and ASCVD.[38]

Cost

- An analysis from the GBD study estimates that high TC accounts for 88.7 million (95% CI, 74.6 million to 105.7 million) DALYs.[39]
- Compared with the Adult Treatment Panel III cholesterol treatment guidelines, the AHA 2013 recommendations are estimated (from years 2016 to 2025) to treat 12.24 million more Americans with statin medications and increase treatment costs by $3.9 billion. However, despite the higher costs, the AHA 2013 guideline is predicted to be cost-effective because it is estimated to save 183 000 more QALYs and prevent 43 700 deaths.[40]
- In patients with ASCVD, the addition of PCSK9 inhibitors to statin therapy was estimated to prevent 4.3 million more MACE than adding ezetimibe to statin therapy. However, because of high drug costs, the addition of PCSK9 is estimated to cost $414 000 per QALY. To achieve cost-effectiveness, the PCSK9 inhibitor cost would need to be reduced to $4536 per year to achieve $100 000 per QALY.[41]
- In the United States, only 47% of prescriptions for PCSK9 inhibitors were approved between July 2015 and August 2016.[42] Approval rates were highest for Medicare (60.9%) and lowest for private third-party payers (24.4%).

Family History and Genetics

Familial Hypercholesterolemia

- There are several known monogenic or mendelian causes of high blood cholesterol and lipids, the most common of which include FH, which affects up to ≈1 in 200 individuals.[43] Patients with FH have elevated TC and LDL-C and a 20-fold increased risk of CVD.[44] Similarly, individuals with the FH phenotype (LDL-C >190 mg/dL) experience an acceleration in CHD risk by 10 to 20 years in males and 20 to 30 years in females.[45]

- FH has been associated with mutations in *LDLR, APOB, LDLRAP1*, and *PCSK9,* which affect uptake and clearance of LDL-C. Individuals with LDL-C >190 mg/dL and a confirmed FH mutation have substantially higher odds for CAD than those with LDL-C >190 mg/dL without pathogenic mutations. Similarly, individuals with an FH pathogenic mutation and an LDL-C <190 mg/dL have substantially higher odds for CAD than those without a pathogenic FH mutation and similar LDL-C levels.[46]
- Individuals who are homozygous for an FH mutation have severe CHD that becomes apparent in childhood and requires plasmapheresis; it may be best treated using novel therapies, including gene therapy.[47] However, the majority of FH cases are heterozygous for the causal mutation, and these patients remain underdiagnosed.[43]
- Cascade screening, which recommends cholesterol testing for all first-degree relatives of an FH patient, can be an effective strategy to identify affected family members who would benefit from therapeutic intervention.[44]

Familial Combined Hyperlipidemia

- Combined hyperlipidemia, which affects ≈1 in 100 individuals, is characterized by elevated LDL-C and triglycerides. Unlike FH, there is little evidence for monogenic causes of combined hyperlipidemia, which indicates that most cases of combined hyperlipidemia might be complex and polygenic.[48]
- High cholesterol is heritable even in families that do not harbor one of these monogenic forms of disease. Extensive efforts have focused on GWASs for lipid traits in large numbers of subjects to identify the genetic architecture of variability in cholesterol levels. With GWASs, 95 loci were identified using >100 000 subjects of European origin.[49] Additional studies in even larger numbers, including individuals of diverse ancestry, use of electronic health record–based samples, and the addition of whole-exome sequencing (which offers more comprehensive coverage of the coding regions of the genome) have brought the number of known lipid loci to >200.[50–52] As expected for a causal biomarker, there is considerable overlap between the genetics of LDL-C and the genetics of CHD. Furthermore, overlap between genetic loci for triglyceride-rich lipoproteins and disease implicate triglycerides as causal in CVD.[35,36,53,54]

Lipid Genetics and Drug Development

- Genetic studies of lipid traits have had some success in identifying new drug targets, particularly the genetic interrogation of extremely high and low LDL-C,[55–57] which led to the development of PCSK9 inhibitors. Furthermore, identification of variants in *ANGPTL4* and *ANGPTL3* that associate with increased triglycerides and CAD risk[52,58] highlight inhibition of these genes as potentially therapeutic.[59]
- As highly effective LDL-C–lowering drugs, statins are widely prescribed to reduce CVD risk, but response to statins varies among individuals. Genetic variants that affect statin responsiveness could predict the lipid-modulating ability of statins[60–62] and modulate cardioprotection.[63] Importantly, variation in *SLCO1B1* predicts risk of statin myopathy, a major potential adverse event, which has prompted recommendations for genotype-guided dosing of simvastatin.[64,65]

Global Burden of Hypercholesterolemia (See Chart 7-5)

- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories. The highest mortality rates attributable to high TC are in Eastern Europe and Central Asia (Chart 7-5).[66]
- TC went from being the 14th-leading risk factor in 1990 for the global burden of disease, as quantified by DALYs, to the number 15 risk factor in 2010.[67]
- The prevalence of elevated TC was highest in the WHO European Region (54% for both sexes), followed by the WHO Region of the Americas (48% for both sexes). The WHO African Region and the WHO South-East Asia Region showed the lowest percentages (23% and 30%, respectively).[39]
- A report on trends in TC in 199 countries and territories indicated that TC declined in high-income regions of the world (Australasia, North America, and Western Europe).[67]

Table 7-1. High TC and LDL-C and Low HDL-C

Population Group	Prevalence of TC ≥200 mg/dL, 2013–2016 Age ≥20 y	Prevalence of TC ≥240 mg/dL, 2013–2016 Age ≥20 y	Prevalence of LDL-C ≥130 mg/ dL, 2011–2014 Age ≥20 y	Prevalence of HDL-C <40 mg/dL, 2013–2016 Age ≥20 y
Both sexes, n (%)*	92 800 000 (38.2)	28 500 000 (11.7)	71 300 000 (30.3)	45 600 000 (19.2)
Males, n (%)*	41 200 000 (35.4)	12 400 000 (10.7)	34 000 000 (30.0)	33 700 000 (29.0)
Females, n (%)*	51 600 000 (40.4)	16 100 000 (12.4)	37 300 000 (30.4)	11 900 000 (9.9)
NH white males, %	35.4	10.5	29.3	29.7
NH white females, %	41.8	13.6	32.1	9.3
NH black males, %	29.8	8.9	29.9	19.8
NH black females, %	33.1	9.0	27.9	8.1
Hispanic males, %	39.9	13.0	36.6	32.6
Hispanic females, %	38.9	10.1	28.7	13.1
NH Asian males, %	38.7	11.7	29.2	25.9
NH Asian females, %	39.6	10.8	25.0	7.9

Prevalence of TC ≥200 mg/dL includes people with TC ≥240 mg/dL. In adults, levels of 200 to 239 mg/dL are considered borderline high. Levels of ≥240 mg/dL are considered high.

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NH, non-Hispanic; and TC, total cholesterol.

*Total data for TC are for Americans ≥20 years of age. Data for LDL-C, HDL-C, and all racial/ethnic groups are age adjusted for age ≥20 years.

Source for TC ≥200 mg/dL, ≥240 mg/dL, LDL-C, and HDL-C: National Health and Nutrition Examination Survey (2013–2016), National Center for Health Statistics, and National Heart, Lung, and Blood Institute. Estimates from National Health and Nutrition Examination Survey 2013 to 2016 (National Center for Health Statistics) were applied to 2016 population estimates.

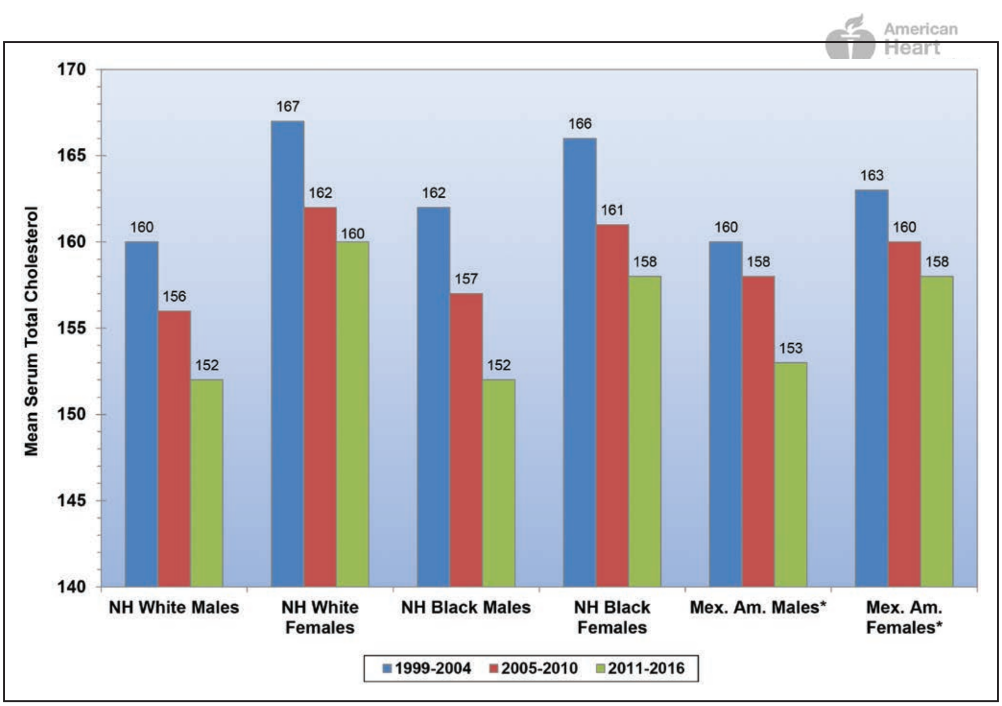

Chart 7-1. Trends in mean serum total cholesterol among adolescents 12 to 19 years of age by race, sex, and survey year (NHANES, 1999–2004, 2005–2010, and 2011–2016).

Values are in mg/dL.

Mex. Am. indicates Mexican American; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*The category of Mexican Americans was consistently collected in all NHANES years, but the combined category of Hispanics was only used starting in 2007. Consequently, for long-term trend data, the category Mexican American is used.

Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

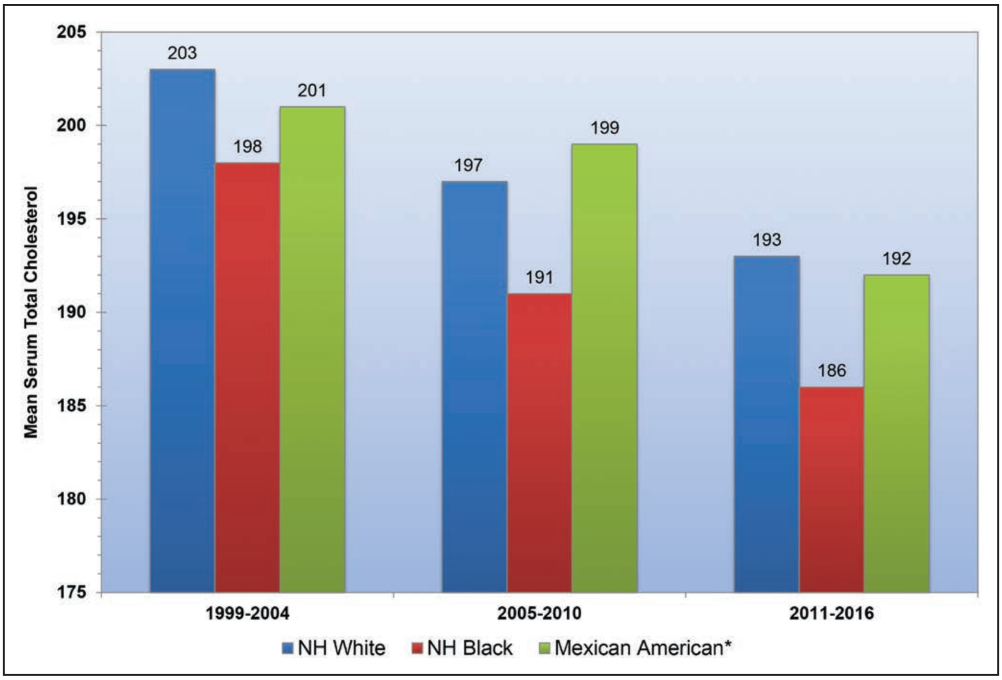

Chart 7-2. Age-adjusted trends in mean serum total cholesterol among adults ≥20 years old by race and survey year (NHANES, 1999–2004, 2005–2010, and 2011–2016).
Values are in mg/dL.
NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
*The category of Mexican Americans was consistently collected in all NHANES years, but the combined category of Hispanics was only used starting in 2007. Consequently, for long-term trend data, the category Mexican American is used.
Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

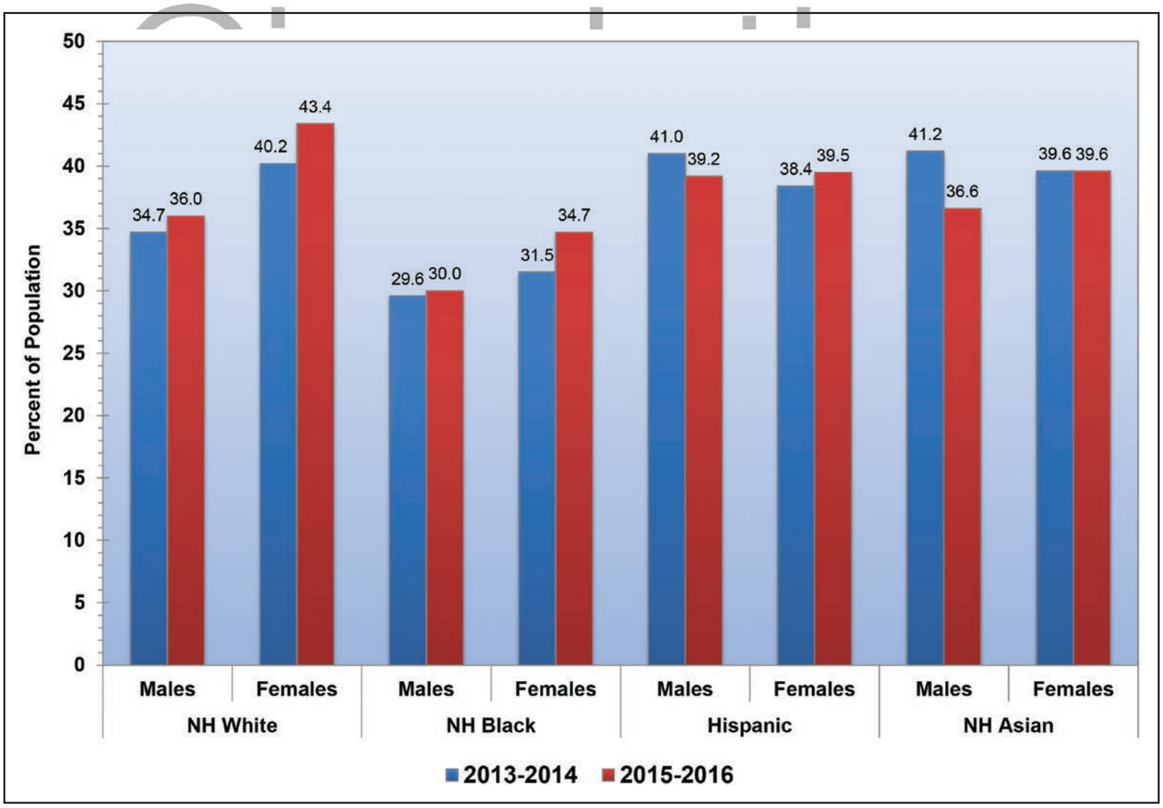

Chart 7-3. Age-adjusted trends in the prevalence of serum total cholesterol ≥200 mg/dL in adults ≥20 years of age by race/ethnicity, sex, and survey year (NHANES, 2013–2014 and 2015–2016).
NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

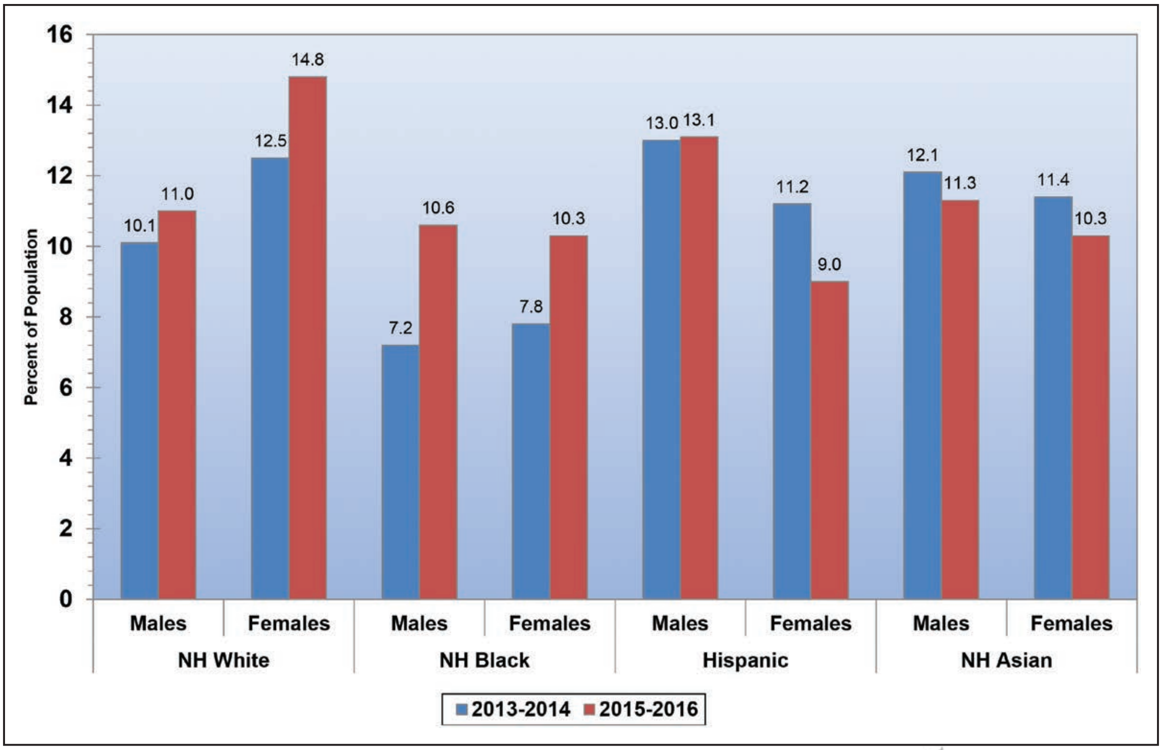

Chart 7-4. Age-adjusted trends in the prevalence of serum total cholesterol ≥240 mg/dL in adults ≥20 years of age by race/ethnicity, sex, and survey year (NHANES, 2013–2014 and 2015–2016).
NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

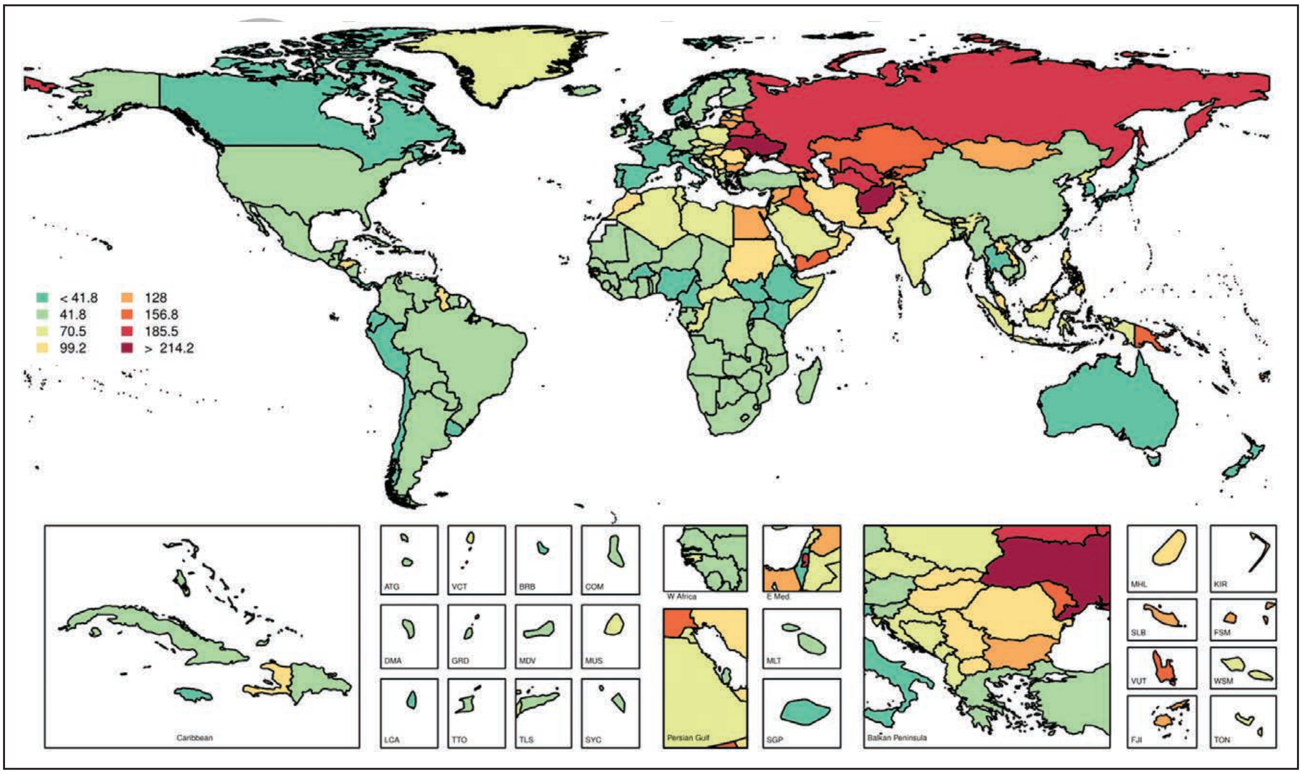

Chart 7-5. Age-standardized global mortality rates attributable to high total cholesterol per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016 with permission.[66] Copyright © 2017, University of Washington.

REFERENCES

1. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
2. Centers for Disease Control and Prevention (CDC). Prevalence of abnormal lipid levels among youths: United States, 1999–2006 [published correction appears in *MMWR Morb Mortal Wkly Rep*. 2010;59:78]. *MMWR Morb Mortal Wkly Rep*. 2010;59:29–33.
3. Ford ES, Li C, Zhao G, Mokdad AH. Concentrations of low-density lipoprotein cholesterol and total cholesterol among children and adolescents in the United States. *Circulation*. 2009;119:1108–1115. doi: 10.1161/CIRCULATIONAHA.108.816769
4. Carroll MD, Kit BK, Lacher DA, Shero ST, Mussolino ME. Trends in lipids and lipoproteins in US adults, 1988-2010. *JAMA*. 2012;308:1545–1554. doi: 10.1001/jama.2012.13260
5. US Department of Health and Human Services. Healthy People.gov website. Healthy People 2020: HDS-8: reduce the mean total blood cholesterol levels among adults. https://www.healthypeople.gov/node/4600/data_details. Accessed July 13, 2016.
6. US Department of Health and Human Services. Healthy People.gov website. Healthy People 2020 Topics & Objectives: Heart Disease and Stroke. https://www.healthypeople.gov/2020/topics-objectives/topic/heart-disease-and-stroke/objectives. Accessed July 13, 2016.
7. Ford ES, Capewell S. Trends in total and low-density lipoprotein cholesterol among U.S. adults: contributions of changes in dietary fat intake and use of cholesterol-lowering medications. *PLoS One*. 2013;8:e65228. doi: 10.1371/journal.pone.0065228
8. Carroll MD, Fryar CD, Kit BK. Total and high-density lipoprotein cholesterol in adults: United States, 2011–2014. *NCHS Data Brief*. 2015;(226):1–8.
9. Ford ES, Li C, Pearson WS, Zhao G, Mokdad AH. Trends in hypercholesterolemia, treatment and control among United States adults. *Int J Cardiol*. 2010;140:226–235. doi: 10.1016/j.ijcard.2008.11.033
10. Muntner P, Levitan EB, Brown TM, Sharma P, Zhao H, Bittner V, Glasser S, Kilgore M, Yun H, Woolley JM, Farkouh ME, Rosenson RS. Trends in the prevalence, awareness, treatment and control of high low density lipoprotein-cholesterol among United States adults from 1999-2000 through 2009-2010. *Am J Cardiol*. 2013;112:664–670. doi: 10.1016/j.amjcard.2013.04.041
11. Centers for Disease Control and Prevention, Division of Population Health. BRFSS Prevalence & Trends Data (2015). Centers for Disease Control and Prevention website. http://www.cdc.gov/brfss/brfssprevalence/. Accessed May 17, 2017.
12. Giugliano RP, Mach F, Zavitz K, Kurtz C, Im K, Kanevsky E, Schneider J, Wang H, Keech A, Pedersen TR, Sabatine MS, Sever PS, Robinson JG, Honarpour N, Wasserman SM, Ott BR; EBBINGHAUS Investigators. Cognitive function in a randomized trial of evolocumab. *N Engl J Med*. 2017;377:633–643. doi: 10.1056/NEJMoa1701131
13. Schmidt AF, Pearce LS, Wilkins JT, Overington JP, Hingorani AD, Casas JP. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2017;4:CD011748. doi: 10.1002/14651858.CD011748.pub2
14. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD Jr, DePalma SM, Minissian MB, Orringer CE, Smith SC Jr. 2017 Focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2017;70:1785–1822. doi: 10.1016/j.jacc.2017.07.745
15. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PWF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published corrections appear in *Circulation*. 2014;129(suppl 2):S46–S48 and *Circulation*. 2015;132:e396]. *Circulation*. 2014;129(suppl 2):S1–45. doi: 10.1161/01.cir.0000437738.63853.7a
16. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PWF. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2014;129(suppl 2):S74–S75]. *Circulation*. 2014;129(suppl 2):S49–S73. doi: 10.1161/01.cir.0000437741.48606.98
17. Pencina MJ, Navar-Boggan AM, D'Agostino RB Sr, Williams K, Neely B, Sniderman AD, Peterson ED. Application of new cholesterol guidelines to a population-based sample. *N Engl J Med*. 2014;370:1422–1431. doi: 10.1056/NEJMoa1315665
18. Bittner V. New ACC-AHA cholesterol guidelines significantly increase potential eligibility for statin treatment. *Evid Based Med*. 2014;19:198. doi: 10.1136/ebmed-2014-110029
19. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999–2012. *JAMA*. 2015;314:1818–1831. doi: 10.1001/jama.2015.13766
20. Qureshi WT, Kaplan RC, Swett K, Burke G, Daviglus M, Jung M, Talavera GA, Chirinos DA, Reina SA, Davis S, Rodriguez CJ. American College of Cardiology/American Heart Association (ACC/AHA) class I guidelines for the treatment of cholesterol to reduce atherosclerotic cardiovascular risk: implications for US Hispanics/Latinos based on findings from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *J Am Heart Assoc*. 2017;6:e005045. doi: 10.1161/JAHA.116.005045
21. Verma AA, Jimenez MP, Subramanian SV, Sniderman AD, Razak F. Race and socioeconomic differences associated with changes in statin eligibility under the 2013 American College of Cardiology/American Heart Association cholesterol guidelines. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003764. doi: 10.1161/CIRCOUTCOMES.117.003764
22. Gamboa CM, Colantonio LD, Brown TM, Carson AP, Safford MM. Race-sex differences in statin use and low-density lipoprotein cholesterol control among people with diabetes mellitus in the Reasons for Geographic and Racial Differences in Stroke Study. *J Am Heart Assoc*. 2017;6:e004264. doi: 10.1161/JAHA.116.004264
23. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: summary report. *Pediatrics*. 2011;128(suppl 5):S213–256. doi: 10.1542/peds.2009-2107C
24. Nguyen D, Kit B, Carroll M. Abnormal cholesterol among children and adolescents in the United States, 2011–2014. *NCHS Data Brief*. 2015;(228):1–8.
25. Johnson NB, Hayes LD, Brown K, Hoo EC, Ethier KA; Centers for Disease Control and Prevention. CDC National Health Report: leading causes of morbidity and mortality and associated behavioral risk and protective factors: United States, 2005–2013. *MMWR Suppl*. 2014;63:3–27.
26. Centers for Disease Control and Prevention (CDC). Vital signs: prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol: United States, 1999–2002 and 2005–2008. *MMWR Morb Mortal Wkly Rep*. 2011;60:109–114.
27. Fernández-Friera L, Fuster V, López-Melgar B, Oliva B, García-Ruiz JM, Mendiguren J, Bueno H, Pocock S, Ibáñez B, Fernández-Ortiz A, Sanz J. Normal LDL-cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors [published correction appears in *J Am Coll Cardiol*. 2018;71:588–589]. *J Am Coll Cardiol*. 2017;70:2979–2991. doi: 10.1016/j.jacc.2017.10.024
28. Navar-Boggan AM, Peterson ED, D'Agostino RB Sr, Neely B, Sniderman AD, Pencina MJ. Hyperlipidemia in early adulthood increases long-term risk of coronary heart disease. *Circulation*. 2015;131:451–458. doi: 10.1161/CIRCULATIONAHA.114.012477
29. Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302:1993–2000. doi: 10.1001/jama.2009.1619
30. Wilkins JT, Ning H, Stone NJ, Criqui MH, Zhao L, Greenland P, Lloyd-Jones DM. Coronary heart disease risks associated with high levels of HDL cholesterol. *J Am Heart Assoc*. 2014;3:e000519. doi: 10.1161/JAHA.113.000519
31. Ko DT, Alter DA, Guo H, Koh M, Lau G, Austin PC, Booth GL, Hogg W, Jackevicius CA, Lee DS, Wijeysundera HC, Wilkins JT, Tu JV. High-density lipoprotein cholesterol and cause-specific mortality in individuals without previous cardiovascular conditions: the CANHEART Study. *J Am Coll Cardiol*. 2016;68:2073–2083. doi: 10.1016/j.jacc.2016.08.038

32. Lincoff AM, Nicholls SJ, Riesmeyer JS, Barter PJ, Brewer HB, Fox KAA, Gibson CM, Granger C, Menon V, Montalescot G, Rader D, Tall AR, McErlean E, Wolski K, Ruotolo G, Vangerow B, Weerakkody G, Goodman SG, Conde D, McGuire DK, Nicolau JC, Leiva-Pons JL, Pesant Y, Li W, Kandath D, Kouz S, Tahirkheli N, Mason D, Nissen SE; ACCELERATE Investigators. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. *N Engl J Med*. 2017;376:1933–1942. doi: 10.1056/NEJMoa1609581
33. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Hólm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, König IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schäfer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study [published correction appears in *Lancet*. 2012;380:564]. *Lancet*. 2012;380:572–580. doi: 10.1016/S0140-6736(12)60312-2
34. HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014;371(3):203–212. doi: 10.1056/NEJMoa1300955
35. Saleheen D, Scott R, Javad S, Zhao W, Rodrigues A, Picataggi A, Lukmanova D, Mucksavage ML, Luben R, Billheimer J, Kastelein JJ, Boekholdt SM, Khaw KT, Wareham N, Rader DJ. Association of HDL cholesterol efflux capacity with incident coronary heart disease events: a prospective case-control study. *Lancet Diabetes Endocrinol*. 2015;3:507–513. doi: 10.1016/S2213-8587(15)00126-6
36. Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, Neeland IJ, Yuhanna IS, Rader DR, de Lemos JA, Shaul PW. HDL cholesterol efflux capacity and incident cardiovascular events. *N Engl J Med*. 2014;371:2383–2393. doi: 10.1056/NEJMoa1409065
37. Khera AV, Demler OV, Adelman SJ, Collins HL, Glynn RJ, Ridker PM, Rader DJ, Mora S. Cholesterol efflux capacity, high-density lipoprotein particle number, and incident cardiovascular events: an analysis from the JUPITER Trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin). *Circulation*. 2017;135:2494–2504. doi: 10.1161/CIRCULATIONAHA.116.025678
38. Holmes MV, Asselbergs FW, Palmer TM, Drenos F, Lanktree MB, Nelson CP, Dale CE, Padmanabhan S, Finan C, Swerdlow DI, Tragante V, van Iperen EP, Sivapalaratnam S, Shah S, Elbers CC, Shah T, Engmann J, Giambartolomei C, White J, Zabaneh D, Sofat R, McLachlan S, Doevendans PA, Balmforth AJ, Hall AS, North KE, Almoguera B, Hoogeveen RC, Cushman M, Fornage M, Patel SR, Redline S, Siscovick DS, Tsai MY, Karczewski KJ, Hofker MH, Verschuren WM, Bots ML, van der Schouw YT, Melander O, Dominiczak AF, Morris R, Ben-Shlomo Y, Price J, Kumari M, Baumert J, Peters A, Thorand B, Koenig W, Gaunt TR, Humphries SE, Clarke R, Watkins H, Farrall M, Wilson JG, Rich SS, de Bakker PI, Lange LA, Davey Smith G, Reiner AP, Talmud PJ, Kivimäki M, Lawlor DA, Dudbridge F, Samani NJ, Keating BJ, Hingorani AD, Casas JP; UCLEB Consortium. Mendelian randomization of blood lipids for coronary heart disease. *Eur Heart J*. 2015;36:539–550. doi: 10.1093/eurheartj/eht571
39. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015 [published correction appears in *Lancet*. 2017;389:e1]. *Lancet*. 2016;388:1659–1724. doi: 10.1016/S0140-6736(16)31679-8
40. Heller DJ, Coxson PG, Penko J, Pletcher MJ, Goldman L, Odden MC, Kazi DS, Bibbins-Domingo K. Evaluating the impact and cost-effectiveness of statin use guidelines for primary prevention of coronary heart disease and stroke. *Circulation*. 2017;136:1087–1098. doi: 10.1161/CIRCULATIONAHA.117.027067
41. Kazi DS, Moran AE, Coxson PG, Penko J, Ollendorf DA, Pearson SD, Tice JA, Guzman D, Bibbins-Domingo K. Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. *JAMA*. 2016;316:743–753. doi: 10.1001/jama.2016.11004
42. Hess GP, Natarajan P, Faridi KF, Fievitz A, Valsdottir L, Yeh RW. Proprotein convertase subtilisin/kexin type 9 inhibitor therapy: payer approvals and rejections, and patient characteristics for successful prescribing. *Circulation*. 2017;136:2210–2219. doi: 10.1161/CIRCULATIONAHA.117.028430
43. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wiegman A, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovanen PT, Boileau C, Averna M, Borén J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AF, Stroes E, Taskinen MR, Tybjærg-Hansen A; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J*. 2013;34:3478–390a. doi: 10.1093/eurheartj/eht273
44. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, Daniels SR, Gidding SS, de Ferranti SD, Ito MK, McGowan MP, Moriarty PM, Cromwell WC, Ross JL, Ziajka PE. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011;5:133–140. doi: 10.1016/j.jacl.2011.03.001
45. Perak AM, Ning H, de Ferranti SD, Gooding HC, Wilkins JT, Lloyd-Jones DM. Long-term risk of atherosclerotic cardiovascular disease in US adults with the familial hypercholesterolemia phenotype. *Circulation*. 2016;134:9–19. doi: 10.1161/CIRCULATIONAHA.116.022335
46. Khera AV, Won HH, Peloso GM, Lawson KS, Bartz TM, Deng X, van Leeuwen EM, Natarajan P, Emdin CA, Bick AG, Morrison AC, Brody JA, Gupta N, Nomura A, Kessler T, Duga S, Bis JC, van Duijn CM, Cupples LA, Psaty B, Rader DJ, Danesh J, Schunkert H, McPherson R, Farrall M, Watkins H, Lander E, Wilson JG, Correa A, Boerwinkle E, Merlini PA, Ardissino D, Saleheen D, Gabriel S, Kathiresan S. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *J Am Coll Cardiol*. 2016;67:2578–2589. doi: 10.1016/j.jacc.2016.03.520
47. Ajufo E, Cuchel M. Recent developments in gene therapy for homozygous familial hypercholesterolemia. *Curr Atheroscler Rep*. 2016;18:22. doi: 10.1007/s11883-016-0579-0
48. Brahm AJ, Hegele RA. Combined hyperlipidemia: familial but not (usually) monogenic. *Curr Opin Lipidol*. 2016;27:131–140. doi: 10.1097/MOL.0000000000000270
49. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee JY, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RY, Wright AF, Witteman JC, Wilson JF, Willemsen G, Wichmann HE, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJ, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BW, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PK, Lucas G, Luben R, Loos RJ, Lokki ML, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, König IR, Khaw KT, Kaprio J, Kaplan LM, Johansson A, Jarvelin MR, Janssens AC, Ingelsson E, Igl W, Kees Hovingh G, Hottenga JJ, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllensten U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Döring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJ, de Faire U, Crawford G, Collins FS, Chen YD, Caulfield MJ, Campbell H, Burtt NP, Bonnycastle LL, Boomsma DI, Boekholdt SM, Bergman RN, Barroso

I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altshuler D, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Adair LS, Taylor HA Jr, Borecki IB, Gabriel SB, Wilson JG, Holm H, Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Rotter JI, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M, Kathiresan S. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature*. 2010;466:707–713. doi: 10.1038/nature09270

50. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang HY, Demirkan A, Den Hertog HM, Do R, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkilä K, Hyppönen E, Isaacs A, Jackson AU, Johansson Å, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lyytikäinen LP, Magnusson PKE, Mangino M, Mihailov E, Montasser ME, Müller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen AK, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney ASF, Döring A, Elliott P, Epstein SE, Ingi Eyjolfsson G, Gigante B, Goodarzi MO, Grallert H, Gravito ML, Groves CJ, Hallmans G, Hartikainen AL, Hayward C, Hernandez D, Hicks AA, Holm H, Hung YJ, Illig T, Jones MR, Kaleebu P, Kastelein JJP, Khaw KT, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimäki T, Lin SY, Lindström J, Loos RJF, Mach F, McArdle WL, Meisinger C, Mitchell BD, Müller G, Nagaraja R, Narisu N, Nieminen TVM, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stančáková A, Stirrups K, Swift AJ, Tiret L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemsen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen YI, Collins FS, Cooper RS, Danesh J, Dedoussis G, de Faire U, Feranil AB, Ferrières J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V, Gyllensten U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Järvelin MR, Jula A, Kähönen M, Kaprio J, Kesäniemi A, Kivimaki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, März W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe PB, Njølstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PEH, Sheu WH, Shuldiner AR, Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BHR, Ordovas JM, Boerwinkle E, Palmer CNA, Thorsteinsdottir U, Chasman DI, Rotter JI, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P, Kathiresan S, Mohlke KL, Ingelsson E, Abecasis GR; Global Lipids Genetics Consortium. Discovery and refinement of loci associated with lipid levels. *Nat Genet*. 2013;45:1274–1283. doi: 10.1038/ng.2797

51. Peloso GM, Auer PL, Bis JC, Voorman A, Morrison AC, Stitziel NO, Brody JA, Khetarpal SA, Crosby JR, Fornage M, Isaacs A, Jakobsdottir J, Feitosa MF, Davies G, Huffman JE, Manichaikul A, Davis B, Lohman K, Joon AY, Smith AV, Grove ML, Zanoni P, Redon V, Demissie S, Lawson K, Peters U, Carlson C, Jackson RD, Ryckman KK, Mackey RH, Robinson JG, Siscovick DS, Schreiner PJ, Mychaleckyj JC, Pankow JS, Hofman A, Uitterlinden AG, Harris TB, Taylor KD, Stafford JM, Reynolds LM, Marioni RE, Dehghan A, Franco OH, Patel AP, Lu Y, Hindy G, Gottesman O, Bottinger EP, Melander O, Orho-Melander M, Loos RJ, Duga S, Merlini PA, Farrall M, Goel A, Asselta R, Girelli D, Martinelli N, Shah SH, Kraus WE, Li M, Rader DJ, Reilly MP, McPherson R, Watkins H, Ardissino D, Zhang Q, Wang J, Tsai MY, Taylor HA, Correa A, Griswold ME, Lange LA, Starr JM, Rudan I, Eiriksdottir G, Launer LJ, Ordovas JM, Levy D, Chen YD, Reiner AP, Hayward C, Polasek O, Deary IJ, Borecki IB, Liu Y, Gudnason V, Wilson JG, van Duijn CM, Kooperberg C, Rich SS, Psaty BM, Rotter JI, O'Donnell CJ, Rice K, Boerwinkle E, Kathiresan S, Cupples LA; NHLBI GO Exome Sequencing Project. Association of low-frequency and rare coding-sequence variants with blood lipids and coronary heart disease in 56,000 whites and blacks. *Am J Hum Genet*. 2014;94:223–232. doi: 10.1016/j.ajhg.2014.01.009

52. Dewey F, Murray M, Overton JD, Habegger L, Leader JB, Fetterolf SN, O'Dushlaine C, Van Hout CV, Staples J, Gonzaga-Jauregui C, Metpally R, Pendergrass SA, Giovanni MA, Kirchner HL, Balasubramanian S, Abul-Husn NS, Hartzel DN, Lavage DR, Kost KA, Packer JS, Lopez AE, Penn J, Mukherjee S, Gosalia N, Kanagaraj M, Li AH, Mitnaul LJ, Adams LJ, Person TN, Praveen K, Marcketta A, Lebo MS, Austin-Tse CA, Mason-Suares HM, Bruse S, Mellis S, Phillips R, Stahl N, Murphy A, Economides A, Skelding KA, Still CD, Elmore JR, Borecki IB, Yancopoulos GD, Davis FD, Faucett WA, Gottesman O, Ritchie MD, Shuldiner AR, Reid JG, Ledbetter DH, Baras A, Carey DJ. Distribution and clinical impact of functional variants in 50,726 whole-exome sequences from the DiscovEHR study. *Science*. 2016;354(6319):aaf6814. doi: 10.1126/science.aaf6814

53. Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies [published correction appears in *Lancet*. 2010;376:90]. *Lancet*. 2010;375:1634–1639. doi: 10.1016/S0140-6736(10)60545-4

54. TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med*. 2014;371:22–31. doi: 10.1056/NEJMoa1307095

55. Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, Erlich D, Derré A, Villéger L, Farnier M, Beucler I, Bruckert E, Chambaz J, Chanu B, Lecerf JM, Luc G, Moulin P, Weissenbach J, Prat A, Krempf M, Junien C, Seidah NG, Boileau C. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet*. 2003;34:154–156. doi: 10.1038/ng1161

56. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med*. 2006;354:1264–1272. doi: 10.1056/NEJMoa054013

57. Cohen J, Pertsemlidis A, Kotowski IK, Graham R, Garcia CK, Hobbs HH. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9 [published correction appears in *Nat Genet*. 2005;37:328]. *Nat Genet*. 2005;37:161–165. doi: 10.1038/ng1509

58. Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators. Coding variation in ANGPTL4, LPL, and SVEP1 and the risk of coronary disease [published correction appears in *N Engl J Med*. 2016;374:1898]. *N Engl J Med*. 2016;374:1134–1144. doi: 10.1056/NEJMoa1507652

59. Graham MJ, Lee RG, Brandt TA, Tai LJ, Fu W, Peralta R, Yu R, Hurh E, Paz E, McEvoy BW, Baker BF, Pham NC, Digenio A, Hughes SG, Geary RS, Witztum JL, Crooke RM, Tsimikas S. Cardiovascular and metabolic effects of ANGPTL3 antisense oligonucleotides. *N Engl J Med*. 2017;377:222–232. doi: 10.1056/NEJMoa1701329

60. Postmus I, Trompet S, Deshmukh HA, Barnes MR, Li X, Warren HR, Chasman DI, Zhou K, Arsenault BJ, Donnelly LA, Wiggins KL, Avery CL, Griffin P, Feng Q, Taylor KD, Li G, Evans DS, Smith AV, de Keyser CE, Johnson AD, de Craen AJ, Stott DJ, Buckley BM, Ford I, Westendorp RG, Slagboom PE, Sattar N, Munroe PB, Sever P, Poulter N, Stanton A, Shields DC, O'Brien E, Shaw-Hawkins S, Chen YD, Nickerson DA, Smith JD, Dubé MP, Boekholdt SM, Hovingh GK, Kastelein JJ, McKeigue PM, Betteridge J, Neil A, Durrington PN, Doney A, Carr F, Morris A, McCarthy MI, Groop L, Ahlqvist E, Bis JC, Rice K, Smith NL, Lumley T, Whitsel EA, Stürmer T, Boerwinkle E, Ngwa JS, O'Donnell CJ, Vasan RS, Wei WQ, Wilke RA, Liu CT, Sun F, Guo X, Heckbert SR, Post W, Sotoodehnia N, Arnold AM, Stafford JM, Ding J, Herrington DM, Kritchevsky SB, Eiriksdottir G, Launer LJ, Harris TB, Chu AY, Giulianini F, MacFadyen JG, Barratt BJ, Nyberg F, Stricker BH, Uitterlinden AG, Hofman A, Rivadeneira F, Emilsson V, Franco OH, Ridker PM, Gudnason V, Liu Y, Denny JC, Ballantyne CM, Rotter JI, Adrienne Cupples L, Psaty BM, Palmer CN, Tardif JC, Colhoun HM, Hitman G, Krauss RM, Wouter Jukema J, Caulfield MJ; Welcome Trust Case Control Consortium. Pharmacogenetic meta-analysis of genome-wide association studies of LDL cholesterol response to statins. *Nat Commun*. 2014;5:5068. doi: 10.1038/ncomms6068

61. Postmus I, Warren HR, Trompet S, Arsenault BJ, Avery CL, Bis JC, Chasman DI, de Keyser CE, Deshmukh HA, Evans DS, Feng Q, Li X, Smit RA, Smith AV, Sun F, Taylor KD, Arnold AM, Barnes MR, Barratt BJ, Betteridge J, Boekholdt SM, Boerwinkle E, Buckley BM, Chen YI, de Craen AJ, Cummings SR, Denny JC, Dubé MP, Durrington PN, Eiriksdottir G, Ford I, Guo X, Harris TB, Heckbert SR, Hofman A, Hovingh GK, Kastelein JJ, Launer LJ, Liu CT, Liu Y, Lumley T, McKeigue PM, Munroe PB, Neil A, Nickerson DA, Nyberg F, O'Brien E, O'Donnell CJ, Post W, Poulter N, Vasan

RS, Rice K, Rich SS, Rivadeneira F, Sattar N, Sever P, Shaw-Hawkins S, Shields DC, Slagboom PE, Smith NL, Smith JD, Sotoodehnia N, Stanton A, Stott DJ, Stricker BH, Stürmer T, Uitterlinden AG, Wei WQ, Westendorp RG, Whitsel EA, Wiggins KL, Wilke RA, Ballantyne CM, Colhoun HM, Cupples LA, Franco OH, Gudnason V, Hitman G, Palmer CN, Psaty BM, Ridker PM, Stafford JM, Stein CM, Tardif JC, Caulfield MJ, Jukema JW, Rotter JI, Krauss RM. Meta-analysis of genome-wide association studies of HDL cholesterol response to statins. *J Med Genet*. 2016;53:835–845. doi: 10.1136/jmedgenet-2016-103966

62. Chu AY, Giulianini F, Barratt BJ, Ding B, Nyberg F, Mora S, Ridker PM, Chasman DI. Differential genetic effects on statin-induced changes across low-density lipoprotein-related measures. *Circ Cardiovasc Genet*. 2015;8:688–695. doi: 10.1161/CIRCGENETICS.114.000962
63. Shiffman D, Trompet S, Louie JZ, Rowland CM, Catanese JJ, Iakoubova OA, Kirchgessner TG, Westendorp RG, de Craen AJ, Slagboom PE, Buckley BM, Stott DJ, Sattar N, Devlin JJ, Packard CJ, Ford I, Sacks FM, Jukema JW. Genome-wide study of gene variants associated with differential cardiovascular event reduction by pravastatin therapy. *PLoS One*. 2012;7:e38240. doi: 10.1371/journal.pone.0038240
64. SEARCH Collaborative Group. SLCO1B1 variants and statin-induced myopathy: a genomewide study. *N Engl J Med*. 2008;359:789–799. doi: 10.1056/NEJMoa0801936
65. Wilke RA, Ramsey LB, Johnson SG, Maxwell WD, McLeod HL, Voora D, Krauss RM, Roden DM, Feng Q, Cooper-Dehoff RM, Gong L, Klein TE, Wadelius M, Niemi M; Clinical Pharmacogenomics Implementation Consortium (CPIC). The clinical pharmacogenomics implementation consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. *Clin Pharmacol Ther*. 2012;92:112–117. doi: 10.1038/clpt.2012.57
66. Global Burden of Disease Study 2016. Global Burden of Disease Study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed May 1, 2018.
67. Farzadfar F, Finucane MM, Danaei G, Pelizzari PM, Cowan MJ, Paciorek CJ, Singh GM, Lin JK, Stevens GA, Riley LM, Ezzati M; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Cholesterol). National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3·0 million participants. *Lancet*. 2011;377:578–586. doi: 10.1016/S0140-6736(10)62038-7

8. HIGH BLOOD PRESSURE

ICD-9 401 to 404; ICD-10 I10 to I15. See Tables 8-1 and 8-2 and Charts 8-1 through 8-6

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HBP is a major risk factor for CVD and stroke.[1] The AHA has identified untreated BP <90th percentile (for children) and <120/<80 mm Hg (for adults aged ≥20 years) as 1 of the 7 components of ideal cardiovascular health.[2] In 2013 to 2014, 88.7% of children and 45.4% of adults met these criteria (Chapter 2, Cardiovascular Health).

Abbreviations Used in Chapter 8

ACC	American College of Cardiology
ACEI	angiotensin-converting enzyme inhibitor
AHA	American Heart Association
BMI	body mass index
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CARDIA	Coronary Artery Risk Development in Young Adults
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
CVD	cardiovascular disease
DALY	disability-adjusted life-year
DBP	diastolic blood pressure
DM	diabetes mellitus
ED	emergency department
ESRD	end-stage renal disease
GBD	Global Burden of Disease
GWAS	genome-wide association studies
HBP	high blood pressure
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
HCUP	Healthcare Cost and Utilization Project
HF	heart failure
HIV	human immunodeficiency virus
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-9-CM	*International Classification of Diseases, Clinical Modification, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
IDACO	International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes
JHS	Jackson Heart Study
MEPS	Medical Expenditure Panel Survey
MESA	Multi-Ethnic Study of Atherosclerosis
MET	metabolic equivalent
MI	myocardial infarction
NAMCS	National Ambulatory Medical Care Survey
NCHS	National Center for Health Statistics
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
OR	odds ratio

(*Continued*)

Abbreviations Used in Chapter 8 Continued

PA	physical activity
PAR	population attributable risk
QALY	quality-adjusted life-year
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SBP	systolic blood pressure
SES	socioeconomic status
SPRINT	Systolic Blood Pressure Intervention Trial
SSB	sugar-sweetened beverage

Prevalence (See Table 8-1, Chart 8-1, and Chart 8-2)

- Although surveillance definitions vary widely in the published literature, including for the CDC and NHLBI, the following definition of HBP has been proposed for surveillance[3]:
  - — SBP ≥130 mm Hg or DBP ≥80 mm Hg or self-reported antihypertensive medicine use, or
  - — Having been told previously, at least twice, by a physician or other health professional that one has HBP.
- With this definition, the age-adjusted prevalence of hypertension among US adults ≥20 years of age was estimated to be 46.0% in NHANES in 2013 to 2016 (49.0% for males and 42.8% for females). This equates to an estimated 116.4 million adults ≥20 years of age who have HBP (58.7 million males and 57.7 million females; Table 8-1; unpublished NHLBI tabulation).
- In 2013 to 2016, the prevalence of HBP was 26.1% among those 20 to 44 years of age, 59.2% among those 45 to 64 years of age, and 78.2% among those ≥65 years of age (unpublished NHLBI tabulation).
- The prevalence of HBP in adults ≥20 years of age is presented by both age and sex in Chart 8-1.
- In 2013 to 2016, a higher percentage of males than females had hypertension up to 64 years of age. For those ≥65 years of age, the percentage of females with hypertension was higher than for males (unpublished NHLBI tabulation).
- Data from NHANES 2013 to 2016 indicate that 35.3% of US adults with hypertension are not aware they have it (unpublished NHLBI tabulation).
- The age-adjusted prevalence of hypertension in 1999 to 2004, 2005 to 2010, and 2011 to 2016 is shown in race/sex subgroups in Chart 8-2.
- Data from the 2015 BRFSS/CDC indicate that the age-adjusted percentage of adults ≥18 years of age who had been told that they had HBP ranged from 24.2% in Minnesota to 39.9% in Mississippi. The age-adjusted percentage for the total United States was 29.7%.[4]

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- A meta-analysis of 24 studies (N=961 035) estimated the prevalence of apparent treatment-resistant hypertension to be 13.7% (95% CI, 11.2%–16.2%).[5]
- In a cohort of patients with established kidney disease, 40.4% had resistant hypertension.[6]
- An analysis of the Spanish Ambulatory Blood Pressure Monitoring Registry using 70 997 patients treated for hypertension estimated the prevalence of resistant hypertension (SBP/DBP ≥140/90 mm Hg on at least 3 antihypertensive medications) was 16.9%, whereas the prevalence of white-coat resistant hypertension was 37.1%. The prevalence of refractory hypertension (SBP/DBP ≥140/90 mm Hg on at least 5 antihypertensive medications) was 1.4%, whereas the prevalence of white-coat refractory hypertension was 26.7%.[7]
- SPRINT demonstrated that an SBP goal of <120 mm Hg resulted in fewer CVD events and a greater reduction in mortality than an SBP goal of <140 mm Hg among people with SBP ≥130 mm Hg and increased cardiovascular risk.[8] Using NHANES 2007 to 2012 data, it was estimated that 7.6% (95% CI, 7.0%–8.3%) or 16.8 million (95% CI, 15.7–17.8 million) US adults meet the SPRINT inclusion and exclusion criteria.[9]
- Among 1677 participants in the IDACO cohort database aged 40 to 79 years with clinic-measured SBP ≥140 mm Hg or DBP ≥90 mm Hg and not taking antihypertensive medication, 35.7% (95% CI, 23.5%–56.2%) had white-coat hypertension. Among 3320 participants from the same database with clinic SBP <140 mm Hg and clinic DBP <90 mm Hg and not taking antihypertensive medication, 16.9% (95% CI, 8.8%–30.5%) had masked hypertension.[10]
- Using data from the 2011 to 2014 NHANES (N=9623), the prevalence of hypertension among US adults was 45.6% (95% CI, 43.6%–47.6%) using BP thresholds from the 2017 ACC/AHA guidelines versus 31.9% (95% CI, 30.1%–33.7%) using Joint National Committee 7 guideline thresholds.[11]
- In a meta-analysis of people ≥16 years of age with HIV (49 studies; N=63 554), the prevalence of hypertension was 25.2% (34.7% among those who were taking or had taken antiretroviral therapy and 12.7% among those who had not ever taken antiretroviral therapy).[12]

Older Adults

- The white-coat effect (clinic minus out-of-clinic BP) is larger at older ages. In IDACO, a pooled analysis of 11 cohorts, the white-coat effect for SBP was 3.8 mm Hg (95% CI, 3.1–4.6 mm Hg) larger for each 10-year increase in age.[13]
- In the English Longitudinal Study of Ageing, the prevalence, awareness, and treatment of hypertension increased progressively between 1998 and 2012 among octogenarians. Although BP control (SBP/DBP <140/90 mm Hg) declined from 1998 to 2004 (37% to 31%), it increased to 47% by 2012.[14]
- Among adults in the REGARDS study ≥65 years of age with hypertension, having more indicators of frailty (low BMI, cognitive impairment, depressive symptoms, exhaustion, impaired mobility, and history of falls) was associated with an increased risk for serious fall injuries (HR associated with 1, 2, and ≥3 versus 0 indicators of frailty, 1.18 [95% CI, 0.99–1.40], 1.49 [95% CI, 1.19–1.87], and 2.04 [95% CI, 1.56–2.67], respectively). In contrast, on-treatment SBP and DBP were not significantly associated with risk for serious fall injuries.[15]

Children and Adolescents

- In 2011 to 2012, 11.0% (95% CI, 8.8%–13.4%) of children and adolescents aged 8 to 17 years had either HBP (SBP or DBP at the 95th percentile or higher) or borderline HBP (SBP or DBP between the 90th and 95th percentile or BP levels of 120/80 mm Hg or higher but <95th percentile).[16]
- Among US children and adolescents, there was no evidence of a change in the prevalence of borderline HBP (7.6% [95% CI, 5.8%–9.8%] versus 9.4% [95% CI, 7.2%–11.9%]; *P*=0.90) or either HBP or borderline HBP (10.6% [95% CI, 8.4%–13.1%] versus 11.0% [95% CI, 8.8%–13.4%]; *P*=0.26) between 1999 to 2000 and 2011 to 2012.[16] In this age group, HBP declined from 3.0% to 1.6% between 1999 to 2000 and 2011 to 2012.[16]
- In 2011 to 2012, HBP was more common among boys (1.8%) than girls (1.4%) and among Hispanics (2.4%) than among NH blacks (1.9%), NH whites (1.1%), and NH Asians (1.7%). Having either HBP or borderline HBP was more common among boys than girls. Also, NH blacks were more likely to have either HBP or borderline HBP than Hispanic, NH white, or NH Asian boys or girls.[16]
- In 2003 to 2010, for girls 8 to 11 years of age, 3.5% had poor BP, 5.0% had intermediate BP, and 91.5% had ideal BP levels according to the AHA 2020 Strategic Impact Goals. For boys 8 to 11 years of age, 2.8% had poor BP, 4.8% had intermediate BP, and 92.5% had ideal BP according to Life's Simple 7.[17]

- Analysis of data for children and adolescents aged 8 to 17 years from NHANES 1999 to 2002 through NHANES 2009 to 2012 found that mean SBP decreased from 105.6 to 104.9 mm Hg and DBP decreased from 60.3 to 56.1 mm Hg.[16,18]
- In NHANES 1999 to 2012, the prevalence of HBP was 9.9% among severely obese US adolescents (BMI ≥120% of 95th percentile of sex-specific BMI for age or BMI ≥35 kg/m²). The OR for HBP was 5.3 (95% CI, 3.8–7.3) when comparing severely obese versus normal-weight adolescents.[19]
- Among normal-weight and overweight/obese US adolescents (12–19 years of age), mean SBP and DBP did not change between 1988 to 1994 and 2007 to 2012. The unadjusted prevalence of pre-HBP was 11.4% and the prevalence of HBP was 0.9% in 1988 to 1994; the prevalence of pre-HBP was 11.1% and that of HBP was 1.4% in 2007 to 2012. Among overweight/obese adolescents, the unadjusted prevalence of pre-HBP was 15.5% and that of HBP was 6.4% in 1988 to 1994; the unadjusted prevalence of pre-HBP was 21.4% and that of HBP was 3.4% in 2007 to 2012.[20]
- The AHA has outlined conditions in which ambulatory BP monitoring may be helpful in children and adolescents. These include secondary hypertension, CKD, type 1 and type 2 DM, obesity, sleep apnea, genetic syndromes, treated patients with hypertension, and for research.[21] In a retrospective study of 500 children screened for potential hypertension with ambulatory BP monitoring, 12% had white-coat hypertension and 10% had masked hypertension.[22]
- In a systematic review of studies evaluating secular trends in BP among children and adolescents (N=18 studies with >2 million participants), BP decreased between 1963 and 2012 in 13 studies, increased in 4 studies, and did not change in 1 study conducted.[23] No formal pooling of data was conducted.
- Among adolescents (mean age 14 years) with CKD, 40% had masked hypertension (clinic SBP and DBP <90th percentile for age, sex, and height, and awake or asleep BP ≥95th percentile or BP load ≥25%).[24]
- Among 30 565 children and adolescents (3–17 years old) receiving health care between 2012 and 2015, 51.2% of those with a first BP reading ≥95th percentile for age, sex, and height and who had a second BP measurement had a mean BP based on 2 consecutive readings that was less than the 95th percentile. Of those with a visit BP ≥95th percentile, 67.8% did not have a follow-up visit within 3 months, and only 2.3% of those individuals with a follow-up visit had a BP ≥95th percentile at this visit.[25]

Race/Ethnicity and HBP (See Table 8-1 and Chart 8-2)

- The prevalence of hypertension in blacks in the United States is among the highest in the world. In 2011 to 2016, the age-adjusted prevalence of hypertension among NH blacks was 57.6% among males and 53.2% among females (Chart 8-2) (unpublished NHLBI tabulation).
- Among >4 million adults who were overweight or obese in 10 healthcare systems, the prevalence of hypertension was 47.3% among blacks, 39.6% among whites, 38.6% among Native Hawaiians/Pacific Islanders, 38.3% among American Indians/Native Americans, 34.8% among Asians, and 24.8% among Hispanics. Within categories defined by BMI and after adjustment for age, sex, and healthcare system, each racial/ethnic group except Hispanics was more likely to have hypertension than whites.[26]
- During 10 years of follow-up in the REGARDS study, a higher percentage of black males (48%) and females (54%) developed hypertension than white males (38%) or females (27% for those 45 to 54 years of age and 40% for those ≥75 years old).[27]
- Higher SBP explains ≈50% of the excess stroke risk among blacks compared with whites.[28]
- Data from the 2014 NHIS showed that black adults ≥18 years of age were more likely (33.0%) to have been told on ≥2 occasions that they had hypertension than American Indian/Alaska Native adults (26.4%), white adults (23.5%), Hispanic or Latino adults (22.9%), or Asian adults (19.5%).[29]
- In HCHS/SOL, for US Hispanic or Latino males, the age-standardized prevalence of hypertension in 2008 to 2011 varied from a low of 19.9% among individuals of South American background to a high of 32.6% among individuals of Dominican background. For US Hispanic or Latino females, the age-standardized prevalence of hypertension was lowest for individuals of South American background (15.9%) and highest for individuals of Puerto Rican background (29.1%).[30]
- Also in HCHS/SOL, the prevalence of awareness, treatment, and control of hypertension among males was lowest in those of Central American background (57%, 39%, and 12%, respectively) and highest among those of Cuban background (78%, 65%, and 40%, respectively). Among females, those of South American background had the lowest prevalence of awareness (72%) and treatment (64%), whereas hypertension

control was lowest among females of Central American background (32%). Only Hispanic females reporting mixed/other background had a hypertension control rate that exceeded 50%.[31]

- Among adults with hypertension, blacks were more likely to have resistant hypertension (19.0%) than whites (13.5%) or Hispanics (11.2%).[32]
- Among 22 705 black adults with hypertension receiving care in the New York City Health and Hospital Corporation outpatient clinics in 2004 to 2009, the percentage with controlled BP (SBP/DBP <140/90 mm Hg) was lower among Caribbean-born individuals (49.0%) than among those born in the United States (58.3%) or West Africa (58.4%).[33]
- In an analysis of NHANES participants from 2003 to 2014, foreign-born NH blacks (N=522) had lower adjusted odds of having hypertension than US-born NH blacks (N=4511; OR, 0.61; 95% CI, 0.49–0.77).[34]
- In NHANES 2011 to 2014, US NH blacks (13.2%) were more likely than NH Asians (11.0%), NH whites (8.6%), or Hispanics (7.4%) to use home BP monitoring on a weekly basis.[35]
- Among 559 participants who reported having hypertension in the AHA's Cardiovascular Health Consumer Survey, 53.8% of participants reported using a home BP monitor.[36]
- Among 441 African Americans in the JHS not taking antihypertensive medication, the prevalence of clinic hypertension (mean SBP ≥140 mm Hg or mean DBP ≥90 mm Hg) was 14.3%, the prevalence of daytime hypertension (mean daytime SBP ≥135 mm Hg or mean daytime DBP ≥85 mm Hg) was 31.8%, and the prevalence of nighttime hypertension (mean nighttime SBP ≥120 mm Hg or mean nighttime DBP ≥70 mm Hg) was 49.4%. Among 575 African Americans taking antihypertensive medication, the prevalence estimates were 23.1% for clinic hypertension, 43.0% for daytime hypertension, and 61.7% for nighttime hypertension.[37]

Mortality (See Table 8-1)

- Using data from the National Vital Statistics System, in 2016, there were 82 735 deaths primarily attributable to HBP (Table 8-1). The 2016 age-adjusted death rate primarily attributable to HBP was 21.6 per 100 000. Age-adjusted death rates attributable to HBP (per 100 000) in 2016 were 21.1 for NH white males, 54.0 for NH black males, 20.1 for Hispanic males, 16.0 for NH Asian/Pacific Islander males, 26.2 for NH American Indian/Alaska Native males, 17.3 for NH white females, 36.7 for NH black females, 15.6 for Hispanic females, 14.0 for NH Asian/Pacific Islander females, and 20.7 for NH American Indian/Alaska Native females.[38]
- From 2006 to 2016, the death rate attributable to HBP increased 18.0%, and the actual number of deaths attributable to HBP rose 46.3%. During this 10-year period, in NH whites, the HBP death rate increased 19.3%, whereas the actual number of deaths attributable to HBP increased 44.5%. In NH blacks, the HBP death rate decreased 2.2%, whereas the actual number of deaths attributable to HBP increased 31.2%. In Hispanics, the HBP death rate increased 13.4%, and the actual number of deaths attributable to HBP increased 96.8% (unpublished NHLBI tabulation).
- When any mention of HBP was present, the overall age-adjusted death rate in 2016 was 115.8 per 100 000. Death rates were 126.5 for NH white males, 221.9 for NH black males, 87.8 for NH Asian or Pacific Islander males, 155.8 for NH American Indian or Alaska Native males (underestimated because of underreporting), and 116.6 for Hispanic males. In females, rates were 95.3 for NH white females, 153.8 for NH black females, 68.0 for NH Asian or Pacific Islander females, 111.7 for NH American Indian or Alaska Native females (underestimated because of underreporting), and 85.9 for Hispanic females.[39,40]
- The hypertension-related death rate increased 6.8% from 523.8 per 100 000 in 2000 to 559.3 in 2005 for NH blacks, and then it decreased 8.8% to 509.9 in 2013. Among Hispanics, the rate increased 21.9% from 233.7 in 2000 to 284.8 in 2013. For the NH white population, the rate increased 29.8% from 228.5 in 2000 to 296.5 in 2013.[41]
- CHD, stroke, cancer, and DM accounted for 65% of all deaths with any mention of hypertension in 2000 and for 54% in 2013.[41]
- The elimination of hypertension could reduce CVD mortality by 30.4% among males and 38.0% among females.[42] The elimination of hypertension is projected to have a larger impact on CVD mortality than the elimination of all other risk factors among females and all except smoking among males.[42]
- Among US adults meeting the eligibility criteria for SPRINT, SBP treatment to a treatment goal of <120 mm Hg versus <140 mm Hg has been projected to prevent ≈107 500 deaths per year (95% CI, 93 300–121 200).[43]
- On the basis of a Swedish cohort study from 2006 to 2012, patients with treatment-resistant hypertension (N=4317) had a 12% higher risk of all-cause mortality (HR, 1.12; 95% CI,

1.03–1.23) than patients with hypertension but not treatment-resistant hypertension (N=32 282). Patients with treatment-resistant hypertension also had a higher risk of cardiovascular mortality (HR, 1.20; 95% CI, 1.03–1.40) than participants with hypertension but not treatment-resistant hypertension.[44]

Risk Factors

- Participants with SSB consumption in the highest versus lowest quantile had a risk ratio for hypertension of 1.12 (95% CI, 1.06–1.17) in a meta-analysis of 240 508 people.[45] This equated to an 8.2% increased risk for hypertension for each additional SSB consumed per day.
- A systematic review identified 48 hypertension risk prediction models reported in 26 studies (N=162 358 enrolled participants). The C statistics from these models ranged from 0.60 to 0.90.[46]
- In the JHS, intermediate and ideal versus poor levels of moderate to vigorous PA were associated with HRs of hypertension of 0.84 (95% CI, 0.67–1.05) and 0.76 (95% CI, 0.58–0.99), respectively.[47]
- Also, anger, depressive symptoms, and stress were associated with increased BP progression in the JHS.[48]
- In the JHS, an additional social contact was associated with a fully adjusted prevalence ratio of 0.87 (95% CI, 0.74–1.0) for having treatment-resistant hypertension in a sample of 1392 participants with treated hypertension who self-reported being adherent to antihypertensive medication.[49]
- In NHANES 2013 to 2014, each additional 1000 mg of usual 24-hour sodium excretion (ie, a marker of sodium consumption) was associated with 4.58 (95% CI, 2.64–6.51) mm Hg higher SBP and 2.25 (0.83–3.67) mm Hg higher DBP. Each additional 1000 mg usual 24-hour potassium intake was associated with 3.72 (95% CI, 1.42 - 6.01) mm Hg lower SBP.[50]
- Among 1741 participants in the JHS with hypertension, 20.1% of those without versus 30.5% of those with CKD developed apparent treatment-resistant hypertension (multivariable-adjusted HR, 1.45; 95% CI, 1.12–1.86).[51]
- In a meta-analysis of 9 population-based studies (N=102 408), the OR for having hypertension among participants with versus without restless leg syndrome was 1.36 (95% CI, 1.18–1.57).[52]
- Among 1878 participants in the JHS who were followed up for a median of 8 years, the cumulative incidence of hypertension was 80.9% among those with 0 of 1 of the Life's Simple 7 components in the ideal range and 66.7%, 54.8%, 32.7%, 25.8% and 10.7% among participants with 2, 3, 4, 5, and 6 ideal components, respectively. No participants had 7 ideal Life's Simple 7 components. A strong and dose-response association between having more ideal Life's Simple 7 components and lower risk for hypertension was present after multivariable adjustment.[53]
- In a meta-analysis of 5 studies, each additional 250 mL of SSBs was associated with an RR for incident hypertension of 1.07 (95% CI, 1.04–1.10).[54]
- In a meta-analysis of 36 trials, randomization to reduction in alcohol consumption was associated with a reduction in SBP for participants who at baseline consumed ≥6 drinks per day (−5.50 mm Hg; 95% CI, −6.70 to −4.30 mm Hg), 4 or 5 drinks per day (−3.00 mm Hg; 95% CI, −3.98 to −2.03 mm Hg), and 3 drinks per day (−1.18 mm Hg; 95% CI, −2.32 to −0.04 mm Hg) but not their counterparts who drank 2 or fewer drinks per day (−0.18; 95% CI, −1.02 to 0.66 mm Hg).[55]
- In the HCHS/SOL Sueño Sleep Ancillary Study of Hispanics (N=2148), a 10% higher sleep fragmentation and frequent napping versus not napping were associated with a 5.2% and 11.6% higher prevalence of hypertension, respectively. A 10% higher sleep efficiency was associated with 7.2% lower prevalence of hypertension.[56]
- In a meta-analysis of 24 cohort studies, each 10 additional MET-hours per week in leisure-time PA was associated with an RR for hypertension of 0.94 (95% CI, 0.92–0.96). In 5 cohort studies, each additional 50 MET-hours per week in total PA time was associated with an RR for hypertension of 0.93 (95% CI, 0.88–0.98).[57]

Aftermath

- In a meta-analysis that included 95 772 US females and 30 555 US males, each 10-mm Hg higher SBP was associated with an effect size (eg, RR or HR) for CVD of 1.25 (95% CI, 1.18–1.32) among females and 1.15 (95% CI, 1.11–1.19) among males. Among 65 806 females and 92 515 males in this meta-analysis, the RR for CVD mortality associated with 10-mm Hg higher SBP was 1.16 (95% CI, 1.10–1.23) among females and 1.17 (95% CI, 1.12–1.22) among males.[58]
- In a meta-analysis of 12 prospective studies (N=2 170 265), participants with a history of hypertension were more likely to develop kidney cancer (RR, 1.67; 95% CI, 1.46–1.90).[59]
- In a study of >1 million adults with hypertension, the lifetime risk of CVD at age 30 years was 63.3% compared with 46.1% for those without hypertension. Those with hypertension developed CVD 5.0 years earlier than their counterparts

without hypertension.[60] The largest lifetime risk differences between people with versus without hypertension were for angina, MI, and stroke. At age 60 years, the lifetime risk for CVD was 60.2% for those with hypertension and 44.6% for their counterparts without hypertension.

- In a cohort of older US adults, both isolated systolic hypertension and systolic-diastolic hypertension were associated with an increased risk for HF (multivariable-adjusted HR, 1.86; 95% CI, 1.51–2.30 and HR, 1.73; 95% CI, 1.24–2.42, respectively) compared with participants without hypertension.[61]
- Overall, in national data, the prevalence of healthy lifestyle behaviors varies widely among those with self-reported hypertension: 20.5% had a normal weight, 82.3% did not smoke, 94.1% reported no or limited alcohol intake, 14.1% consumed the recommended amounts of fruits or vegetables, and 46.6% engaged in the recommended amount of PA.[62]
- The association of hypertension with CHD has not changed from 1983 to 1990 (HR, 1.14; 95% CI, 1.11–1.16) versus 1996 to 2002 (HR, 1.13; 95% CI, 1.10–1.15). The PAR associated with hypertension was 39.6% in the early time period and 40.0% in the later time period.[63]
- Among 17312 participants with hypertension, nondipping BP was associated with an HR for CVD of 1.40 (95% CI, 1.20–1.63).[64]
- In the JHS, a cohort composed exclusively of African Americans, masked hypertension was associated with an HR for CVD of 2.49 (95% CI, 1.26–4.93).[65]
- A meta-analysis (23 cohorts with 20445 participants) showed that white- coat hypertension is associated with an increased risk for CVD among untreated individuals (adjusted HR, 1.38; 95% CI, 1.15–1.65) but not among treated individuals (HR, 1.16; 95% CI, 0.91–1.49).[66]
- In a pooled analysis of 63559 people without hypertension from 49 countries, sodium excretion >7 g/d was associated with an HR for CVD of 1.23 (95% CI, 1.11–1.37), and sodium excretion <3 g/d was associated with an HR of 1.34 (95% CI, 1.23–1.47), each compared with sodium excretion of 4.5 g/d.[67]
- Among adults with established CKD, apparent treatment-resistant hypertension has been associated with increased risk for CVD (HR, 1.38; 95% CI, 1.22–1.56), renal outcomes including a 50% decline in estimated glomerular filtration rate or end-stage renal disease (HR, 1.28; 95% CI, 1.11–1.46), HF (HR, 1.66; 95% CI, 1.38–2.00), and all-cause mortality (HR, 1.24; 95% CI, 1.06–1.45).[6]
- In an international case-control study (N=13447 cases of stroke and N=13472 control subjects), a previous history of hypertension or SBP/DBP ≥140/90 mm Hg was associated with an OR for stroke of 2.98 (95% CI, 2.72–3.28). The PAR for stroke accounted for by hypertension was 47.9%.[68]
- Among adults 45 years of age without HF, HF-free survival was shorter among those with versus without hypertension in males (30.4 versus 34.3 years), females (33.5 versus 37.6 years), blacks (33.2 versus 37.3 years), and whites (31.9 versus 36.3 years).[69]
- In prospective follow-up of the REGARDS, MESA, and JHS cohorts (N=31856), 63.0% (95% CI, 54.9%–71.1%) of the 2584 incident CVD events occurred in participants with SBP <140 and DBP <90 mm Hg.[70]

Hospital Discharges/Ambulatory Care Visits (See Table 8-1)

- From 2004 to 2014, the number of inpatient discharges from short-stay hospitals with HBP as the principal diagnosis was stable at 285000 and 292000, respectively (HCUP, unpublished NHLBI tabulation) The number of discharges with any listing of HBP increased from 12461000 to 15638000 (HCUP, unpublished NHLBI tabulation).
- In 2014, there were 90000 principal diagnosis discharges for essential hypertension (HCUP, unpublished NHLBI tabulation).
- In 2014, there were 11584000 all-listed discharges for essential hypertension (HCUP, unpublished NHLBI tabulation).
- Data from the NIS from the years 2000 to 2011 found the frequency of hospitalizations for malignant hypertension and hypertensive encephalopathy increased, whereas hospitalizations for essential hospitalization decreased, which coincided with the introduction of medical severity diagnosis-related group billing. Overall, the annual incidence of hypertension-related hospitalizations increased over the time period from ≈87000 in 2000 to ≈120000 in 2011.[71]
- In 2006 to 2010, 7.1% of patients with hypertension attending outpatient visits had treatment-resistant hypertension. The use of thiazide diuretic agents and chlorthalidone was low (56.4% and 1.2%, respectively).[72]
- In 2015, 42749000 of 990808000 physician office visits had a primary diagnosis of essential hypertension (*ICD-9-CM* 401; NCHS, NAMCS, NHLBI tabulation).[73] A total of 1182000 of

136 943 000 ED visits in 2015 and 3 743 000 of 125 721 000 hospital outpatient visits in 2011 were for essential hypertension (NCHS, NHAMCS, NHLBI tabulation).[74]

- Among REGARDS study participants ≥65 years of age with hypertension, compared with those without apparent treatment-resistant hypertension, participants with apparent treatment-resistant hypertension and uncontrolled BP had more primary care visits (2.77 versus 2.27 per year) and more cardiologist visits (0.50 versus 0.35 per year). In this same study, there were no statistically significant differences in laboratory testing for end-organ damage or secondary causes of hypertension among participants with apparent treatment-resistant hypertension and uncontrolled BP (72.4%), apparent treatment-resistant hypertension and controlled BP (76.5%), and with hypertension but not apparent treatment-resistant hypertension (71.8%).[75]

Awareness, Treatment, and Control (See Table 8-2 and Charts 8-3 through 8-5)

- Using NHANES 2013 to 2016 data, the extent of awareness, treatment, and control of HBP is provided by race/ethnicity (Chart 8-3), by age (Chart 8-4), and by race/ethnicity and sex (Chart 8-5) (unpublished NHLBI tabulation). Awareness, treatment, and control of hypertension were higher at older ages (Chart 8-4). Overall, females were more likely than males in all race/ethnicity groups to be aware of their condition, under treatment, or in control of their hypertension (Chart 8-5).
- Analysis of NHANES 1999 to 2006 and 2007 to 2014 found the proportion of adults aware of their hypertension increased within each race/ethnicity and sex subgroup. Similarly, large increases in hypertension treatment and control (≈10%) occurred in each of these groups (Table 8-2).
- Among US adults taking prescription antihypertensive medication, the age-adjusted percentage with BP control increased from 61.9% to 70.4% from 2003 to 2004 to 2011 to 2012.[76]
- Data from NHANES 1999 to 2012 show that the use of various classes of antihypertensive treatment had increased substantially among people ≥20 years of age. During this period, the use of ACEIs increased from 6.3% of the US population to 12%, angiotensin receptor blockers from 2.1% to 5.8%, β-blockers from 6.0% to 11%, and thiazide diuretic drugs from 5.6% to 9.4%. The use of calcium channel blockers remained the same, at 6%.[77]
- In a multinational study of 63 014 adults from high-, middle-, and low-income countries, 55.6% of participants were aware of their diagnosis of hypertension, 44.1% were treated, and 17.1% had controlled BP. Awareness and control were less common in upper-middle-income countries, whereas treatment was lowest in low-income countries.[78]
- Among US adults in NHANES 2007 to 2012, 55% of those with a usual source of care compared with 14% of their counterparts without a usual source of care had controlled hypertension (SBP/DBP <140/90 mm Hg). In addition, 31% of those who reported using the ED as their usual source of care had controlled hypertension.[79]
- According to the 2006 to 2010 NAMCS, 16.3% of patients with uncontrolled BP were prescribed a new antihypertensive medication. Patients receiving care at community health clinics versus private physician's offices had a greater odds of being prescribed a new antihypertensive medication (adjusted OR, 1.6; 95% CI, 1.1–2.4).[80]
- Self-reported antihypertensive medication use increased from 2.2% in 1971 to 1975 to 7.7% in 2009 to 2012 among US adults 25 to 49 years of age.[81]
- In a cohort study of Korean patients from 2009 to 2013 with health insurance claims for hypertension (N=38 520), those with poor adherence to antihypertensive medication (defined as <50% of days of follow up covered by a medication prescription fill) had an adjusted risk ratio for stroke of 1.27 (95% CI, 1.17–1.38) compared with those with high adherence (>80% of days covered by prescription fill).[82]
- Using national prescription data in Denmark, the use of antihypertensive medications increased from 184 to 379 defined daily doses per 1000 inhabitants per day. Over this time period, increases were present for ACEIs (29 to 105 defined daily doses), angiotensin II receptor blockers (13 to 73 defined daily doses), β-blockers (17 to 34 defined daily doses), and calcium channel blockers (34 to 82 defined daily doses).[83]
- Among 3358 African Americans taking antihypertensive medication in the JHS, 25.4% of participants reported not taking ≥1 of their prescribed antihypertensive medications within the 24 hours before their baseline study visit in 2000 to 2004. This percentage was 28.7% at examination 2 (2005–2008) and 28.5% at examination 3 (2009–2012). Nonadherence was associated with higher likelihood of having SBP ≥140 mm Hg or

DBP ≥90 mm Hg (prevalence ratio, 1.26; 95% CI, 1.16–1.37).[84]

- In an analysis of 1590 healthcare providers who completed the DocStyles survey, a web-based survey of healthcare providers, 86.3% reported using a prescribing strategy to increase their patients' adherence. The most common strategies were prescribing once-daily regimens (69.4%), prescribing medications covered by the patient's insurance (61.8%), and using longer fills (59.9%).[85]

Cost (See Table 8-1)

- The estimated direct and indirect cost of HBP for 2014 to 2015 (annual average) was $55.9 billion (MEPS, NHLBI tabulation).
- Adjusted to 2012 US dollars, the monetary savings and QALYs gained with lifetime treatment were $7387 and 1.14 for white males, $7796 and 0.89 for white females, $8400 and 1.66 for black males, and $10 249 and 1.79 for black females, respectively.[86]
- Projections show that by 2035, the total direct costs of HBP could increase to an estimated $220.9 billion (based on methodology described in Heidenreich et al[87]).[88]
- According to IMS Health's National Prescription Audit, the number of prescriptions for antihypertensive medication increased from 614 million to 653 million between 2010 and 2014. The 653 million antihypertensive prescriptions filled in 2014 cost $28.81 billion.[89]
- Among a 5% sample of US Medicare beneficiaries initiating antihypertensive treatment in 2012 (N=41 135), 21.3% discontinued treatment within 1 year and an additional 31.7% had low adherence.[90]
- Using data from MEPS for 2011 to 2014, among persons with a diagnosis code for hypertension who were ≥18 years of age (N=26 049), the mean annual costs of hypertension ranged from $3914 (95% CI, $3456–$4372) for those with no comorbidities to $13 920 (95% CI, $13 166–$14 674) for those with ≥3 comorbidities.[91]
- Among US adults, medical expenditures associated with having versus not having hypertension were $1494 in 2012 to 2013 and $1399 in 2000 to 2001. Outpatient expenditures increased from $322 in 2000 to 2001 to $416 in 2012 to 2013.[92]

Social Determinants

- In a meta-analysis of 51 studies, lower SES measured by income, occupation, or education was linked to increased risk of hypertension. Findings were particularly pronounced for education, with a 2-fold higher rate of hypertension observed in lower- compared with higher-educated individuals. Associations were stronger among women and in higher-income countries.[93] Additional research among Hispanics has found that lower education is also a risk factor for lower BP dipping.[94]
- Racial segregation (residing in a neighborhood composed primarily of others from the same racial/ethnic background) and neighborhood poverty have also been linked to hypertension prevalence, particularly among African Americans.[95] Recent data from the CARDIA study also found that for African Americans, moving from highly segregated census tracts to areas lower in segregation over a 25-year follow-up was associated with up to a 5.71 mm Hg reduction in SBP, even after adjustment for poverty and other relevant risk factors.[96]
- Self-reported experiences of discrimination and unfair treatment have also been linked to hypertension and BP. In a meta-analysis of 44 studies, higher reports of discrimination were linked to a greater prevalence of hypertension, particularly among African Americans (compared with other racial/ethnic groups), participants of older ages, males, and individuals with a lower versus higher level of education. Associations between reports of discrimination and BP were most striking for ambulatory nighttime BP; effect sizes for overall associations between self-reported experiences of discrimination and resting SBP or DBP were not significant.[97]
- At least 1 study has found that social integration, defined as the number of social contacts of an individual, may be an important factor to consider in treatment-resistant hypertension. In the JHS, a study of African Americans, each additional social contact was associated with a 19% lower prevalence of treatment-resistant hypertension.[49]

Family History and Genetics

- BP is a heritable trait; family studies have yielded heritability estimates of 48% to 60% (SBP) and 34% to 67% (DBP).[98]
- Genetic studies have been conducted to identify the genetic architecture of hypertension. Several large-scale GWASs and whole-exome studies, with interrogation of common and rare variants in >300 000 individuals, have established >100 well-replicated hypertension loci, with several hundred additional suggestive loci.[99–105]

- Genetic risk scores for hypertension are also associated with increased risk of CVD and MI.[99]
- Given strong effects of environmental factors on hypertension, gene-environment interactions are important in the pathophysiology of hypertension. Large-scale gene-environment interaction studies have not yet been conducted; however, studies of several thousand people have to date revealed several loci of interest that interact with smoking[106,107] and with dietary intake of alcohol[108] and sodium.[109]
- The clinical implications and utility of hypertension genes remain unclear, although some genetic variants have been shown to influence response to antihypertensive agents.[110]

Global Burden of Hypertension (See Chart 8-6)

- From 1980 to 2008, the global age-adjusted prevalence of uncontrolled hypertension decreased from 33% to 29% among males and from 29% to 25% among females.[111]
- HBP went from being the fourth-leading risk factor for global disease burden in 1990, as quantified by DALYs, to being the number 1 risk factor in 2010.[112]
- In a cross-sectional study of 628 communities (3 high-income countries, 10 upper-middle-income and low-middle-income countries, and 4 low-income countries), low-income countries had the lowest percentages of awareness (40.8%) and treatment (31.7%) of hypertension (self-reported treated hypertension or SBP/DBP ≥140/90 mm Hg). Low-middle-income countries had the lowest percentage of controlled hypertension (9.9%).[113]
- In 2010, HBP was 1 of the 5 leading risk factors for the burden of disease (years of life lost and DALYs) in all regions with the exception of Oceania.[112]
- In a meta-analysis of population-studies conducted in Africa, the prevalence of hypertension was 55.2% among adults ≥55 years of age.[114]
- In a systematic review, a higher percentage of hypertension guidelines developed in high-income countries used high-quality systematic reviews of relevant evidence compared with low- and middle-income countries (63.5% versus 10%).[115]
- On the basis of data from 135 population-based studies (N=968 419 adults from 90 countries), it was estimated that 31.1% (95% CI, 30.0%–32.2%) of the world adult population had hypertension in 2010. The prevalence was 28.5% (95% CI, 27.3%–29.7%) in high-income countries and 31.5% (95% CI, 30.2%–32.9%) in low-middle-income countries. It was also estimated that 1.39 billion adults worldwide had hypertension in 2010 (349 million in high-income countries and 1.04 billion in low- and middle-income countries).[116]
- In 2015, the prevalence of SBP ≥140 mm Hg was estimated to be 20 526 per 100 000. This represents an increase from 17 307 per 100 000 in 1990.[117] Also, the prevalence of SBP 110 to 115 mm Hg or higher increased from 73 119 per 100 000 to 81 373 per 100 000 between 1990 and 2015. There were 3.47 billion adults worldwide with SBP of 110 to 115 mm Hg or higher in 2015. Of this group, 847 million adults had SBP ≥140 mm Hg.[117]
- It has been estimated that 7.834 million deaths and 143.037 million DALYs in 2015 could be attributed to SBP ≥140 mm Hg.[117] In addition, 10.7 million deaths and 211 million DALYs in 2015 could be attributed to SBP of 110 to 115 mm Hg or higher.[117]
- Between 1990 and 2015, the number of deaths related to SBP ≥140 mm Hg did not increase in high-income countries (from 2.197 to 1.956 million deaths) but did in high-middle-income (from 1.288 to 2.176 million deaths), middle-income (from 1.044 to 2.253 million deaths), low-middle-income (from 0.512 to 1.151 million deaths), and low-income (from 0.146 to 0.293 million deaths) countries.[117]
- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories. The highest mortality rates attributable to high SBP are in Eastern Europe and Central Asia (Chart 8-6).[118]
- Among ≈1.7 million participants from the Chinese mainland aged 35 to 75 years from 2014 to 2017, the age- and sex-standardized prevalence of hypertension was 37.2%.[119]
- In a meta-analysis of 25 studies (N=54 196 participants aged 2 to 19 years) conducted in Africa, the pooled prevalence of SBP or DBP ≥95th percentile was 5.5% and the pooled prevalence of SBP or DBP ≥90th percentile was 12.7%. The prevalence of SBP/DBP ≥95th percentile was 30.8% among children with obesity versus 5.5% among normal-weight children.[120]
- Among 12 971 Turkish adults who completed the Chronic Diseases and Risk Factors Survey, a nationwide study, the prevalence of hypertension in 2011 was 27.1%, 65% of participants were aware they had hypertension, 59% were treated, and 30% had SBP/DBP <140/90 mm Hg.[121]

- In a meta-analysis of studies in Africa among older adults (≥55 years of age; 91 studies with 54 198 participants), the prevalence of hypertension was 55.2%.[114]

Prehypertension

- Among adults without hypertension, prehypertension is defined by an untreated SBP of 120 to 139 mm Hg or untreated DBP of 80 to 89 mm Hg.
- Between 1999 to 2000 and 2011 to 2012, the prevalence of prehypertension decreased among US adults from 31.2% to 28.2%.[122] In NHANES, the prevalence of prehypertension decreased in all age groups for US adults between 1999 to 2000 through 2013 to 2014, with the largest decline occurring among those 18 to 39 years of age (32.2% in 1999–2000 to 23.4% in 2013–2014).[123]
- Among US adults with prehypertension, between 1999 to 2000 and 2011 to 2012, there was an increase in the prevalence of overweight (from 33.5% to 37.3%), obesity (30.6% to 35.2%), no weekly leisure-time PA (40.0% to 43.9%), pre-DM (9.6% to 21.6%), and DM (6.0% to 8.5%). There was a decrease in the prevalence of current smoking over the time period (from 25.9% to 23.2%).[122]
- Among young adults (18–30 years old at baseline) with and without prehypertension in CARDIA, 23.1% and 3.8%, respectively, developed hypertension over 5 years of follow-up.[124]
- Multiple meta-analyses have demonstrated that prehypertension is associated with an increased risk for CVD, ESRD, and mortality. These risks are greater for people in the upper (130–139/85–89 mm Hg) versus lower (120–129/80–84 mm Hg) range of prehypertension.[125–133]

Table 8-1. High Blood Pressure in the United States

Population Group	Prevalence, 2013–2016, Age ≥20 y	Mortality,* 2016, All Ages	Hospital Discharges, 2014, All Ages	Estimated Cost, 2014–2015
Both sexes	116 400 000 (46.0%)	82 735	292 000	$55.9 Billion
Males	58 700 000 (49.0%)	39 577 (47.8%)†	142 000	…
Females	57 700 000 (42.8%)	43 158 (52.2 %)†	150 000	…
NH white males	48.2%	26 402	…	…
NH white females	41.3%	30 638	…	…
NH black males	58.6%	8429	…	…
NH black females	56.0%	7897	…	…
Hispanic males	47.4%	3063	…	…
Hispanic females	40.8%	2856	…	…
NH Asian males	46.4%	1153‡	…	…
NH Asian females	36.4%	1362‡	…	…
NH American Indian/Alaska Native	…	520	…	…

Hypertension is defined in terms of NHANES (National Health and Nutrition Examination Survey) blood pressure measurements and health interviews. A subject was considered to have hypertension if systolic blood pressure was ≥130 mm Hg or diastolic blood pressure was ≥80 mm Hg, if the subject said "yes" to taking antihypertensive medication, or if the subject was told on 2 occasions that he or she had hypertension. A previous publication that used NHANES 2011 to 2014 data estimated there were 103.3 million noninstitutionalized US adults with hypertension.[11] The number of US adults with hypertension in this table includes both noninstitutionalized and institutionalized US individuals. Also, the previous study did not include individuals who reported having been told on 2 occasions that they had hypertension as having hypertension unless they met another criterion (systolic blood pressure was ≥130 mm Hg or diastolic blood pressure was ≥80 mm Hg, if the subject said "yes" to taking antihypertensive medication). Ellipses indicate data not available; and NH, non-Hispanic.

*Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian, and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total high blood pressure mortality that is for males vs females.

‡Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander.

Sources: Prevalence: NHANES (2013–2016), National Center for Health Statistics (NCHS), and National Heart, Lung, and Blood Institute (NHLBI). Percentages for racial/ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2016 US population estimates. Mortality: Centers for Disease Control and Prevention/NCHS, 2016 Mortality Multiple Cause-of-Death–United States. These data represent underlying cause of death only. Mortality for NH Asians includes Pacific Islanders. Hospital discharges: Healthcare Cost and Utilization Project, National (Nationwide) Inpatient Sample, 2014. Agency for Healthcare Research and Quality. Cost: Medical Expenditure Panel Survey data include estimated direct costs for 2014 to 2015 (annual average); indirect costs calculated by NHLBI for 2014 to 2015 (annual average).

Table 8-2. Hypertension Awareness, Treatment, and Control: NHANES 1999 to 2004, 2005 to 2010, and 2011 to 2016 Age-Adjusted Percent With Hypertension in Adults by Sex and Race/Ethnicity

	Awareness, %			Treatment, %			Control, %		
	1999–2004	2005–2010	2011–2016	1999–2004	2005–2010	2011–2016	1999–2004	2005–2010	2011–2016
NH white males	46.7	55.8	61.2	35.0	45.7	48.9	13.3	20.4	24.8
NH white females	58.7	65.5	68.9	47.4	57.8	60.6	16.8	26.0	28.6
NH black males	47.6	59.1	62.3	35.5	46.5	48.4	11.2	18.0	17.2
NH black females	67.6	74.5	74.7	55.5	65.9	64.6	19.0	28.7	26.4
Mexican American males*	30.8	37.8	43.8	18.5	27.1	30.3	6.5	11.7	11.6
Mexican American females*	51.6	56.7	66.2	39.0	47.2	53.2	11.7	20.0	27.0

Values are percentages. Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A subject was considered to have hypertension if systolic blood pressure was ≥140 mm Hg or diastolic blood pressure was ≥90 mm Hg, or if the subject said "yes" to taking antihypertensive medication. NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*The category of Mexican Americans was consistently collected in all NHANES years, but the combined category of Hispanics was only used starting in 2007. Consequently, for long-term trend data, the category Mexican American is used.

Sources: NHANES (1999–2004, 2005–2010, 2011–2016) and National Heart, Lung, and Blood Institute.

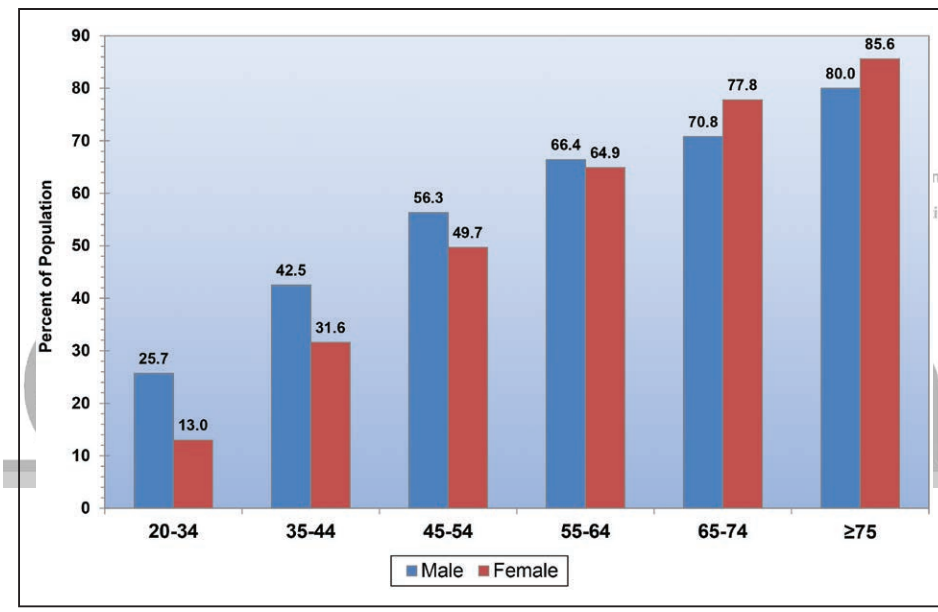

Chart 8-1. Prevalence of hypertension in adults ≥20 years of age by sex and age (NHANES, 2013–2016).

Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A person was considered to have hypertension if he or she had systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg, if he or she said "yes" to taking antihypertensive medication, or if the person was told on 2 occasions that he or she had hypertension.

NHANES indicates National Health and Nutrition Examination Survey.

Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

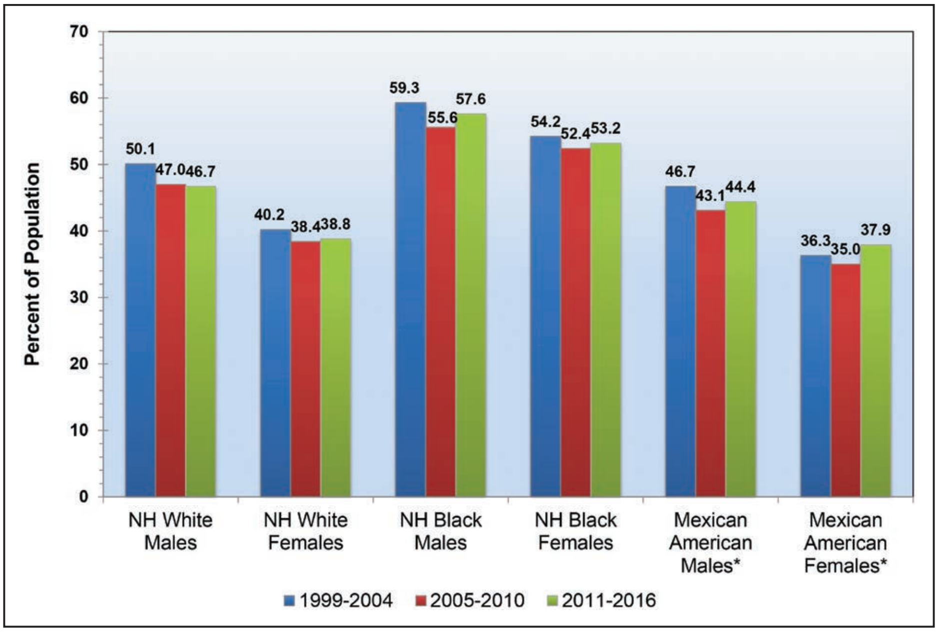

Chart 8-2. Age-adjusted prevalence trends for hypertension in adults ≥20 years of age by race/ethnicity, sex, and survey year (NHANES, 1999–2004, 2005–2010, and 2010–2016).

Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A person was considered to have hypertension if he or she had systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg, if he or she said "yes" to taking antihypertensive medication, or if the person was told on 2 occasions that he or she had hypertension.

NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*The category of Mexican Americans was consistently collected in all NHANES years, but the combined category of Hispanics was only used starting in 2007. Consequently, for long-term trend data, the category Mexican American is used.

Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

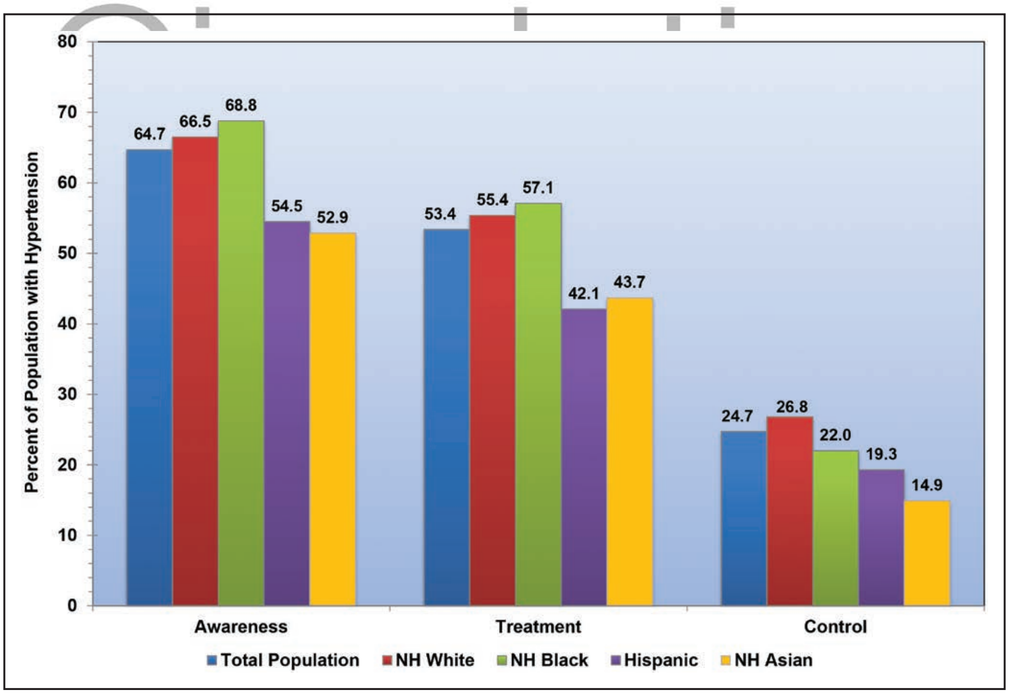

Chart 8-3. Extent of awareness, treatment, and control of high blood pressure by race/ethnicity (NHANES, 2013–2016).

Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A person was considered to have hypertension if he or she had systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg, if he or she said "yes" to taking antihypertensive medication, or if the person was told on 2 occasions that he or she had hypertension.

NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

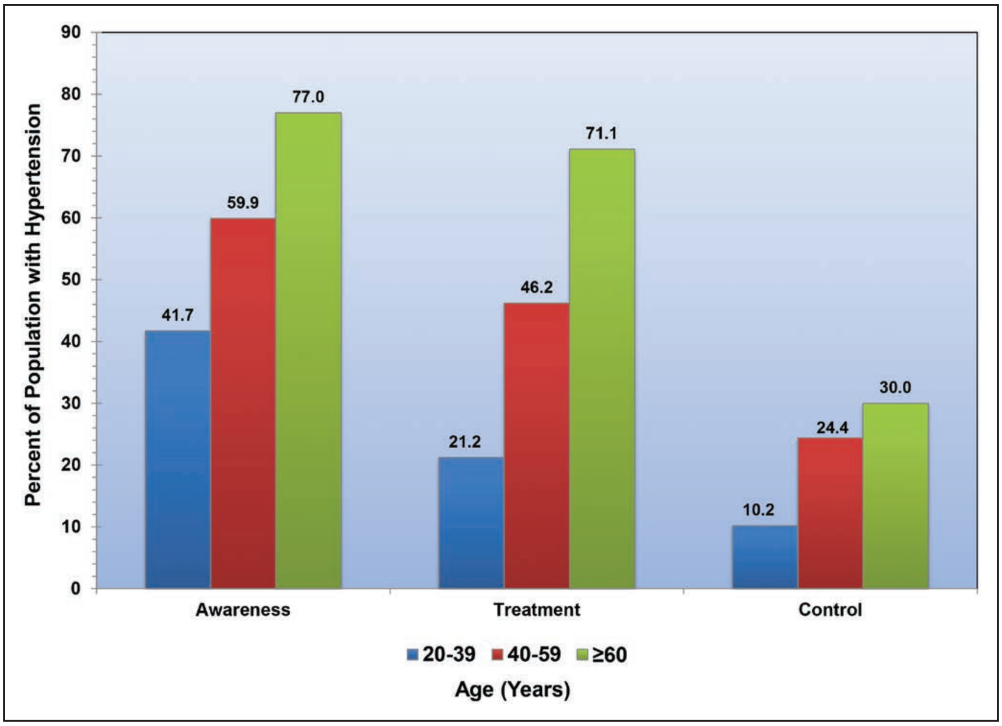

Chart 8-4. Extent of awareness, treatment, and control of high blood pressure by age (NHANES, 2013–2016).
Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A person was considered to have hypertension if he or she had systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg, if he or she said "yes" to taking antihypertensive medication, or if the person was told on 2 occasions that he or she had hypertension.
NHANES indicates National Health and Nutrition Examination Survey.
Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

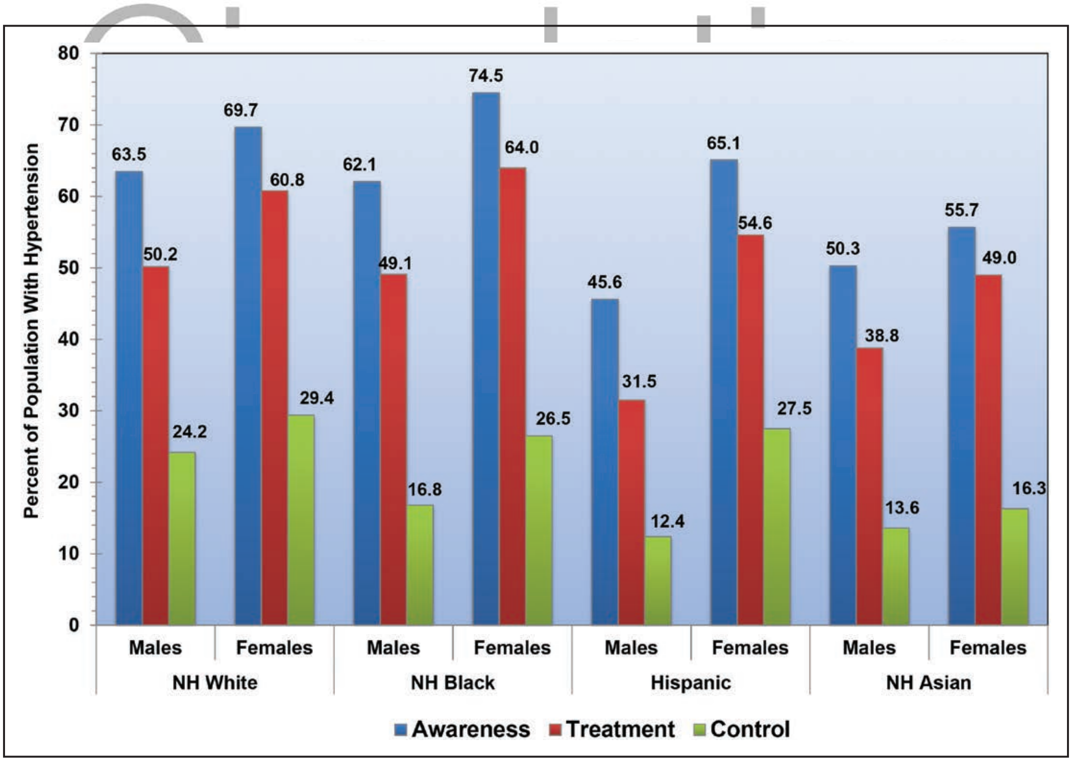

Chart 8-5. Extent of awareness, treatment, and control of high blood pressure by race/ethnicity and sex (NHANES, 2013–2016).
Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A person was considered to have hypertension if he or she had systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg, if he or she said "yes" to taking antihypertensive medication, or if the person was told on 2 occasions that he or she had hypertension.
NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

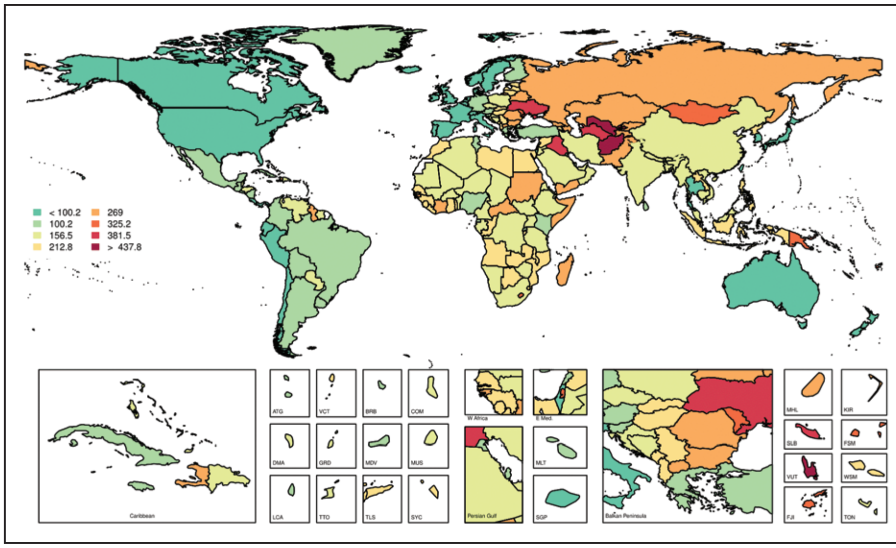

Chart 8-6. Age-standardized global mortality rates attributable to high systolic blood pressure per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[118] Printed with permission. Copyright © 2017, University of Washington.

REFERENCES

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–1252. doi: 10.1161/01.HYP.0000107251.49515.c2
2. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
3. Crim MT, Yoon SS, Ortiz E, Wall HK, Schober S, Gillespie C, Sorlie P, Keenan N, Labarthe D, Hong Y. National surveillance definitions for hypertension prevalence and control among adults. *Circ Cardiovasc Qual Outcomes*. 2012;5:343–351. doi: 10.1161/CIRCOUTCOMES.111.963439
4. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health website. BRFSS Prevalence & Trends Data (2015). https://www.cdc.gov/brfss/brfssprevalence/index.html. Accessed April 30, 2018.
5. Achelrod D, Wenzel U, Frey S. Systematic review and meta-analysis of the prevalence of resistant hypertension in treated hypertensive populations. *Am J Hypertens*. 2015;28:355–361. doi: 10.1093/ajh/hpu151
6. Thomas G, Xie D, Chen HY, Anderson AH, Appel LJ, Bodana S, Brecklin CS, Drawz P, Flack JM, Miller ER 3rd, Steigerwalt SP, Townsend RR, Weir MR, Wright JT Jr, Rahman M; CRIC Study Investigators. Prevalence and prognostic significance of apparent treatment resistant hypertension in chronic kidney disease: report from the Chronic Renal Insufficiency Cohort Study. *Hypertension*. 2016;67:387–396. doi: 10.1161/HYPERTENSIONAHA.115.06487
7. Armario P, Calhoun DA, Oliveras A, Blanch P, Vinyoles E, Banegas JR, Gorostidi M, Segura J, Ruilope LM, Dudenbostel T, de la Sierra A. Prevalence and clinical characteristics of refractory hypertension. *J Am Heart Assoc*. 2017;6:e007365. DOI: 10.1161/JAHA.117.007365.
8. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control [published correction appears in *N Engl J Med*. 2017;377:2506]. *N Engl J Med*. 2015;373:2103–2116. doi: 10.1056/NEJMoa1511939
9. Bress AP, Tanner RM, Hess R, Colantonio LD, Shimbo D, Muntner P. Generalizability of SPRINT results to the U.S. adult population. *J Am Coll Cardiol*. 2016;67:463–472. doi: 10.1016/j.jacc.2015.10.037
10. Melgarejo JD, Maestre GE, Thijs L, Asayama K, Boggia J, Casiglia E, Hansen TW, Imai Y, Jacobs L, Jeppesen J, Kawecka-Jaszcz K, Kuznetsova T, Li Y, Malyutina S, Nikitin Y, Ohkubo T, Stolarz-Skrzypek K, Wang JG, Staessen JA; on behalf of the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) Investigators. Prevalence, treatment, and control rates of conventional and ambulatory hypertension across 10 populations in 3 continents. *Hypertension*. 2017;70:50–58. doi: 10.1161/HYPERTENSIONAHA.117.09188
11. Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright JT Jr, Whelton PK. Potential US population impact of the 2017 ACC/AHA high blood pressure guideline. *Circulation*. 2018;137:109–118. doi: 10.1161/CIRCULATIONAHA.117.032582
12. Xu Y, Chen X, Wang K. Global prevalence of hypertension among people living with HIV: a systematic review and meta-analysis. *J Am Soc Hypertens*. 2017;11:530–540. doi: 10.1016/j.jash.2017.06.004
13. Franklin SS, Thijs L, Asayama K, Li Y, Hansen TW, Boggia J, Jacobs L, Zhang Z, Kikuya M, Björklund-Bodegård K, Ohkubo T, Yang WY, Jeppesen J, Dolan E, Kuznetsova T, Stolarz-Skrzypek K, Tikhonoff V, Malyutina S, Casiglia E, Nikitin Y, Lind L, Sandoya E, Kawecka-Jaszcz K, Filipovský J, Imai Y, Wang JG, O'Brien E, Staessen JA; IDACO Investigators. The cardiovascular risk of white-coat hypertension. *J Am Coll Cardiol*. 2016;68:2033–2043. doi: 10.1016/j.jacc.2016.08.035
14. Dregan A, Ravindrarajah R, Hazra N, Hamada S, Jackson SH, Gulliford MC. Longitudinal trends in hypertension management and mortality among octogenarians: prospective cohort study. *Hypertension*. 2016;68:97–105. doi: 10.1161/HYPERTENSIONAHA.116.07246
15. Bromfield SG, Ngameni CA, Colantonio LD, Bowling CB, Shimbo D, Reynolds K, Safford MM, Banach M, Toth PP, Muntner P. Blood pressure, antihypertensive polypharmacy, frailty, and risk for serious fall injuries among older treated adults with hypertension. *Hypertension*. 2017;70:259–266. doi: 10.1161/HYPERTENSIONAHA.116.09390
16. Kit BK, Kuklina E, Carroll MD, Ostchega Y, Freedman DS, Ogden CL. Prevalence of and trends in dyslipidemia and blood pressure among US children and adolescents, 1999-2012. *JAMA Pediatr*. 2015;169:272–279. doi: 10.1001/jamapediatrics.2014.3216
17. Ning H, Labarthe DR, Shay CM, Daniels SR, Hou L, Van Horn L, Lloyd-Jones DM. Status of cardiovascular health in US children up to 11 years of age: the National Health and Nutrition Examination Surveys

2003-2010. *Circ Cardiovasc Qual Outcomes*. 2015;8:164–171. doi: 10.1161/CIRCOUTCOMES.114.001274

18. Xi B, Zhang T, Zhang M, Liu F, Zong X, Zhao M, Wang Y. Trends in elevated blood pressure among US children and adolescents: 1999-2012. *Am J Hypertens*. 2016;29:217–225. doi: 10.1093/ajh/hpv091
19. Li L, Pérez A, Wu LT, Ranjit N, Brown HS, Kelder SH. Cardiometabolic risk factors among severely obese children and adolescents in the United States, 1999-2012. *Child Obes*. 2016;12:12–19. doi: 10.1089/chi.2015.0136
20. Yang Q, Zhong Y, Merritt R, Cogswell ME. Trends in high blood pressure among United States adolescents across body weight category between 1988 and 2012. *J Pediatr*. 2016;169:166–173.e3. doi: 10.1016/j.jpeds.2015.10.007
21. Flynn JT, Daniels SR, Hayman LL, Maahs DM, McCrindle BW, Mitsnefes M, Zachariah JP, Urbina EM; on behalf of the American Heart Association Atherosclerosis, Hypertension and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young. Update: ambulatory blood pressure monitoring in children and adolescents: a scientific statement from the American Heart Association. *Hypertension*. 2014;63:1116–1135. doi: 10.1161/HYP.0000000000000007
22. Lubrano R, Paoli S, Spiga S, Falsaperla R, Vitaliti G, Gentile I, Elli M. Impact of ambulatory blood pressure monitoring on the diagnosis of hypertension in children. *J Am Soc Hypertens*. 2015;9:780–784. doi: 10.1016/j.jash.2015.07.016
23. Roulet C, Bovet P, Brauchli T, Simeoni U, Xi B, Santschi V, Paradis G, Chiolero A. Secular trends in blood pressure in children: a systematic review. *J Clin Hypertens (Greenwich)*. 2017;19:488–497. doi: 10.1111/jch.12955
24. Mitsnefes MM, Pierce C, Flynn J, Samuels J, Dionne J, Furth S, Warady B; CKiD study group. Can office blood pressure readings predict masked hypertension? *Pediatr Nephrol*. 2016;31:163–166. doi: 10.1007/s00467-015-3212-5
25. Koebnick C, Mohan Y, Li X, Porter AH, Daley MF, Luo G, Kuizon BD. Failure to confirm high blood pressures in pediatric care: quantifying the risks of misclassification. *J Clin Hypertens (Greenwich)*. 2018;20:174–182. doi: 10.1111/jch.13159
26. Young DR, Fischer H, Arterburn D, Bessesen D, Cromwell L, Daley MF, Desai J, Ferrara A, Fitzpatrick SL, Horberg MA, Koebnick C, Nau CL, Oshiro C, Waitzfelder B, Yamamoto A. Associations of overweight/obesity and socioeconomic status with hypertension prevalence across racial and ethnic groups. *J Clin Hypertens (Greenwich)*. 2018;20:532–540. doi: 10.1111/jch.13217
27. Carson AP, Howard G, Burke GL, Shea S, Levitan EB, Muntner P. Ethnic differences in hypertension incidence among middle-aged and older adults: the Multi-ethnic Study of Atherosclerosis. *Hypertension*. 2011;57:1101–1107. doi: 10.1161/HYPERTENSIONAHA.110.168005
28. Howard G, Safford MM, Moy CS, Howard VJ, Kleindorfer DO, Unverzagt FW, Soliman EZ, Flaherty ML, McClure LA, Lackland DT, Wadley VG, Pulley L, Cushman M. Racial differences in the incidence of cardiovascular risk factors in older black and white adults. *J Am Geriatr Soc*. 2017;65:83–90. doi: 10.1111/jgs.14472
29. National Center for Health Statistics. Centers for Disease Control and Prevention website. National Health Interview Survey: 2014 data release. Public-use data file and documentation. http://www.cdc.gov/nchs/nhis/nhis_2014_data_release.htm. Accessed April 30, 2018.
30. Daviglus ML, Talavera GA, Avilés-Santa ML, Allison M, Cai J, Criqui MH, Gellman M, Giachello AL, Gouskova N, Kaplan RC, LaVange L, Penedo F, Perreira K, Pirzada A, Schneiderman N, Wassertheil-Smoller S, Sorlie PD, Stamler J. Prevalence of major cardiovascular risk factors and cardiovascular diseases among Hispanic/Latino individuals of diverse backgrounds in the United States. *JAMA*. 2012;308:1775–1784. doi: 10.1001/jama.2012.14517
31. Sorlie PD, Allison MA, Avilés-Santa ML, Cai J, Daviglus ML, Howard AG, Kaplan R, Lavange LM, Raij L, Schneiderman N, Wassertheil-Smoller S, Talavera GA. Prevalence of hypertension, awareness, treatment, and control in the Hispanic Community Health Study/Study of Latinos. *Am J Hypertens*. 2014;27:793–800. doi: 10.1093/ajh/hpu003
32. Sim JJ, Bhandari SK, Shi J, Liu IL, Calhoun DA, McGlynn EA, Kalantar-Zadeh K, Jacobsen SJ. Characteristics of resistant hypertension in a large, ethnically diverse hypertension population of an integrated health system. *Mayo Clin Proc*. 2013;88:1099–1107. doi: 10.1016/j.mayocp.2013.06.017
33. Gyamfi J, Butler M, Williams SK, Agyemang C, Gyamfi L, Seixas A, Zinsou GM, Bangalore S, Shah NR, Ogedegbe G. Blood pressure control and mortality in US- and foreign-born blacks in New York City. *J Clin Hypertens (Greenwich)*. 2017;19:956–964. doi: 10.1111/jch.13045
34. Brown AGM, Houser RF, Mattei J, Mozaffarian D, Lichtenstein AH, Folta SC. Hypertension among US-born and foreign-born non-Hispanic Blacks: National Health and Nutrition Examination Survey 2003-2014 data. *J Hypertens*. 2017;35:2380–2387. doi: 10.1097/HJH.0000000000001489
35. Ostchega Y, Zhang G, Kit BK, Nwankwo T. Factors associated with home blood pressure monitoring among US adults: National Health and Nutrition Examination Survey, 2011-2014. *Am J Hypertens*. 2017;30:1126–1132. doi: 10.1093/ajh/hpx101
36. Ayala C, Tong X, Neeley E, Lane R, Robb K, Loustalot F. Home blood pressure monitoring among adults: American Heart Association Cardiovascular Health Consumer Survey, 2012. *J Clin Hypertens (Greenwich)*. 2017;19:584–591. doi: 10.1111/jch.12983
37. Thomas SJ, Booth JN 3rd, Bromfield SG, Seals SR, Spruill TM, Ogedegbe G, Kidambi S, Shimbo D, Calhoun D, Muntner P. Clinic and ambulatory blood pressure in a population-based sample of African Americans: the Jackson Heart Study. *J Am Soc Hypertens*. 2017;11:204–212.e5. doi: 10.1016/j.jash.2017.02.001
38. National Center for Health Statistics. Centers for Disease Control and Prevention website. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2016. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed May 21, 2018.
39. Kochanek KD, Murphy SL, Xu JQ, Tejada-Vera B. Deaths: final data for 2014. *National Vital Statistics Reports*. 2016. Vol 65, No 4. Hyattsville, MD: National Center for Health Statistics; 2016.
40. Centers for Disease Control and Prevention website. About underlying cause of death, 1999-2016. https://wonder.cdc.gov/ucd-icd10.html. Accessed June 18, 2018.
41. Kung HC, Xu J. Hypertension-related mortality in the United States, 2000–2013. *NCHS Data Brief*. 2015;(193):1–8.
42. Patel SA, Winkel M, Ali MK, Narayan KM, Mehta NK. Cardiovascular mortality associated with 5 leading risk factors: national and state preventable fractions estimated from survey data. *Ann Intern Med*. 2015;163:245–253. doi: 10.7326/M14-1753
43. Bress AP, Kramer H, Khatib R, Beddhu S, Cheung AK, Hess R, Bansal VK, Cao G, Yee J, Moran AE, Durazo-Arvizu R, Muntner P, Cooper RS. Potential deaths averted and serious adverse events incurred from adoption of the SPRINT (Systolic Blood Pressure Intervention Trial) intensive blood pressure regimen in the United States: projections from NHANES (National Health and Nutrition Examination Survey). *Circulation*. 2017;135:1617–1628. doi: 10.1161/CIRCULATIONAHA.116.025322
44. Holmqvist L, Boström KB, Kahan T, Schiöler L, Hasselström J, Hjerpe P, Wettermark B, Manhem K. Cardiovascular outcome in treatment-resistant hypertension: results from the Swedish Primary Care Cardiovascular Database (SPCCD). *J Hypertens*. 2018;36:402–409. doi: 10.1097/HJH.0000000000001561
45. Jayalath VH, de Souza RJ, Ha V, Mirrahimi A, Blanco-Mejia S, Di Buono M, Jenkins AL, Leiter LA, Wolever TM, Beyene J, Kendall CW, Jenkins DJ, Sievenpiper JL. Sugar-sweetened beverage consumption and incident hypertension: a systematic review and meta-analysis of prospective cohorts. *Am J Clin Nutr*. 2015;102:914–921. doi: 10.3945/ajcn.115.107243
46. Sun D, Liu J, Xiao L, Liu Y, Wang Z, Li C, Jin Y, Zhao Q, Wen S. Recent development of risk-prediction models for incident hypertension: an updated systematic review. *PLoS One*. 2017;12:e0187240. doi: 10.1371/journal.pone.0187240
47. Diaz KM, Booth JN 3rd, Seals SR, Abdalla M, Dubbert PM, Sims M, Ladapo JA, Redmond N, Muntner P, Shimbo D. Physical activity and incident hypertension in African Americans: the Jackson Heart Study. *Hypertension*. 2017;69:421–427. doi: 10.1161/HYPERTENSIONAHA.116.08398
48. Ford CD, Sims M, Higginbotham JC, Crowther MR, Wyatt SB, Musani SK, Payne TJ, Fox ER, Parton JM. Psychosocial factors are associated with blood pressure progression among African Americans in the Jackson Heart Study. *Am J Hypertens*. 2016;29:913–924. doi: 10.1093/ajh/hpw013
49. Shallcross AJ, Butler M, Tanner RM, Bress AP, Muntner P, Shimbo D, Ogedegbe G, Sims M, Spruill TM. Psychosocial correlates of apparent treatment-resistant hypertension in the Jackson Heart Study [published correction appears in *J Hum Hypertens*. 2017;31:486]. *J Hum Hypertens*. 2017;31:474–478. doi: 10.1038/jhh.2016.100
50. Jackson SL, Cogswell ME, Zhao L, Terry AL, Wang CY, Wright J, Coleman King SM, Bowman B, Chen TC, Merritt R, Loria CM. Association between urinary sodium and potassium excretion and blood pressure among adults in the United States: National Health and Nutrition Examination Survey, 2014. *Circulation*. 2018;137:237–246. doi: 10.1161/CIRCULATIONAHA.117.029193
51. Tanner RM, Shimbo D, Irvin MR, Spruill TM, Bromfield SG, Seals SR, Young BA, Muntner P. Chronic kidney disease and incident apparent

treatment-resistant hypertension among blacks: data from the Jackson Heart Study. *J Clin Hypertens (Greenwich)*. 2017;19:1117–1124. doi: 10.1111/jch.13065
52. Shen Y, Liu H, Dai T, Guan Y, Tu J, Nie H. Association between restless legs syndrome and hypertension: a meta-analysis of nine population-based studies. *Neurol Sci*. 2018;39:235–242. doi: 10.1007/s10072-017-3182-4
53. Booth JN 3rd, Abdalla M, Tanner RM, Diaz KM, Bromfield SG, Tajeu GS, Correa A, Sims M, Ogedegbe G, Bress AP, Spruill TM, Shimbo D, Muntner P. Cardiovascular health and incident hypertension in blacks: JHS (the Jackson Heart Study). *Hypertension*. 2017;70:285–292. doi: 10.1161/HYPERTENSIONAHA.117.09278
54. Schwingshackl L, Schwedhelm C, Hoffmann G, Knüppel S, Iqbal K, Andriolo V, Bechthold A, Schlesinger S, Boeing H. Food groups and risk of hypertension: a systematic review and dose-response meta-analysis of prospective studies. *Adv Nutr*. 2017;8:793–803. doi: 10.3945/an.117.017178
55. Roerecke M, Kaczorowski J, Tobe SW, Gmel G, Hasan OSM, Rehm J. The effect of a reduction in alcohol consumption on blood pressure: a systematic review and meta-analysis. *Lancet Public Health*. 2017;2:e108–e120. doi: 10.1016/S2468-2667(17)30003-8
56. Ramos AR, Weng J, Wallace DM, Petrov MR, Wohlgemuth WK, Sotres-Alvarez D, Loredo JS, Reid KJ, Zee PC, Mossavar-Rahmani Y, Patel SR. Sleep patterns and hypertension using actigraphy in the Hispanic Community Health Study/Study of Latinos. *Chest*. 2018;153:87–93. doi: 10.1016/j.chest.2017.09.028
57. Liu X, Zhang D, Liu Y, Sun X, Han C, Wang B, Ren Y, Zhou J, Zhao Y, Shi Y, Hu D, Zhang M. Dose-response association between physical activity and incident hypertension: a systematic review and meta-analysis of cohort studies. *Hypertension*. 2017;69:813–820. doi: 10.1161/HYPERTENSIONAHA.116.08994
58. Wei YC, George NI, Chang CW, Hicks KA. Assessing sex differences in the risk of cardiovascular disease and mortality per increment in systolic blood pressure: a systematic review and meta-analysis of follow-up studies in the United States. *PLoS One*. 2017;12:e0170218. doi: 10.1371/journal.pone.0170218
59. Hidayat K, Du X, Zou SY, Shi BM. Blood pressure and kidney cancer risk: meta-analysis of prospective studies. *J Hypertens*. 2017;35:1333–1344. doi: 10.1097/HJH.0000000000001286
60. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, White IR, Caulfield MJ, Deanfield JE, Smeeth L, Williams B, Hingorani A, Hemingway H. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. *Lancet*. 2014;383:1899–1911. doi: 10.1016/S0140-6736(14)60685-1
61. Tsimploulis A, Sheriff HM, Lam PH, Dooley DJ, Anker MS, Papademetriou V, Fletcher RD, Faselis C, Fonarow GC, Deedwania P, White M, Valentova M, Blackman MR, Banach M, Morgan CJ, Alagiakrishnan K, Allman RM, Aronow WS, Anker SD, Ahmed A. Systolic-diastolic hypertension versus isolated systolic hypertension and incident heart failure in older adults: Insights from the Cardiovascular Health Study [published correction appears in *Int J Cardiol*. 2017;238:181]. *Int J Cardiol*. 2017;235:11–16. doi: 10.1016/j.ijcard.2017.02.139
62. Fang J, Moore L, Loustalot F, Yang Q, Ayala C. Reporting of adherence to healthy lifestyle behaviors among hypertensive adults in the 50 states and the District of Columbia, 2013. *J Am Soc Hypertens*. 2016;10:252–262. e3. doi: 10.1016/j.jash.2016.01.008
63. Navar AM, Peterson ED, Wojdyla D, et al. Temporal changes in the association between modifiable risk factors and coronary heart disease incidence [published correction appears in JAMA. 2016;316:*2433*]. *JAMA*. 2016;316:2041–2043. doi: 10.1001/jama.2016.13614
64. Salles GF, Reboldi G, Fagard RH, Cardoso CR, Pierdomenico SD, Verdecchia P, Eguchi K, Kario K, Hoshide S, Polonia J, de la Sierra A, Hermida RC, Dolan E, O'Brien E, Roush GC; ABC-H Investigators. Prognostic effect of the nocturnal blood pressure fall in hypertensive patients: the Ambulatory Blood Pressure Collaboration in Patients With Hypertension (ABC-H) meta-analysis. *Hypertension*. 2016;67:693–700. doi: 10.1161/HYPERTENSIONAHA.115.06981
65. Booth JN 3rd, Diaz KM, Seals SR, Sims M, Ravenell J, Muntner P, Shimbo D. Masked hypertension and cardiovascular disease events in a prospective cohort of blacks: the Jackson Heart Study. *Hypertension*. 2016;68:501–510. doi: 10.1161/HYPERTENSIONAHA.116.07553
66. Huang Y, Huang W, Mai W, Cai X, An D, Liu Z, Huang H, Zeng J, Hu Y, Xu D. White-coat hypertension is a risk factor for cardiovascular diseases and total mortality. *J Hypertens*. 2017;35:677–688. doi: 10.1097/HJH.0000000000001226
67. Mente A, O'Donnell M, Rangarajan S, Dagenais G, Lear S, McQueen M, Diaz R, Avezum A, Lopez-Jaramillo P, Lanas F, Li W, Lu Y, Yi S, Rensheng L, Iqbal R, Mony P, Yusuf R, Yusoff K, Szuba A, Oguz A, Rosengren A, Bahonar A, Yusufali A, Schutte AE, Chifamba J, Mann JF, Anand SS, Teo K, Yusuf S; PURE, EPIDREAM and ONTARGET/TRANSCEND Investigators. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. *Lancet*. 2016;388:465–475. doi: 10.1016/S0140-6736(16)30467-6
68. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, Rao-Melacini P, Zhang X, Pais P, Agapay S, Lopez-Jaramillo P, Damasceno A, Langhorne P, McQueen MJ, Rosengren A, Dehghan M, Hankey GJ, Dans AL, Elsayed A, Avezum A, Mondo C, Diener HC, Ryglewicz D, Czlonkowska A, Pogosova N, Weimar C, Iqbal R, Diaz R, Yusoff K, Yusufali A, Oguz A, Wang X, Penaherrera E, Lanas F, Ogah OS, Ogunniyi A, Iversen HK, Malaga G, Rumboldt Z, Oveisgharan S, Al Hussain F, Magazi D, Nilanont Y, Ferguson J, Pare G, Yusuf S; INTERSTROKE Investigators. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet*. 2016;388:761–775. doi: 10.1016/S0140-6736(16)30506-2
69. Ahmad FS, Ning H, Rich JD, Yancy CW, Lloyd-Jones DM, Wilkins JT. Hypertension, obesity, diabetes, and heart failure-free survival: the Cardiovascular Disease Lifetime Risk Pooling Project. *JACC Heart Fail*. 2016;4:911–919. doi: 10.1016/j.jchf.2016.08.001
70. Tajeu GS, Booth JN 3rd, Colantonio LD, Gottesman RF, Howard G, Lackland DT, O'Brien EC, Oparil S, Ravenell J, Safford MM, Seals SR, Shimbo D, Shea S, Spruill TM, Tanner RM, Muntner P. Incident cardiovascular disease among adults with blood pressure <140/90 mmHg. *Circulation*. 2017;136:798–812. doi: 10.1161/CIRCULATIONAHA.117.027362
71. Polgreen LA, Suneja M, Tang F, Carter BL, Polgreen PM. Increasing trend in admissions for malignant hypertension and hypertensive encephalopathy in the United States. *Hypertension*. 2015;65:1002–1007. doi: 10.1161/HYPERTENSIONAHA.115.05241
72. Fontil V, Pletcher MJ, Khanna R, Guzman D, Victor R, Bibbins-Domingo K. Physician underutilization of effective medications for resistant hypertension at office visits in the United States: NAMCS 2006-2010. *J Gen Intern Med*. 2014;29:468–476. doi: 10.1007/s11606-013-2683-y
73. Centers for Disease Control and Prevention website. National Ambulatory Medical Care Survey: 2015 State and National Summary Tables. https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2015_namcs_web_tables.pdf. Accessed June 18, 2018.
74. Centers for Disease Control and Prevention website. National Hospital Ambulatory Medical Care Survey: 2015 Emergency Department Summary Tables. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2015_ed_web_tables.pdf. Accessed June 18, 2018.
75. Vemulapalli S, Deng L, Patel MR, Kilgore ML, Jones WS, Curtis LH, Irvin MR, Svetkey LP, Shimbo D, Calhoun DA, Muntner P. National patterns in intensity and frequency of outpatient care for apparent treatment-resistant hypertension. *Am Heart J*. 2017;186:29–39. doi: 10.1016/j.ahj.2017.01.008
76. Yoon SS, Gu Q, Nwankwo T, Wright JD, Hong Y, Burt V. Trends in blood pressure among adults with hypertension: United States, 2003 to 2012. *Hypertension*. 2015;65:54–61. doi: 10.1161/HYPERTENSIONAHA.114.04012
77. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999–2012. *JAMA*. 2015;314:1818–1831. doi: 10.1001/jama.2015.13766
78. Yang F, Qian D, Hu D; Healthy Aging and Development Study Group, Nanjing Medical University; Data Mining Group of Biomedical Big Data, Nanjing Medical University. Prevalence, awareness, treatment, and control of hypertension in the older population: results from the multiple national studies on ageing. *J Am Soc Hypertens*. 2016;10:140–148. doi: 10.1016/j.jash.2015.11.016
79. Dinkler JM, Sugar CA, Escarce JJ, Ong MK, Mangione CM. Does age matter? Association between usual source of care and hypertension control in the US population: data from NHANES 2007-2012. *Am J Hypertens*. 2016;29:934–940. doi: 10.1093/ajh/hpw010
80. Fontil V, Bibbins-Domingo K, Nguyen OK, Guzman D, Goldman LE. Management of hypertension in primary care safety-net clinics in the United States: a comparison of community health centers and private physicians' offices. *Health Serv Res*. 2017;52:807–825. doi: 10.1111/1475-6773.12516
81. Casagrande SS, Menke A, Cowie CC. Cardiovascular risk factors of adults age 20-49 years in the United States, 1971-2012: a

series of cross-sectional studies. *PLoS One*. 2016;11:e0161770. doi: 10.1371/journal.pone.0161770
82. Lee HJ, Jang SI, Park EC. Effect of adherence to antihypertensive medication on stroke incidence in patients with hypertension: a population-based retrospective cohort study. *BMJ Open*. 2017;7:e014486. doi: 10.1136/bmjopen-2016-014486
83. Sundbøll J, Adelborg K, Mansfield KE, Tomlinson LA, Schmidt M. Seventeen-year nationwide trends in antihypertensive drug use in Denmark. *Am J Cardiol*. 2017;120:2193–2200. doi: 10.1016/j.amjcard.2017.08.042
84. Butler MJ, Tanner RM, Muntner P, Shimbo D, Bress AP, Shallcross AJ, Sims M, Ogedegbe G, Spruill TM. Adherence to antihypertensive medications and associations with blood pressure among African Americans with hypertension in the Jackson Heart Study. *J Am Soc Hypertens*. 2017;11:581–588.e5. doi: 10.1016/j.jash.2017.06.011
85. Chang TE, Ritchey MD, Ayala C, Durthaler JM, Loustalot F. Use of strategies to improve antihypertensive medication adherence within United States outpatient health care practices, DocStyles 2015-2016. *J Clin Hypertens (Greenwich)*. 2018;20:225–232. doi: 10.1111/jch.13188
86. Tajeu GS, Mennemeyer S, Menachemi N, Weech-Maldonado R, Kilgore M. Cost-effectiveness of antihypertensive medication: exploring race and sex differences using data from the REasons for Geographic and Racial Differences in Stroke study. *Med Care*. 2017;55:552–560. doi: 10.1097/MLR.0000000000000719
87. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, Lloyd-Jones DM, Nelson SA, Nichol G, Orenstein D, Wilson PW, Woo YJ; on behalf of the American Heart Association Advocacy Coordinating Committee; Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Cardiopulmonary; Critical Care; Perioperative and Resuscitation; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease; Council on Cardiovascular Surgery and Anesthesia, and Interdisciplinary Council on Quality of Care and Outcomes Research. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123:933–944. doi: 10.1161/CIR.0b013e31820a55f5
88. RTI International. Projections of Cardiovascular Disease Prevalence and Costs: 2015–2035: Technical Report [report prepared for the American Heart Association]. Research Triangle Park, NC: RTI International; November 2016. RTI project number 021480.003.001.001. https://healthmetrics.heart.org/wp-content/uploads/2017/10/Projections-of-Cardiovascular-Disease.pdf. Accessed May 4, 2017.
89. Ritchey M, Tsipas S, Loustalot F, Wozniak G. Use of pharmacy sales data to assess changes in prescription- and payment-related factors that promote adherence to medications commonly used to treat hypertension, 2009 and 2014. *PLoS One*. 2016;11:e0159366. doi: 10.1371/journal.pone.0159366
90. Tajeu GS, Kent ST, Kronish IM, Huang L, Krousel-Wood M, Bress AP, Shimbo D, Muntner P. Trends in antihypertensive medication discontinuation and low adherence among Medicare beneficiaries initiating treatment from 2007 to 2012. *Hypertension*. 2016;68:565–575. doi: 10.1161/HYPERTENSIONAHA.116.07720
91. Park C, Fang J, Hawkins NA, Wang G. Comorbidity status and annual total medical expenditures in U.S. hypertensive adults. *Am J Prev Med*. 2017;53(6S2):S172–S181. doi: 10.1016/j.amepre.2017.07.014
92. Zhang D, Wang G, Zhang P, Fang J, Ayala C. Medical expenditures associated with hypertension in the U.S., 2000-2013. *Am J Prev Med*. 2017;53:S164–S171. doi: 10.1016/j.amepre.2017.05.014
93. Leng B, Jin Y, Li G, Chen L, Jin N. Socioeconomic status and hypertension: a meta-analysis. *J Hypertens*. 2015;33:221–229. doi: 10.1097/HJH.0000000000000428
94. Rodriguez CJ, Jin Z, Schwartz JE, Turner-Lloveras D, Sacco RL, Di Tullio MR, Homma S. Socioeconomic status, psychosocial factors, race and nocturnal blood pressure dipping in a Hispanic cohort. *Am J Hypertens*. 2013;26:673–682. doi: 10.1093/ajh/hpt009
95. Kershaw KN, Diez Roux AV, Burgard SA, Lisabeth LD, Mujahid MS, Schulz AJ. Metropolitan-level racial residential segregation and black-white disparities in hypertension. *Am J Epidemiol*. 2011;174:537–545. doi: 10.1093/aje/kwr116
96. Kershaw KN, Robinson WR, Gordon-Larsen P, Hicken MT, Goff DC Jr, Carnethon MR, Kiefe CI, Sidney S, Diez Roux AV. Association of changes in neighborhood-level racial residential segregation with changes in blood pressure among black adults: the CARDIA study. *JAMA Intern Med*. 2017;177:996–1002. doi: 10.1001/jamainternmed.2017.1226
97. Dolezsar CM, McGrath JJ, Herzig AJ, Miller SB. Perceived racial discrimination and hypertension: a comprehensive systematic review. *Health Psychol*. 2014;33:20–34. doi: 10.1037/a0033718
98. Hottenga JJ, Boomsma DI, Kupper N, Posthuma D, Snieder H, Willemsen G, de Geus EJ. Heritability and stability of resting blood pressure. *Twin Res Hum Genet*. 2005;8:499–508. doi: 10.1375/183242705774310123
99. Liu C, Kraja AT, Smith JA, Brody JA, Franceschini N, Bis JC, Rice K, Morrison AC, Lu Y, Weiss S, Guo X, Palmas W, Martin LW, Chen YD, Surendran P, Drenos F, Cook JP, Auer PL, Chu AY, Giri A, Zhao W, Jakobsdottir J, Lin LA, Stafford JM, Amin N, Mei H, Yao J, Voorman A, Larson MG, Grove ML, Smith AV, Hwang SJ, Chen H, Huan T, Kosova G, Stitziel NO, Kathiresan S, Samani N, Schunkert H, Deloukas P, Li M, Fuchsberger C, Pattaro C, Gorski M, Kooperberg C, Papanicolaou GJ, Rossouw JE, Faul JD, Kardia SL, Bouchard C, Raffel LJ, Uitterlinden AG, Franco OH, Vasan RS, O'Donnell CJ, Taylor KD, Liu K, Bottinger EP, Gottesman O, Daw EW, Giulianini F, Ganesh S, Salfati E, Harris TB, Launer LJ, Dörr M, Felix SB, Rettig R, Völzke H, Kim E, Lee WJ, Lee IT, Sheu WH, Tsosie KS, Edwards DR, Liu Y, Correa A, Weir DR, Völker U, Ridker PM, Boerwinkle E, Gudnason V, Reiner AP, van Duijn CM, Borecki IB, Edwards TL, Chakravarti A, Rotter JI, Psaty BM, Loos RJ, Fornage M, Ehret GB, Newton-Cheh C, Levy D, Chasman DI; CHD Exome+ Consortium; ExomeBP Consortium; GoT2DGenes Consortium; T2D-GENES Consortium; Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia; CKDGen Consortium. Meta-analysis identifies common and rare variants influencing blood pressure and overlapping with metabolic trait loci. *Nat Genet*. 2016;48:1162–1170. doi: 10.1038/ng.3660
100. Surendran P, Drenos F, Young R, Warren H, Cook JP, Manning AK, Grarup N, Sim X, Barnes DR, Witkowska K, Staley JR, Tragante V, Tukiainen T, Yaghootkar H, Masca N, Freitag DF, Ferreira T, Giannakopoulou O, Tinker A, Harakalova M, Mihailov E, Liu C, Kraja AT, Fallgaard Nielsen S, Rasheed A, Samuel M, Zhao W, Bonnycastle LL, Jackson AU, Narisu N, Swift AJ, Southam L, Marten J, Huyghe JR, Stančáková A, Fava C, Ohlsson T, Matchan A, Stirrups KE, Bork-Jensen J, Gjesing AP, Kontto J, Perola M, Shaw-Hawkins S, Havulinna AS, Zhang H, Donnelly LA, Groves CJ, Rayner NW, Neville MJ, Robertson NR, Yiorkas AM, Herzig KH, Kajantie E, Zhang W, Willems SM, Lannfelt L, Malerba G, Soranzo N, Trabetti E, Verweij N, Evangelou E, Moayyeri A, Vergnaud AC, Nelson CP, Poveda A, Varga TV, Caslake M, de Craen AJ, Trompet S, Luan J, Scott RA, Harris SE, Liewald DC, Marioni R, Menni C, Farmaki AE, Hallmans G, Renström F, Huffman JE, Hassinen M, Burgess S, Vasan RS, Felix JF, Uria-Nickelsen M, Malarstig A, Reily DF, Hoek M, Vogt T, Lin H, Lieb W, Traylor M, Markus HF, Highland HM, Justice AE, Marouli E, Lindström J, Uusitupa M, Komulainen P, Lakka TA, Rauramaa R, Polasek O, Rudan I, Rolandsson O, Franks PW, Dedoussis G, Spector TD, Jousilahti P, Männistö S, Deary IJ, Starr JM, Langenberg C, Wareham NJ, Brown MJ, Dominiczak AF, Connell JM, Jukema JW, Sattar N, Ford I, Packard CJ, Esko T, Mägi R, Metspalu A, de Boer RA, van der Meer P, van der Harst P, Gambaro G, Ingelsson E, Lind L, de Bakker PI, Numans ME, Brandslund I, Christensen C, Petersen ER, Korpi-Hyövälti E, Oksa H, Chambers JC, Kooner JS, Blakemore AI, Franks S, Jarvelin MR, Husemoen LL, Linneberg A, Skaaby T, Thuesen B, Karpe F, Tuomilehto J, Doney AS, Morris AD, Palmer CN, Holmen OL, Hveem K, Willer CJ, Tuomi T, Groop L, Käräjämäki A, Palotie A, Ripatti S, Salomaa V, Alam DS, Shafi Majumder AA, Di Angelantonio E, Chowdhury R, McCarthy MI, Poulter N, Stanton AV, Sever P, Amouyel P, Arveiler D, Blankenberg S, Ferrières J, Kee F, Kuulasmaa K, Müller-Nurasyid M, Veronesi G, Virtamo J, Deloukas P, Elliott P, Zeggini E, Kathiresan S, Melander O, Kuusisto J, Laakso M, Padmanabhan S, Porteous D, Hayward C, Scotland G, Collins FS, Mohlke KL, Hansen T, Pedersen O, Boehnke M, Stringham HM, Frossard P, Newton-Cheh C, Tobin MD, Nordestgaard BG, Caulfield MJ, Mahajan A, Morris AP, Tomaszewski M, Samani NJ, Saleheen D, Asselbergs FW, Lindgren CM, Danesh J, Wain LV, Butterworth AS, Howson JM, Munroe PB; CHARGE-Heart Failure Consortium; EchoGen Consortium; METASTROKE Consortium; GIANT Consortium; EPIC-InterAct Consortium; Lifelines Cohort Study; Wellcome Trust Case Control Consortium; Understanding Society Scientific Group; EPIC-CVD Consortium; CHARGE+ Exome Chip Blood Pressure Consortium; T2D-GENES Consortium; GoT2DGenes Consortium; ExomeBP Consortium; CHD Exome+ Consortium. Trans-ancestry meta-analyses identify rare and common variants associated with blood pressure and hypertension. *Nat Genet*. 2016;48:1151–1161. doi: 10.1038/ng.3654
101. Ehret GB, Ferreira T, Chasman DI, Jackson AU, Schmidt EM, Johnson T, Thorleifsson G, Luan J, Donnelly LA, Kanoni S, Petersen AK, Pihur V, Strawbridge RJ, Shungin D, Hughes MF, Meirelles O, Kaakinen M, Bouatia-Naji N, Kristiansson K, Shah S, Kleber ME, Guo X, Lyytikäinen

LP, Fava C, Eriksson N, Nolte IM, Magnusson PK, Salfati EL, Rallidis LS, Theusch E, Smith AJP, Folkersen L, Witkowska K, Pers TH, Joehanes R, Kim SK, Lataniotis L, Jansen R, Johnson AD, Warren H, Kim YJ, Zhao W, Wu Y, Tayo BO, Bochud M, Absher D, Adair LS, Amin N, Arking DE, Axelsson T, Baldassarre D, Balkau B, Bandinelli S, Barnes MR, Barroso I, Bevan S, Bis JC, Bjornsdottir G, Boehnke M, Boerwinkle E, Bonnycastle LL, Boomsma DI, Bornstein SR, Brown MJ, Burnier M, Cabrera CP, Chambers JC, Chang IS, Cheng CY, Chines PS, Chung RH, Collins FS, Connell JM, Döring A, Dallongeville J, Danesh J, de Faire U, Delgado G, Dominiczak AF, Doney ASF, Drenos F, Edkins S, Eicher JD, Elosua R, Enroth S, Erdmann J, Eriksson P, Esko T, Evangelou E, Evans A, Fall T, Farrall M, Felix JF, Ferrières J, Ferrucci L, Fornage M, Forrester T, Franceschini N, Duran OHF, Franco-Cereceda A, Fraser RM, Ganesh SK, Gao H, Gertow K, Gianfagna F, Gigante B, Giulianini F, Goel A, Goodall AH, Goodarzi MO, Gorski M, Gräßler J, Groves C, Gudnason V, Gyllensten U, Hallmans G, Hartikainen AL, Hassinen M, Havulinna AS, Hayward C, Hercberg S, Herzig KH, Hicks AA, Hingorani AD, Hirschhorn JN, Hofman A, Holmen J, Holmen OL, Hottenga JJ, Howard P, Hsiung CA, Hunt SC, Ikram MA, Illig T, Iribarren C, Jensen RA, Kähönen M, Kang H, Kathiresan S, Keating BJ, Khaw KT, Kim YK, Kim E, Kivimaki M, Klopp N, Kolovou G, Komulainen P, Kooner JS, Kosova G, Krauss RM, Kuh D, Kutalik Z, Kuusisto J, Kvaløy K, Lakka TA, Lee NR, Lee IT, Lee WJ, Levy D, Li X, Liang KW, Lin H, Lin L, Lindström J, Lobbens S, Männistö S, Müller G, Müller-Nurasyid M, Mach F, Markus HS, Marouli E, McCarthy MI, McKenzie CA, Meneton P, Menni C, Metspalu A, Mijatovic V, Moilanen L, Montasser ME, Morris AD, Morrison AC, Mulas A, Nagaraja R, Narisu N, Nikus K, O'Donnell CJ, O'Reilly PF, Ong KK, Paccaud F, Palmer CD, Parsa A, Pedersen NL, Penninx BW, Perola M, Peters A, Poulter N, Pramstaller PP, Psaty BM, Quertermous T, Rao DC, Rasheed A, Rayner NWNWR, Renström F, Rettig R, Rice KM, Roberts R, Rose LM, Rossouw J, Samani NJ, Sanna S, Saramies J, Schunkert H, Sebert S, Sheu WH, Shin YA, Sim X, Smit JH, Smith AV, Sosa MX, Spector TD, Stančáková A, Stanton A, Stirrups KE, Stringham HM, Sundstrom J, Swift AJ, Syvänen AC, Tai ES, Tanaka T, Tarasov KV, Teumer A, Thorsteinsdottir U, Tobin MD, Tremoli E, Uitterlinden AG, Uusitupa M, Vaez A, Vaidya D, van Duijn CM, van Iperen EPA, Vasan RS, Verwoert GC, Virtamo J, Vitart V, Voight BF, Vollenweider P, Wagner A, Wain LV, Wareham NJ, Watkins H, Weder AB, Westra HJ, Wilks R, Wilsgaard T, Wilson JF, Wong TY, Yang TP, Yao J, Yengo L, Zhang W, Zhao JH, Zhu X, Bovet P, Cooper RS, Mohlke KL, Saleheen D, Lee JY, Elliott P, Gierman HJ, Willer CJ, Franke L, Hovingh GK, Taylor KD, Dedoussis G, Sever P, Wong A, Lind L, Assimes TL, Njølstad I, Schwarz PE, Langenberg C, Snieder H, Caulfield MJ, Melander O, Laakso M, Saltevo J, Rauramaa R, Tuomilehto J, Ingelsson E, Lehtimäki T, Hveem K, Palmas W, März W, Kumari M, Salomaa V, Chen YI, Rotter JI, Froguel P, Jarvelin MR, Lakatta EG, Kuulasmaa K, Franks PW, Hamsten A, Wichmann HE, Palmer CNA, Stefansson K, Ridker PM, Loos RJF, Chakravarti A, Deloukas P, Morris AP, Newton-Cheh C, Munroe PB; CHARGE-EchoGen consortium; CHARGE-HF consortium; Wellcome Trust Case Control Consortium. The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals. *Nat Genet*. 2016;48:1171–1184. doi: 10.1038/ng.3667

102. Hoffmann TJ, Ehret GB, Nandakumar P, Ranatunga D, Schaefer C, Kwok PY, Iribarren C, Chakravarti A, Risch N. Genome-wide association analyses using electronic health records identify new loci influencing blood pressure variation. *Nat Genet*. 2017;49:54–64. doi: 10.1038/ng.3715
103. Yu B, Pulit SL, Hwang SJ, Brody JA, Amin N, Auer PL, Bis JC, Boerwinkle E, Burke GL, Chakravarti A, Correa A, Dreisbach AW, Franco OH, Ehret GB, Franceschini N, Hofman A, Lin DY, Metcalf GA, Musani SK, Muzny D, Palmas W, Raffel L, Reiner A, Rice K, Rotter JI, Veeraraghavan N, Fox E, Guo X, North KE, Gibbs RA, van Duijn CM, Psaty BM, Levy D, Newton-Cheh C, Morrison AC; on behalf of the CHARGE Consortium and the National Heart, Lung, and Blood Institute GO ESP. Rare exome sequence variants in *CLCN6* reduce blood pressure levels and hypertension risk. *Circ Cardiovasc Genet*. 2016;9:64–70. doi: 10.1161/CIRCGENETICS.115.001215
104. Tragante V, Barnes MR, Ganesh SK, Lanktree MB, Guo W, Franceschini N, Smith EN, Johnson T, Holmes MV, Padmanabhan S, Karczewski KJ, Almoguera B, Barnard J, Baumert J, Chang YP, Elbers CC, Farrall M, Fischer ME, Gaunt TR, Gho JM, Gieger C, Goel A, Gong Y, Isaacs A, Kleber ME, Mateo Leach I, McDonough CW, Meijs MF, Melander O, Nelson CP, Nolte IM, Pankratz N, Price TS, Shaffer J, Shah S, Tomaszewski M, van der Most PJ, Van Iperen EP, Vonk JM, Witkowska K, Wong CO, Zhang L, Beitelshees AL, Berenson GS, Bhatt DL, Brown M, Burt A, Cooper-DeHoff RM, Connell JM, Cruickshanks KJ, Curtis SP, Davey-Smith G, Delles C, Gansevoort RT, Guo X, Haiqing S, Hastie CE, Hofker MH, Hovingh GK, Kim DS, Kirkland SA, Klein BE, Klein R, Li YR, Maiwald S, Newton-Cheh C, O'Brien ET, Onland-Moret NC, Palmas W, Parsa A, Penninx BW, Pettinger M, Vasan RS, Ranchalis JE, M Ridker P, Rose LM, Sever P, Shimbo D, Steele L, Stolk RP, Thorand B, Trip MD, van Duijn CM, Verschuren WM, Wijmenga C, Wyatt S, Young JH, Zwinderman AH, Bezzina CR, Boerwinkle E, Casas JP, Caulfield MJ, Chakravarti A, Chasman DI, Davidson KW, Doevendans PA, Dominiczak AF, FitzGerald GA, Gums JG, Fornage M, Hakonarson H, Halder I, Hillege HL, Illig T, Jarvik GP, Johnson JA, Kastelein JJ, Koenig W, Kumari M, März W, Murray SS, O'Connell JR, Oldehinkel AJ, Pankow JS, Rader DJ, Redline S, Reilly MP, Schadt EE, Kottke-Marchant K, Snieder H, Snyder M, Stanton AV, Tobin MD, Uitterlinden AG, van der Harst P, van der Schouw YT, Samani NJ, Watkins H, Johnson AD, Reiner AP, Zhu X, de Bakker PI, Levy D, Asselbergs FW, Munroe PB, Keating BJ. Gene-centric meta-analysis in 87,736 individuals of European ancestry identifies multiple blood-pressure-related loci. *Am J Hum Genet*. 2014;94:349–360. doi: 10.1016/j.ajhg.2013.12.016
105. Warren HR, Evangelou E, Cabrera CP, Gao H, Ren M, Mifsud B, Ntalla I, Surendran P, Liu C, Cook JP, Kraja AT, Drenos F, Loh M, Verweij N, Marten J, Karaman I, Lepe MP, O'Reilly PF, Knight J, Snieder H, Kato N, He J, Tai ES, Said MA, Porteous D, Alver M, Poulter N, Farrall M, Gansevoort RT, Padmanabhan S, Mägi R, Stanton A, Connell J, Bakker SJ, Metspalu A, Shields DC, Thom S, Brown M, Sever P, Esko T, Hayward C, van der Harst P, Saleheen D, Chowdhury R, Chambers JC, Chasman DI, Chakravarti A, Newton-Cheh C, Lindgren CM, Levy D, Kooner JS, Keavney B, Tomaszewski M, Samani NJ, Howson JM, Tobin MD, Munroe PB, Ehret GB, Wain LV; International Consortium of Blood Pressure (ICBP) 1000G Analyses; BIOS Consortium; Lifelines Cohort Study; Understanding Society Scientific Group; CHD Exome+ Consortium; ExomeBP Consortium; T2D-GENES Consortium; GoT2DGenes Consortium; Cohorts for Heart and Ageing Research in Genome Epidemiology (CHARGE) BP Exome Consortium; International Genomics of Blood Pressure (iGEN-BP) Consortium; UK Biobank CardioMetabolic Consortium BP Working Group. Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk [published correction appears in *Nat Genet*. 2017;49:1558]. *Nat Genet*. 2017;49:403–415. doi: 10.1038/ng.3768
106. Basson J, Sung YJ, Fuentes LL, Schwander K, Cupples LA, Rao DC. Influence of smoking status and intensity on discovery of blood pressure loci through gene-smoking interactions. *Genet Epidemiol*. 2015;39:480–488. doi: 10.1002/gepi.21904
107. Sung YJ, de Las Fuentes L, Schwander KL, Simino J, Rao DC. Gene-smoking interactions identify several novel blood pressure loci in the Framingham Heart Study. *Am J Hypertens*. 2015;28:343–354. doi: 10.1093/ajh/hpu149
108. Simino J SY, Kume R, Schwander K, Rao DC. Gene-alcohol interactions identify several novel blood pressure loci including a promising locus near SLC16A9. *Front Genet*. 2013;12:277. doi: 10.3389/fgene.2013.00277
109. Li C, He J, Chen J, Zhao J, Gu D, Hixson JE, Rao DC, Jaquish CE, Gu CC, Chen J, Huang J, Chen S, Kelly TN. Genome-wide gene-sodium interaction analyses on blood pressure: the Genetic Epidemiology Network of Salt-Sensitivity study. *Hypertension (Dallas, Tex: 1979)*. 2016;68:348–355. doi: 10.1161/HYPERTENSIONAHA.115.06765
110. Cooper-DeHoff RM, Johnson JA. Hypertension pharmacogenomics: in search of personalized treatment approaches. *Nat Rev Nephrol*. 2016;12:11–22. doi: 10.1038/nrneph.2015.176
111. Danaei G, Finucane MM, Lin JK, Singh GM, Paciorek CJ, Cowan MJ, Farzadfar F, Stevens GA, Lim SS, Riley LM, Ezzati M; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Blood Pressure). National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5·4 million participants. *Lancet*. 2011;377:568–577. doi: 10.1016/S0140-6736(10)62036-3
112. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, Atkinson C, Bacchus LJ, Bahalim AN, Balakrishnan K, Balmes J, Barker-Collo S, Baxter A, Bell ML, Blore JD, Blyth F, Bonner C, Borges G, Bourne R, Boussinesq M, Brauer M, Brooks P, Bruce NG, Brunekreef B, Bryan-Hancock C, Bucello C, Buchbinder R, Bull F, Burnett RT, Byers TE, Calabria B, Carapetis J, Carnahan E, Chafe Z, Charlson F, Chen H, Chen JS, Cheng AT, Child JC, Cohen A, Colson KE, Cowie BC, Darby S, Darling S, Davis A, Degenhardt L, Dentener F, Des Jarlais DC, Devries K, Dherani M, Ding EL, Dorsey ER, Driscoll T, Edmond K, Ali SE, Engell RE, Erwin PJ, Fahimi S, Falder G, Farzadfar F, Ferrari A, Finucane MM, Flaxman S, Fowkes FG, Freedman G,

Freeman MK, Gakidou E, Ghosh S, Giovannucci E, Gmel G, Graham K, Grainger R, Grant B, Gunnell D, Gutierrez HR, Hall W, Hoek HW, Hogan A, Hosgood HD 3rd, Hoy D, Hu H, Hubbell BJ, Hutchings SJ, Ibeanusi SE, Jacklyn GL, Jasrasaria R, Jonas JB, Kan H, Kanis JA, Kassebaum N, Kawakami N, Khang YH, Khatibzadeh S, Khoo JP, Kok C, Laden F, Lalloo R, Lan Q, Lathlean T, Leasher JL, Leigh J, Li Y, Lin JK, Lipshultz SE, London S, Lozano R, Lu Y, Mak J, Malekzadeh R, Mallinger L, Marcenes W, March L, Marks R, Martin R, McGale P, McGrath J, Mehta S, Mensah GA, Merriman TR, Micha R, Michaud C, Mishra V, Mohd Hanafiah K, Mokdad AA, Morawska L, Mozaffarian D, Murphy T, Naghavi M, Neal B, Nelson PK, Nolla JM, Norman R, Olives C, Omer SB, Orchard J, Osborne R, Ostro B, Page A, Pandey KD, Parry CD, Passmore E, Patra J, Pearce N, Pelizzari PM, Petzold M, Phillips MR, Pope D, Pope CA 3rd, Powles J, Rao M, Razavi H, Rehfuess EA, Rehm JT, Ritz B, Rivara FP, Roberts T, Robinson C, Rodriguez-Portales JA, Romieu I, Room R, Rosenfeld LC, Roy A, Rushton L, Salomon JA, Sampson U, Sanchez-Riera L, Sanman E, Sapkota A, Seedat S, Shi P, Shield K, Shivakoti R, Singh GM, Sleet DA, Smith E, Smith KR, Stapelberg NJ, Steenland K, Stöckl H, Stovner LJ, Straif K, Straney L, Thurston GD, Tran JH, Van Dingenen R, van Donkelaar A, Veerman JL, Vijayakumar L, Weintraub R, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams W, Wilson N, Woolf AD, Yip P, Zielinski JM, Lopez AD, Murray CJ, Ezzati M, AlMazroa MA, Memish ZA. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010 [published corrections appear in *Lancet*. 2013;381:628 and *Lancet*. 2013;381:1276]. *Lancet*. 2012;380:2224–2260. doi: 10.1016/S0140-6736(12)61766-8

113. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, Bahonar A, Chifamba J, Dagenais G, Diaz R, Kazmi K, Lanas F, Wei L, Lopez-Jaramillo P, Fanghong L, Ismail NH, Puoane T, Rosengren A, Szuba A, Temizhan A, Wielgosz A, Yusuf R, Yusufali A, McKee M, Liu L, Mony P, Yusuf S; PURE (Prospective Urban Rural Epidemiology) Study Investigators. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA*. 2013;310:959–968. doi: 10.1001/jama.2013.184182
114. Kaze AD, Schutte AE, Erqou S, Kengne AP, Echouffo-Tcheugui JB. Prevalence of hypertension in older people in Africa: a systematic review and meta-analysis. *J Hypertens*. 2017;35:1345–1352. doi: 10.1097/HJH.0000000000001345
115. Owolabi M, Olowoyo P, Miranda JJ, Akinyemi R, Feng W, Yaria J, Makanjuola T, Yaya S, Kaczorowski J, Thabane L, Van Olmen J, Mathur P, Chow C, Kengne A, Saulson R, Thrift AG, Joshi R, Bloomfield GS, Gebregziabher M, Parker G, Agyemang C, Modesti PA, Norris S, Ogunjimi L, Farombi T, Melikam ES, Uvere E, Salako B, Ovbiagele B; for the COUNCIL Initiative. Gaps in hypertension guidelines in low- and middle-income versus high-income countries: a systematic review. *Hypertension*. 2016;68:1328–1337. doi: 10.1161/HYPERTENSIONAHA.116.08290
116. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, He J. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation*. 2016;134:441–450. doi: 10.1161/CIRCULATIONAHA.115.018912
117. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, Alexander L, Estep K, Hassen Abate K, Akinyemiju TF, Ali R, Alvis-Guzman N, Azzopardi P, Banerjee A, Bärnighausen T, Basu A, Bekele T, Bennett DA, Biadgilign S, Catalá-López F, Feigin VL, Fernandes JC, Fischer F, Gebru AA, Gona P, Gupta R, Hankey GJ, Jonas JB, Judd SE, Khang YH, Khosravi A, Kim YJ, Kimokoti RW, Kokubo Y, Kolte D, Lopez A, Lotufo PA, Malekzadeh R, Melaku YA, Mensah GA, Misganaw A, Mokdad AH, Moran AE, Nawaz H, Neal B, Ngalesoni FN, Ohkubo T, Pourmalek F, Rafay A, Rai RK, Rojas-Rueda D, Sampson UK, Santos IS, Sawhney M, Schutte AE, Sepanlou SG, Shifa GT, Shiue I, Tedla BA, Thrift AG, Tonelli M, Truelsen T, Tsilimparis N, Ukwaja KN, Uthman OA, Vasankari T, Venketasubramanian N, Vlassov VV, Vos T, Westerman R, Yan LL, Yano Y, Yonemoto N, Zaki ME, Murray CJ. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015 [published correction appears in *JAMA*. 2017;317:648]. *JAMA*. 2017;317:165–182. doi: 10.1001/jama.2016.19043
118. Global Burden of Disease Study 2016. Global Burden of Disease Study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed May 1, 2018.
119. Lu J, Lu Y, Wang X, Li X, Linderman GC, Wu C, Cheng X, Mu L, Zhang H, Liu J, Su M, Zhao H, Spatz ES, Spertus JA, Masoudi FA, Krumholz HM, Jiang L. Prevalence, awareness, treatment, and control of hypertension in China: data from 1·7 million adults in a population-based screening study (China PEACE Million Persons Project) [published correction appears in *Lancet*. 2017;390:2548]. *Lancet*. 2017;390:2549–2558. doi: 10.1016/S0140-6736(17)32478-9
120. Noubiap JJ, Essouma M, Bigna JJ, Jingi AM, Aminde LN, Nansseu JR. Prevalence of elevated blood pressure in children and adolescents in Africa: a systematic review and meta-analysis. *Lancet Public Health*. 2017;2:e375–e386. doi: 10.1016/S2468-2667(17)30123-8
121. Dastan I, Erem A, Cetinkaya V. Awareness, treatment, control of hypertension, and associated factors: results from a Turkish national study. *Clin Exp Hypertens*. 2018;40:90–98. doi: 10.1080/10641963.2017.1334797
122. Booth JN 3rd, Li J, Zhang L, Chen L, Muntner P, Egan B. Trends in prehypertension and hypertension risk factors in US adults: 1999–2012. *Hypertension*. 2017;70:275–284. doi: 10.1161/HYPERTENSIONAHA.116.09004
123. Zhang Y, Moran AE. Trends in the prevalence, awareness, treatment, and control of hypertension among young adults in the United States, 1999 to 2014. *Hypertension*. 2017;70:736–742. doi: 10.1161/HYPERTENSIONAHA.117.09801
124. Carson AP, Lewis CE, Jacobs DR Jr, Peralta CA, Steffen LM, Bower JK, Person SD, Muntner P. Evaluating the Framingham hypertension risk prediction model in young adults: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Hypertension*. 2013;62:1015–1020. doi: 10.1161/HYPERTENSIONAHA.113.01539
125. Guo X, Zhang X, Guo L, Li Z, Zheng L, Yu S, Yang H, Zhou X, Zhang X, Sun Z, Li J, Sun Y. Association between pre-hypertension and cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Curr Hypertens Rep*. 2013;15:703–716. doi: 10.1007/s11906-013-0403-y
126. Guo X, Zhang X, Zheng L, Guo L, Li Z, Yu S, Yang H, Zhou X, Zou L, Zhang X, Sun Z, Li J, Sun Y. Prehypertension is not associated with all-cause mortality: a systematic review and meta-analysis of prospective studies. *PLoS One*. 2013;8:e61796. doi: 10.1371/journal.pone.0061796
127. Huang Y, Cai X, Li Y, Su L, Mai W, Wang S, Hu Y, Wu Y, Xu D. Prehypertension and the risk of stroke: a meta-analysis. *Neurology*. 2014;82:1153–1161. doi: 10.1212/WNL.0000000000000268
128. Huang YW, Gu F, Dombkowski A, Wang LS, Stoner GD. Black raspberries demethylate Sfrp4, a WNT pathway antagonist, in rat esophageal squamous cell papilloma. *Mol Carcinog*. 2016;55:1867–1875. doi: 10.1002/mc.22435
129. Huang Y, Cai X, Zhang J, Mai W, Wang S, Hu Y, Ren H, Xu D. Prehypertension and incidence of ESRD: a systematic review and meta-analysis. *Am J Kidney Dis*. 2014;63:76–83. doi: 10.1053/j.ajkd.2013.07.024
130. Huang Y, Su L, Cai X, Mai W, Wang S, Hu Y, Wu Y, Tang H, Xu D. Association of all-cause and cardiovascular mortality with prehypertension: a meta-analysis. *Am Heart J*. 2014;167:160–168.e1. doi: 10.1016/j.ahj.2013.10.023
131. Huang Y, Wang S, Cai X, Mai W, Hu Y, Tang H, Xu D. Prehypertension and incidence of cardiovascular disease: a meta-analysis. *BMC Med*. 2013;11:177. doi: 10.1186/1741-7015-11-177
132. Shen L, Ma H, Xiang MX, Wang JA. Meta-analysis of cohort studies of baseline prehypertension and risk of coronary heart disease. *Am J Cardiol*. 2013;112:266–271. doi: 10.1016/j.amjcard.2013.03.023
133. Wang S, Wu H, Zhang Q, Xu J, Fan Y. Impact of baseline prehypertension on cardiovascular events and all-cause mortality in the general population: a meta-analysis of prospective cohort studies. *Int J Cardiol*. 2013;168:4857–4860. doi: 10.1016/j.ijcard.2013.07.063

9. DIABETES MELLITUS

ICD-9 250; ICD-10 E10 to E11. See Tables 9-1 and 9-2 and Charts 9-1 through 9-10

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DM is a heterogeneous mix of health conditions characterized by glucose dysregulation. In the United States, the most common forms are type 2 DM, which affects 90% to 95% of those with DM,[1] and type 1 DM, which constitutes 5% to 10% of DM.[2] DM is diagnosed based on fasting glucose ≥126 mg/dL, 2-hour postchallenge glucose ≥200 mg/dL during an oral glucose tolerance test, random glucose ≥200 mg/dL with presentation of hyperglycemia symptoms, or HbA_{1c} ≥6.5%.[2a] DM is a major risk factor for CVD, including CHD and stroke.[3] The AHA has identified untreated fasting blood glucose levels of <100 mg/dL for children and adults as 1 of the 7 components of ideal cardiovascular health.[4]

Abbreviations Used in Chapter 9

ABI	ankle-brachial index
ACC	American College of Cardiology
ACS	acute coronary syndrome
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AF	atrial fibrillation
AHA	American Heart Association
AP	angina pectoris
ARIC	Atherosclerosis Risk in Communities Study
BMI	body mass index
BP	blood pressure
CAC	coronary artery calcification
CAD	coronary artery disease
CANVAS	Canagliflozin Cardiovascular Assessment Study
CARDIA	Coronary Artery Risk Development in Young Adults
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
CVD	cardiovascular disease
DM	diabetes mellitus
ED	emergency department
eGFR	estimated glomerular filtration rate
EMPA-REG OUTCOME	BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
ESRD	end-stage renal disease
EVEREST	Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan
EXAMINE	Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care
FOURIER	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk
GBD	Global Burden of Disease
GWAS	genome-wide association studies
GWTG	Get With The Guidelines
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
HDL	high-density lipoprotein

(Continued)

Abbreviations Used in Chapter 9 Continued

HF	heart failure
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
IHD	ischemic heart disease
IRR	incidence rate ratio
JHS	Jackson Heart Study
LDL-C	low-density lipoprotein cholesterol
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
MACE	major adverse cardiovascular events
MEPS	Medical Expenditure Panel Survey
MESA	Multi-Ethnic Study of Atherosclerosis
MET	metabolic equivalent
NCHS	National Center for Health Statistics
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
OR	odds ratio
PA	physical activity
PCSK9	proprotein convertase subtilisin kexin 9
PWV	pulse-wave velocity
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SEARCH	SEARCH for Diabetes in Youth
SNP	single-nucleotide polymorphism
SSB	sugar-sweetened beverage
SUSTAIN-6	Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes
TC	total cholesterol
TODAY	Treatment Options for Type 2 Diabetes in Adolescents and Youth
VTE	venous thromboembolism
WC	waist circumference

Prevalence

Youth

- Approximately 193 000 people <20 years of age were diagnosed with DM in 2015.[1]
- During 2001 to 2009, the prevalence of type 1 DM increased 30% from 1.48 per 1000 youth to 1.93 per 1000 youth.[5]
  - Among youths with type 1 DM, the prevalence of overweight is 22.1% and the prevalence of obesity is 12.6%.[6]
- Type 2 DM, a disease usually diagnosed in adults ≥40 years of age, is being diagnosed among people <20 years of age. Between 2001 and 2009, the prevalence of type 2 DM in youths increased by 30.5%.[5]
  - Among youths with type 2 DM, 10.4% are overweight and 79.4% have obesity.[6]
- According to NHANES data from 1999 to 2000 through 2007 to 2008, among US adolescents

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aged 12 to 19 years, the prevalence of prediabetes and type 2 DM increased from 9% to 23%.[7]

- Among US adolescents aged 12 to 19 years in 2005 to 2014, the prevalence of DM was 0.8% (95% CI, 0.6%–1.1%). Of those with DM, 28.5% (95% CI, 16.4%–44.8%) were undiagnosed.[8]
- Among US adolescents aged 12 to 19 years in 2005 to 2014, the prevalence of prediabetes was 17.7% (95% CI, 15.8%–19.8%).[8] Males were more likely to have prediabetes than females (22.0% [95% CI, 19.5%–24.7%] versus 13.2% [95% CI, 10.4%–16.7%]). Also, the prevalence of prediabetes was higher in NH blacks (21.0% [95% CI, 17.7%–24.7%]) and Hispanics (22.9% [95% CI, 19.9%–26.3%]) than in NH white participants (15.1% [95% CI, 12.3%–18.6%]).[8]
- Between 1996 and 2010, the number of youths with type 1 DM increased by 5.7% per year.[9]

Adults
(See Table 9-1 and Charts 9-1 through 9-5)

- On the basis of data from NHANES 2013 to 2016, an estimated 26 million adults have diagnosed DM, 9.4 million adults have undiagnosed DM, and 91.8 million adults (37.6%) have prediabetes. The prevalence of prediabetes and DM differs by sex and race/ethnicity (Table 9-1; unpublished NHLBI tabulation).
- After adjustment for population age differences, 2013 to 2016 NHANES national survey data for people ≥20 years of age indicate that the prevalence of diagnosed DM was 9.4% in NH white males and 7.3% in NH white females, 14.7% in NH black males and 13.4% in NH black females, 15.1% in Hispanic males and 14.1% in Hispanic females, and 12.8% in NH Asian males and 9.9% in NH Asian females (Table 9-1 and Chart 9-1; unpublished NCHS/NHLBI tabulation).
- On the basis of 2015 data from the Indian Health Service, the age-adjusted prevalence of diagnosed DM among American Indians/Alaska Natives was 14.9% for males and 15.3% for females.[1]
- On the basis of NHANES 2013 to 2016 data, the age-adjusted prevalence of diagnosed DM in adults ≥20 years of age varies by race/ethnicity and years of education. NH white adults with more than a high school education had the lowest prevalence (7.6%), and Hispanic adults with a high school education had the highest prevalence (17.7%; Chart 9-2; unpublished NCHS/NHLBI tabulation).
- In the prospective, multicenter, population-based HCHS/SOL, 16 415 adults of Hispanic/Latino descent aged 18 to 74 years were enrolled from 4 US metropolitan areas from 2008 to 2011. The prevalence of DM varied for adults with different Hispanic backgrounds. DM prevalence ranged from 10.2% in South Americans to 13.4% in Cubans, 17.7% in Central Americans, 18.0% in Dominicans and Puerto Ricans, and 18.3% in Mexicans.[10]
- Among foreign-born participants of the US NHANES 1999 to 2012, the prevalence of DM increased with duration of time spent in the United States and was 6.1%, 9.3%, 11.1%, and 20.0% among those in the United States for <1, 1 to 9, 10 to 19, and ≥20 years, respectively.[11]
- The prevalence of diagnosed DM in adults was higher for both males and females in the 2013 to 2016 NHANES data than in the 1988 to 1994 NHANES data. Males had a higher prevalence of diagnosed DM and undiagnosed DM than females in 2013 to 2016. Prevalence of diagnosed and undiagnosed DM increased for both males and females between study periods (Chart 9-3; unpublished NCHS/NHLBI tabulation). During this time period, 2 DM diagnostic changes occurred: the threshold definition for diagnosed DM was lowered from ≥140 mg/dL to ≥126 mg/dL in 1997,[12] and HbA_{1c} ≥6.5% was added as a diagnostic test in 2010.[2a]
- Geographic variations in DM prevalence have been reported in the United States (Chart 9-4).
  - Across counties in the United States during 1999 to 2012, the prevalence of diagnosed DM ranged from 5.6% to 20.4%, the prevalence of undiagnosed DM ranged from 3.2% to 6.8%, and the prevalence of total DM ranged from 8.8% to 26.4%.[14] The prevalence of diagnosed DM was highest in the Deep South, near the Texas-Mexico border, and in counties with Native American reservations and was lowest in counties in the upper Midwest and parts of Alaska and New England.
  - Using data from the REGARDS study, the median (range) predicted prevalence of DM was 14% (10%–20%) among whites and 31% (28%–41%) among blacks.[15] DM was most prevalent in the west and central Southeast among whites (Louisiana, Arkansas, Mississippi, Alabama, Tennessee, and south Kentucky, as well as parts of North Carolina and South Carolina).
- The age-adjusted prevalence of diagnosed DM and undiagnosed DM increased from 5.0% and 3.5%, respectively, in 1999 to 2000 to 7.8% and 4.4%, respectively, in 2009 to 2010.[16] The

prevalence of diagnosed DM increased among NH whites and blacks over this time period.

- The prevalence of diagnosed DM in adults was higher for NH black, NH white, and Hispanic adults in NHANES 1988 to 2010 than in NHANES 1988 to 1994. Prevalence of undiagnosed DM increased slightly between studies (Chart 9-5; unpublished NCHS/NHLBI tabulation).

Incidence

Youth

- During 2011 to 2012, an estimated 17 900 people <20 years of age in the United States were diagnosed with incident type 1 DM, and 5300 individuals aged 10 to 19 years were newly diagnosed with type 2 DM annually.[1]
- In the SEARCH study, the incidence rate of type 1 DM increased by 1.4% annually (from 19.5 to 21.7 cases per 100 000 youths per year in 2003 to 2012).[17] The increase was larger for males than for females and for Hispanics and Asian or Pacific Islanders than for other ethnic groups. Also, the incidence of type 2 DM increased by 7.1% annually (from 9.0 to 12.5 cases per 100 000 youths per year from 2003 to 2012). The annual increase was larger among females than males and among NH blacks, Hispanics, Asian or Pacific Islanders, and Native Americans compared with NH whites.
- Projecting disease burden for the US population <20 years of age by 2050, the number of youths with type 1 DM is expected to increase from 166 018 to 203 382, and the number with type 2 DM will increase from 20 203 to 30 111. Less conservative modeling projects the number of youths with type 1 DM at 587 488 and those with type 2 DM at 84 131 by 2050.[18]

Adults (See Table 9-1)

- Approximately 1.5 million US adults ≥18 years old were diagnosed with incident DM in 2015 (Table 9-1).[1]
- In the CARDIA study, the risk of DM was higher for black females than white females (HR, 2.86 [95% CI, 2.19–3.72]) and for black males than white males (HR, 1.68 [95% CI, 1.28–2.17]) after adjustment for age and field center.[19]

Mortality (See Table 9-1)

- DM was listed as the underlying cause of mortality for 80 058 people (43 763 males and 36 295 females) in the United States in 2016 (Table 9-1).[20]
- There were 258 852 deaths with DM listed as any cause of death in 2016.[20] The 2016 overall underlying-cause, age-adjusted death rate attributable to DM was 21.0 per 100 000. For males, the death rates per 100 000 population were 23.5 for NH whites, 44.8 for NH blacks, 29.6 for Hispanics, 18.8 for NH Asian/Pacific Islanders, and 52.2 for NH American Indian/Alaska Natives. For females, the death rates per 100 000 population were 14.4 for NH whites, 32.7 for NH blacks, 20.7 for Hispanics, 13.0 for NH Asian/Pacific Islanders, and 40.6 for NH American Indian/Alaska Natives.[20]
- In a study of NHIS 1997 to 2009 participants followed up through 2011, DM was the underlying cause for 3.3% of deaths and a contributing cause for 10.8% of deaths. The population attributable fraction for death associated with DM was 11.5%. Although DM was more often cited as an underlying and contributing cause of death for NH blacks and Hispanics than for NH whites, the population attributable fraction was similar in each racial/ethnic group.[21]
- In a collaborative meta-analysis of 820 900 individuals from 97 prospective studies, DM was associated with the following risks: all-cause mortality (HR, 1.80 [95% CI, 1.71–1.90]), cancer death (HR, 1.25 [95% CI, 1.19–1.31]), and vascular death (HR, 2.32 [95% CI, 2.11–2.56]). In particular, DM was associated with death attributable to the following cancers: liver, pancreatic, ovarian, colorectal, lung, bladder, and breast. A 50-year-old with DM dies on average 6 years earlier than an individual without DM.[22]
- Among NHIS participants enrolled in 2000 to 2009 and followed up through 2011, males and females with diagnosed DM had 1.56 and 1.69 times as high risk of all-cause mortality as those without diagnosed DM (HR, 1.56 [95% CI, 1.49–1.64] and 1.69 [95% CI, 1.61–1.78], respectively).[23]
- In the Swedish National Diabetes Register, there was a significant decline in all-cause mortality from 1998 to 2014 among patients with type 1 DM (HR, 0.71 [95% CI, 0.66–0.78]), but this decline was not statistically different from the decline observed among control subjects without DM (HR, 0.77 [95% CI, 0.72–0.83]). In contrast, the decline in all-cause mortality from 1998 to 2014 among patients with type 2 DM (HR, 0.79 [95% CI, 0.78–0.80]) was less than the decline observed among control subjects without DM (HR, 0.69 [95% CI, 0.68–0.70]).[24]
- In the Swedish National Diabetes Register, compared with control subjects without DM, the adjusted HR for all-cause mortality for patients

with type 1 DM who met all risk factor targets was 1.31 (95% CI, 0.93–1.85), whereas the HR for patients with type 1 DM who met no risk factor targets was 7.33 (95% CI, 5.08–10.57).[25]

- The leading cause of death among patients with type 1 DM is CVD, which accounted for 22% of deaths among those in the Allegheny County, PA, type 1 DM registry, followed by renal (20%) and infectious (18%) causes.[26]

Complications (See Chart 9-6)

Microvascular Complications

- Among those ≤21 years old with newly diagnosed DM in a US managed care network, 20% of youth with type 1 DM and 7.2% of youth with type 2 DM developed diabetic retinopathy over a median follow-up of 3 years.[27]
- On the basis of analyses of data from the NIS, the United States Renal Data System, and the US National Vital Statistics System, between 1995 and 2014 (Chart 9-6), substantial declines have been observed in the age-standardized rates of hospitalization for lower-extremity amputation, incident DM-related ESRD, and mortality attributable to hyperglycemic crisis (32.8%, 40.7%, and 37.5%, respectively).
- Among adults with DM in NHANES 2007 to 2012, the overall age-adjusted prevalence of CKD was 40.2% in 2007 to 2008, 36.9% in 2009 to 2010, and 37.6% in 2011 to 2012.[28] The prevalence of CKD was 58.7% in US adults with DM aged ≥65 years, 25.7% in those <65 years of age, 43.5% in NH blacks and Mexican Americans, and 38.7% in NH whites.
- The prevalence of any diabetic kidney disease, defined as persistent albuminuria, persistent reduced eGFR, or both, did not significantly change from the period 1988 to 1994 (28.4% [95% CI, 23.8%–32.9%]) to 2009 to 2014 (26.2% [95% CI, 22.6%–29.9%]). However, the prevalence of albuminuria decreased from 20.8% (95% CI, 16.3%–25.3%) to 15.9% (95% CI, 12.7%–19.0%) and the prevalence of reduced eGFR increased from 9.2% (95% CI, 6.2%–12.2%) to 14.1% (95% CI, 11.3%–17.0%) over this time period.[29] DM accounted for 46% of the new cases of ESRD in 2011 to 2015.[30]

CVD Complications

- Among NHIS participants enrolled in 2000 to 2009 and followed up through 2011, DM was associated with increased risk for CVD mortality among males and females.[23]
- On the basis of analyses of data from the NHIS, between 1995 and 2014, the rate of hospitalizations for IHD declined 66.4% and the rate of hospitalization for stroke declined 35.6% among patients with DM (Chart 9-6).[31]
- The HRs of CHD events comparing participants with DM only, DM and prevalent CHD, and neither DM nor prevalent CHD with those with prevalent CHD were 0.65 (95% CI, 0.54–0.77), 1.54 (95% CI, 1.30–1.83), and 0.41 (95% CI, 0.35–0.47), respectively, after adjustment for demographics and risk factors.[32] Compared with participants who had prevalent CHD, the HR of CHD events for participants with severe DM was 0.88 (95% CI, 0.72–1.09).
- In a meta-analysis of 19 studies, DM was not associated with an increased risk for VTE (pooled RR, 1.10 [95% CI, 0.94–1.29]).[33]
- Compared with those with normal glucose, carotid-femoral PWV was 95.8 (95% CI, 69.4–122.1) and 21.3 (95% CI, −0.8 to 43.4) cm/s higher for participants with DM and prediabetes, respectively.[34] A similar pattern was present for brachial-ankle PWV.
- In MESA, 63% of participants with DM had a CAC >0 compared with 48% of those without DM.[35]
- In CARDIA, a longer duration of DM was associated with CAC presence (per 5-year longer duration: HR, 1.15 [95% CI, 1.06–1.25]) and worse cardiac function, including early diastolic relaxation and higher diastolic filling pressure.[36]
- In a nationwide Danish registry, the adjusted IRRs (95% CIs) for AF comparing people with and without DM were 2.34 (1.52–3.60), 1.52 (1.47–1.56), 1.20 (1.18–1.23), and 0.99 (0.97–1.01) for adults 18 to 39, 40 to 64, 65 to 74, and 75 to 100 years of age, respectively.[37]
- A meta-analysis of published observational data comprising 11 studies and >1.6 million participants reported DM was associated with a 24% increased risk for AF (RR, 1.24 [95% CI, 1.06–1.44]) after multivariable adjustment.[38]
- In an analysis of NHANES 2001 to 2010, the prevalence of AP among participants with CHD was similar for adults with and without DM (49% and 46%, respectively).[39]
- DM increases the risk of HF and adversely affects outcomes among patients with HF.
  - DM alone qualifies for the most recent ACC/AHA diagnostic criteria for stages A and B HF, a classification of patients without HF but at notably high risk for its development.[40]
  - DM should be treated similarly for patients with HF as for the general population.[40]

- — In a meta-analysis of 10 prospective cohort studies, the HR for HF per 1-mmol/L (≈18 mg/dL) increase in fasting plasma glucose level was 1.11 (95% CI, 1.04–1.17), which suggests an independent and continuous positive association between fasting plasma glucose and HF.[41]
- — Post hoc analysis of data from the EVEREST randomized trial of patients hospitalized with decompensated systolic HF demonstrated that DM increased the risk of the composite outcome of cardiovascular mortality and HF hospitalization (HR, 1.17 [95% CI, 1.04–1.31]) over a median 9.9 months of follow-up.[42]
- — The association between glycemia and outcomes has been mixed in patients with HF, and there is insufficient evidence to recommend specific glucose treatment goals in patients hospitalized with HF.[43]

Hypoglycemia

- Hypoglycemia is a major factor that limits glycemic control in DM. In 2010, among Medicare beneficiaries with DM, hospitalizations for hypoglycemia and hyperglycemia were 612 and 367 per 100 000 person-years, respectively.[44]
- In ADVANCE, severe hypoglycemia was associated with an increased risk of major macrovascular events (HR, 2.88 [95% CI, 2.01–4.12]), cardiovascular death (HR, 2.68 [95% CI, 1.72–4.19]), and all-cause death (HR, 2.69 [95% CI, 1.97–3.67]), including nonvascular outcomes. The lack of specificity of hypoglycemia with vascular outcomes suggests that it might be a marker for overall susceptibility or frailty.[45]
- In ARIC, severe hypoglycemia was associated with an increased risk of CHD (HR, 2.02 [95% CI, 1.27–3.20]), all-cause mortality (HR, 1.73 [95% CI, 1.38–2.17]), cardiovascular mortality (HR, 1.64 [95% CI, 1.15–2.34]), and cancer mortality (HR, 2.49 [95% CI, 1.46–4.24]).[46]
- In the EXAMINE trial, severe hypoglycemia was associated with an increased risk of MACE (HR, 2.42 [95% CI, 1.27–4.60]).[47]
- Severe hypoglycemia is more common with increasing age, with use of insulin or sulfonylureas, and in those with impaired renal function, type 1 DM, and prior severe hypoglycemia.[48] HbA_{1c} shows a U-shaped relationship with hypoglycemia.[49] Higher rates of hypoglycemia have also been reported in African Americans compared with NH whites.[50] Furthermore, dementia and decreased cognitive function have been associated with hypoglycemia.[45,51]

Healthcare Utilization

- Among Medicare beneficiaries with type 2 DM hospitalized between 2012 and 2014, 17.1% were readmitted within 30 days.[52]
- According to the 2014 NIS, the rate of hospitalization among adults with DM was 327.2 per 1000 people with DM for any causes (7.2 million discharges), 70.4 per 1000 people with DM for major CVD (1.5 million discharges), 5.0 per 1000 people with DM for lower-extremity amputation (108 000 discharges), and 7.7 per 1000 people with DM for diabetic ketoacidosis (168 000 discharges).[1]
- According to the 2014 Nationwide Emergency Department Sample, the rate of ED visits was 648.9 per 1000 people with DM for any causes (14.2 million visits), 11.2 per 1000 people with DM for hypoglycemia (245 000 visits), and 9.5 per 1000 people with DM for hyperglycemia (207 000 visits).[1]
- Among participants in the ARIC study, without a prior diagnosis of DM, hospitalization rates were 163 (95% CI, 158–169), 217 (95% CI, 206–228), and 254 (95% CI, 226–281) per 1000 person-years with HbA_{1c} <5.7%, 5.7% to <6.5%, and ≥6.5% respectively. Among those with diagnosed DM, the hospitalization rates were 340 (95% CI, 297–384) and 504 (95% CI, 462–547) for participants with HbA_{1c} <7.0% and ≥7.0%, respectively.[53]

Cost
(See Table 9-1)

- In 2017, the cost of DM was estimated at $327 billion (Table 9-1), up 26% from 2012, accounting for 1 in 4 healthcare dollars.[30] Of these costs, $237 billion were direct medical costs and $90 billion resulted from reduced productivity.
- After adjustment for age and sex, medical costs for patients with DM were 2.3 times higher than for people without DM.[30] In 2017, the average medical expenditure for people with DM was $16 752 per year, of which $9601 was attributed to DM.[30] Informal care is estimated to cost $1192 to $1321 annually per person with DM.[54]

Risk Factors for Developing DM

- In MESA, the incidence rate of DM per 1000 person-years associated with having 0, 1, 2, 3, 4, and 5 to 6 ideal cardiovascular health factors was 21.8, 18.6, 13.0, 11.2, 4.7, and 3.6, respectively.[55] Lower DM risk was associated with more ideal cardiovascular health factors for NH whites, Chinese Americans, African Americans, and Hispanic Americans. Ideal cardiovascular health factors included TC, BP, dietary intake, tobacco use, PA, and BMI.

- In CARDIA, adjustment for fasting glucose, BMI, WC, SBP, use of antihypertensive medications, triglyceride to HDL ratio, and parental history of DM explained the higher incidence of DM observed for black adults compared with white adults, respectively, over 30 years of follow-up.[19]
- In a meta-analysis, each 1-SD higher BMI in childhood was associated with an increased risk for developing DM as an adult (pooled OR, 1.23 [95% CI, 1.10–1.37] for children ≤6 years of age; 1.78 [95% CI, 1.51–2.10] for age 7 to 11 years; and 1.70 [95% CI, 1.30 – 2.22] for those 12 to 18 years).[56]
- Compared with birth weight of 3.63 to 4.5 kg, low birth weight (<2.72 kg) increased the risk of type 2 DM (OR, 2.15 [95% CI, 1.54–3.00]), with 47% of this association mediated by insulin resistance.[57]
- Of the 20.9 million new cases of DM predicted to occur over 10 years in the United States, 1.8 million could be attributable to consumption of SSBs. A recent meta-analysis showed that each 1 serving per day higher consumption of SSBs was associated with an 18% increased risk for DM.[58]
- In a meta-analysis, 600 to 3999, 4000 to 7999, and ≥8000 MET min/week of PA versus <600 MET min/week were associated with a decreased risk for developing DM of 0.86 (95% CI, 0.82–0.90), 0.75 (95% CI, 0.70–0.80), and 0.72 (95% CI, 0.68–0.77), respectively.[59]
- In the CARDIA study, higher cardiorespiratory fitness was associated with lower risk for incident prediabetes/DM (difference of 1 MET: HR, 0.99898 [95% CI, 0.99861–0.99940]; *P*<0.01), which persisted after adjustment for covariates.[60]
- A systematic review by Biswas et al[61] identified 5 studies (4 were prospective) that assessed the association between sedentary time and type 2 DM and found that even after adjustment for PA, higher sedentary time was associated with elevated risk of type 2 DM (RR, 1.91 [95% CI, 1.64–2.22]). These findings suggest prolonged sedentary time might have deleterious metabolic effects independent of PA.[62]
- In the ARIC study, the risk of DM was higher for participants with an ABI ≤0.9 (HR, 1.41 [95% CI, 1.17–1.68]) than their counterparts with an ABI of 1.11 to 1.20, but this association was attenuated after multivariable adjustment (HR, 1.18 [95% CI, 0.98–1.41]).[63]
- In the FOURIER trial, evolocumab, a PCSK9 inhibitor, was not associated with an increased risk of DM (HR, 1.05 [95% CI, 0.94–1.17]) over a median of 2.2 years of follow-up.[64]

Prediabetes and Prevention

- In 2015, 33.9% of US adults aged ≥18 years had prediabetes, defined as fasting glucose 100 to 125 mg/dL or HbA_{1c} 5.7 to 6.4%.[1] The prevalence of prediabetes increased with age and was higher for males (36.6%) than females (29.3%).
- Among adults aged ≥20 years with overweight or obesity from 4 integrated health systems in the United States, 47.2% had prediabetes in 2012 to 2013.[65]
- The awareness of prediabetes is low, with only 11.6% of adults with prediabetes reporting being told they have prediabetes by a healthcare professional.[1]
- In the Diabetes Prevention Program of adults with prediabetes (defined as 2-hour postchallenge glucose of 140–199 mg/dL), the absolute risk reduction for DM was 20% for those adherent to the lifestyle modification intervention and 9% for those adherent to the metformin intervention compared with placebo over a median 3-year follow-up. Metformin was effective among those with higher predicted risk at baseline, whereas lifestyle intervention was effective regardless of baseline predicted risk.[66]

Awareness, Treatment, and Control (See Chart 9-7)

- From 2004 through 2011 in the TODAY study, less than half of children (41.1% of Hispanic and 31.5% of NH black children) with recent-onset type 2 DM maintained durable glycemic control with metformin monotherapy, which is a higher rate of treatment failure than observed in adult cohorts.[67] Youths with recent-onset type 2 DM were sedentary >56 minutes longer per day (via accelerometry) than obese youths from NHANES.[68]
- On the basis of NHANES 2013 to 2016 data for adults with DM, 20.9% had their DM treated and controlled, 45.2% had their DM treated but uncontrolled, 9.2% were aware they had DM but were not treated, and 24.7% were undiagnosed and not treated (Chart 9-7; unpublished NHLBI tabulations).
- In a pooled analysis of ARIC, MESA, and JHS, 41.8%, 32.1%, and 41.9% of participants were at target levels for BP, LDL-C, and HbA_{1c}, respectively; 41.1%, 26.5%, and 7.2% were at target

levels for any 1, 2, or all 3 factors, respectively. Having 1, 2, and 3 factors at goal was associated with 36%, 52%, and 62%, respectively, lower risk of CVD events compared with participants with no risk factors at goal.[69]

- In 2007 to 2010 NHANES data, 52.5% of adults with DM had an HbA_{1c} <7.0%, 51.1% achieved a BP <130/80 mm Hg, 56.2% had an LDL-C <100 mg/dL, and 18.8% had reached all 3 treatment targets. Compared with NH whites, Mexican Americans were less likely to meet HbA_{1c} and LDL-C goals, and NH blacks were less likely to meet BP and LDL-C goals.[70] Additionally, 22.3% of adults with DM reported being current smokers.[71]
- Among HCHS/SOL study participants with DM, 43.0% had HbA_{1c} <7.0%, 48.7% had BP <130/80 mm Hg, 36.6% had LDL-C <100 mg/dL, and 8.4% had reached all 3 treatment targets.[72]
  - HCHS/SOL participants in the lowest versus highest tertile of sedentary time were more likely to have controlled their HbA_{1c} to <7% (OR, 1.76 [95% CI, 1.10–2.82]) and their triglycerides to <150 mg/dL (OR, 2.16 [95% CI, 1.36–3.46]).[73]
- According to NHANES 2007 to 2012, 17% of US adults with DM met the criteria for major depression or subsyndromal symptomatic depression. This represents 3.7 million US adults with these conditions.[74]
- Treatment of hypercholesterolemia is recommended for adults with DM, with statin therapy recommended for all patients with DM 40 to 75 years of age independent of baseline cholesterol.[75]
- In the AHA's GWTG Program, patients with ACS and DM were less likely to have LDL-C checked or a statin prescribed than patients with ACS but without DM.[76]
- Treatment of hypertension is also recommended for adults with DM, with a target BP of 130/80 mm Hg for most people with DM.[77]
- In MEPS, 70% (95% CI, 68%–71%), 67% (95% CI, 66%–69%), and 68% (95% CI, 66%–71%) of US adults with DM received appropriate DM care (HbA_{1c} measurement, foot examination, and an eye examination) in 2002, 2007, and 2013, respectively[78]; however, only 39.6% of adults with DM reported receiving dilated eye examinations annually.[79]
- In 2008, the US Food and Drug Administration issued guidance to the pharmaceutical industry mandating cardiovascular outcomes trials for new glucose-lowering medications. As of early 2018, 9 cardiovascular outcomes trials have been reported, all demonstrating noninferiority of the new glucose-lowering agents relative to placebo for their primary outcomes. Four of the trials had a decrease in the primary cardiovascular end point.[80]
  - The LEADER trial had a decrease in MACE events for liraglutide versus placebo (HR, 0.87 [95% CI, 0.78–0.97]).[81]
  - The SUSTAIN-6 trial had a decrease in MACE events for semaglutide versus placebo (HR, 0.74 [95% CI, 0.58–0.95]).[82]
  - The EMPA-REG OUTCOME trial had a decrease in MACE events for empagliflozin versus placebo (HR, 0.86 [95% CI, 0.74–0.99]).[83]
  - The CANVAS Program trial had a decrease in MACE events for canagliflozin versus placebo (HR, 0.86 [95% CI, 0.75–0.97]).[84]

Family History and Genetics

- DM is heritable; twin or family studies have demonstrated a range of heritability estimates from 30% to 70% depending on age of onset.[85,86] In the Framingham Heart Study, having a parent or sibling with DM conferred a 3.4 times increased risk of DM, which increased to 6.1 if both parents were affected.[87]
- There are parent-of-origin effects in DM, whereby the effects of genetic variants depend on the parent from whom they are inherited.[88]
- There are monogenic forms of DM, such as maturity-onset DM of the young, that are caused by genetic mutations in the *GCK* (glucokinase) and 28 other genes, but these affect <5% of patients with DM; genetic testing can be considered in these patients.[89,90]
- The majority of DM is a complex disease characterized by multiple genetic variants with gene-gene and gene-environment interactions. Genome-wide genetic studies of common DM conducted in large sample sizes through meta-analyses have identified >100 genetic variants associated with DM, with the most consistent being a common intronic variant in the *TCF7L2* (transcription factor 7 like 2) gene.[91–93]
- Other risk loci for DM identified from GWAS include variants in the genes *SLC30A8* and *HHEX* (related to β-cell development or function) and in the *NAT2* (N-acetyltransferase 2) gene, associated with insulin sensitivity.[93,94]
- GWASs in non-European ethnicities have also identified significant risk loci for DM, including variants in the gene *KCNQ1* (identified from a GWAS in Japanese individuals and replicated in

other ethnicities).[93,95] Transethnic analyses have identified genetic variants that are specific to certain ethnicities, for example, within the *PEPD* gene (specific to East Asian ancestry) and *KLF14* (specific to European ancestry).[91,92]

- Lifestyle appears to overcome risk conferred by a polygenic risk score composed of a combination of these common variants. In a recent study of the United Kingdom Biobank, genetic composition and combined health behaviors had a log-additive effect on the risk of developing DM, but ideal lifestyle returned the risk of incident DM toward the referent (low genetic risk) group in both the intermediate- and high-genetic-risk groups.[96]
- Some studies have suggested that genetic variants may predict response to DM therapies. For example, the response to metformin is heritable, and a SNP in the *ATM* (ataxia telangiectasia mutated) gene has been associated with this response.[97,98]
- The utility of clinical genetic testing for common DM is currently unclear. Recent genetic technological advances, including whole-genome sequencing, have enabled identification of novel genes that harbor rare variants associated with common DM, with the strongest being for a variant in the gene *CCND2* (encoding a protein that helps regulate cell cycle), which reduces the risk of DM by half.[99]
- Inactivation of rare variants in the *ANGPTL4* (angiopoietin-like 4) gene, which leads to loss of the gene's ability to inhibit lipoprotein lipase, has been associated with reduced DM risk.[100]
- Type 1 DM is also heritable. Early genetic studies identified the role of the *MHC* (major histocompatibility complex) gene in this disease, with the greatest contributor being the human leukocyte antigen region, estimated to contribute to ≈50% of the genetic risk.[101]
- A genotype risk score composed of 9 type 1 DM–associated risk variants has been shown to be able to discriminate type 1 DM from type 2 DM (area under the curve 0.87), which could be clinically useful given the increasing prevalence of obesity in young adults.[102]
- The risk of complications from DM is also heritable. For example, diabetic kidney disease shows familial clustering, with diabetic siblings of patients with diabetic kidney disease having a 2-fold increased risk of also developing diabetic kidney disease.[103] Genetic variants have also been identified that appear to increase the risk of CAD in patients with DM.[104]

Global Burden of DM (See Table 9-2 and Charts 9-8 through 9-10)

- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories.[105]
  - — The prevalence of DM increased 119.1% for males and 106.1% for females between 1990 and 2016. Overall, 198.7 million males and 184.7 million females worldwide have DM (Table 9-2).
  - — Mortality rates attributable to high fasting plasma glucose are lowest in Western Europe, Australia, and New Zealand (Chart 9-8).
  - — Mortality attributable to DM is high in the Pacific Island countries, South Asia, sub-Saharan Africa, the North Africa/Middle East region, and Central and Latin America (Chart 9-9).
  - — The prevalence of DM is highest in the Pacific Island countries, Central Latin America, and the North Africa/Middle East region (Chart 9-10).
- The global economic burden of DM was $1.3 trillion in 2015. It is estimated to increase to $2.1 to 2.5 trillion by 2030.[106]

CLINICAL STATEMENTS AND GUIDELINES

Table 9-1. Diabetes Mellitus

Population Group	Prevalence of Diagnosed DM, 2013–2016: Age ≥20 y	Prevalence of Undiagnosed DM, 2013–2016: Age ≥20 y	Prevalence of Prediabetes, 2013–2016: Age ≥20 y	Incidence of Diagnosed DM, 2015: Age ≥18 y*	Mortality, 2016: All Ages†	Hospital Discharges, 2014: All Ages	Cost, 2017‡
Both sexes	26 000 000 (9.8%)	9 400 000 (3.7%)	91 800 000 (37.6%)	1 500 000	80 058	551 000	$327 Billion
Males	13 700 000 (10.9%)	5 500 000 (4.6%)	51 700 000 (44.0%)	…	43 763 (54.7%)§	301 000	…
Females	12 300 000 (8.9%)	3 900 000 (2.8%)	40 100 000 (31.3%)	…	36 295 (45.3%)§	250 000	…
NH white males	9.4%	4.7%	43.7%	…	30 010	…	…
NH white females	7.3%	2.6%	32.2%	…	23 389	…	…
NH black males	14.7%	1.7%	31.9%	…	6976	…	…
NH black females	13.4%	3.3%	24.0%	…	7077	…	…
Hispanic males	15.1%	6.3%	48.1%	…	4603	…	…
Hispanic females	14.1%	4.0%	31.7%	…	3943	…	…
NH Asian males	12.8%	6.1%	47.1%	…	1414	…	…
NH Asian females	9.9%	2.1%	29.4%	…	1283	…	…
NH American Indian or Alaska Native	…	…	…	…	1078	…	…

Undiagnosed DM is defined as those whose fasting glucose is ≥126 mg/dL but who did not report being told by a healthcare provider that they had DM. Prediabetes is a fasting blood glucose of 100 to <126 mg/dL (impaired fasting glucose); prediabetes includes impaired glucose tolerance. DM indicates diabetes mellitus; ellipses (…), data not available; and NH, non-Hispanic.

*Centers for Disease Control and Prevention (CDC), National Diabetes Statistics Report, 2017.[1]

†Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

‡American Diabetes Association.[2a]

§These percentages represent the portion of total DM mortality that is for males vs females.

Sources: Prevalence: Prevalence of diagnosed and undiagnosed DM: National Health and Nutrition Examination Survey 2013 to 2016, National Center for Health Statistics (NCHS), and National Heart, Lung, and Blood Institute. Percentages for sex and racial/ethnic groups are age adjusted for Americans ≥20 years of age. Mortality: CDC/NCHS, 2016 Mortality Multiple Cause-of-Death–US. These data represent underlying cause of death only. Mortality for NH Asians includes Pacific Islanders. Hospital discharges: Healthcare Cost and Utilization Project, Hospital Discharges, 2014.

Table 9-2. Global Prevalence and Mortality of DM, 2016

	Both Sexes Combined		Males		Females	
	Death	Prevalence	Death	Prevalence	Death	Prevalence
Total number (millions)	1.4 (1.4 to 1.5)	383.5 (352.6 to 414.6)	0.7 (0.7 to 0.7)	198.7 (182.9 to 215.3)	0.8 (0.7 to 0.8)	184.7 (169.6 to 199.5)
Percent change total number 1990 to 2016	127.0 (120.3 to 133.0)	112.6 (107.7 to 117.2)	145.0 (137.2 to 152.3)	119.1 (113.8 to 124.1)	113.1 (102.9 to 121.8)	106.1 (100.8 to 111.0)
Percent change total number 2006 to 2016	31.1 (28.9 to 33.4)	22.0 (19.3 to 24.8)	35.7 (32.8 to 38.6)	23.1 (20.3 to 26.3)	27.3 (23.7 to 30.9)	20.8 (18.3 to 23.3)
Rate per 100 000	22.1 (21.6 to 22.7)	5334.8 (4908.6 to 5759.7)	23.3 (22.6 to 24.0)	5672.5 (5225.5 to 6136.6)	21.2 (20.4 to 21.9)	5009.5 (4612.8 to 5412.9)
Percent change rate 1990 to 2016	16.0 (12.6 to 19.1)	19.6 (16.7 to 22.0)	21.6 (17.8 to 25.1)	21.8 (18.9 to 24.4)	11.2 (5.9 to 15.8)	17.2 (14.2 to 19.7)
Percent change rate 2006 to 2016	−0.9 (−2.5 to 0.8)	−1.9 (−4.1 to 0.3)	1.3 (−0.9 to 3.4)	−1.1 (−3.3 to 1.6)	−3.0 (−5.7 to −0.3)	−2.9 (−4.9 to −0.9)

DM indicates diabetes mellitus. Values in parentheses represent 95% confidence intervals.

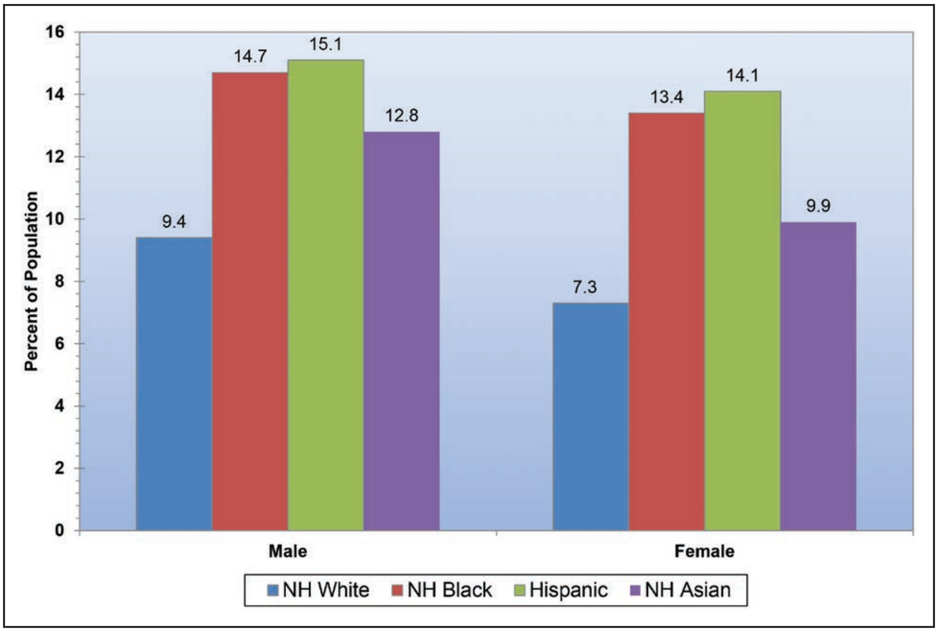

Chart 9-1. Age-adjusted prevalence of diagnosed diabetes mellitus in adults ≥20 years of age by race/ethnicity and sex (NHANES, 2013–2016).
NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

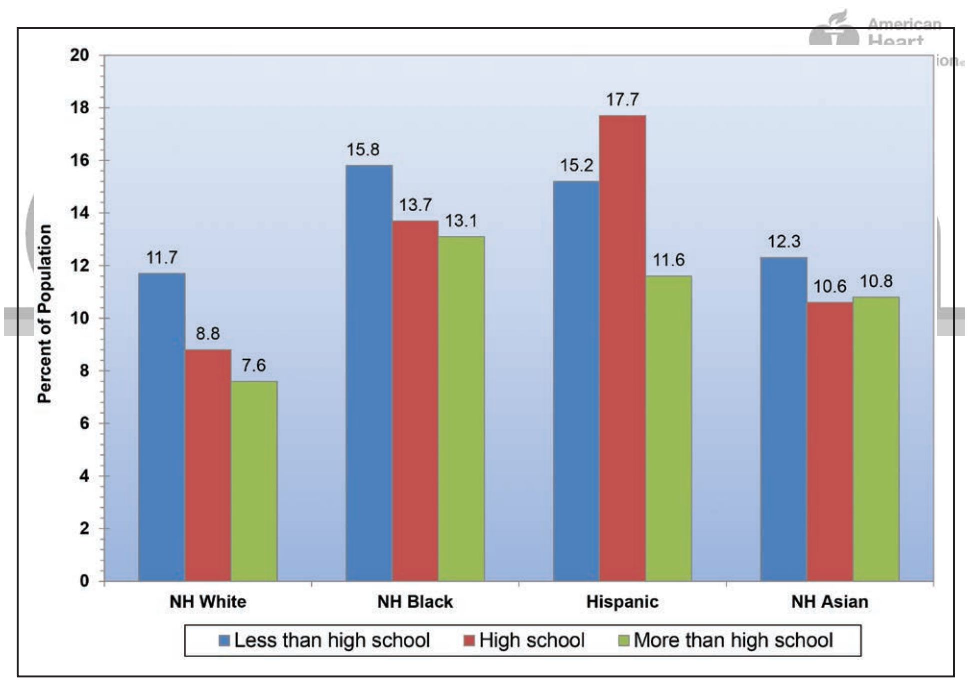

Chart 9-2. Age-adjusted prevalence of diagnosed diabetes mellitus in adults ≥20 years of age by race/ethnicity and years of education (NHANES, 2013–2016).
NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

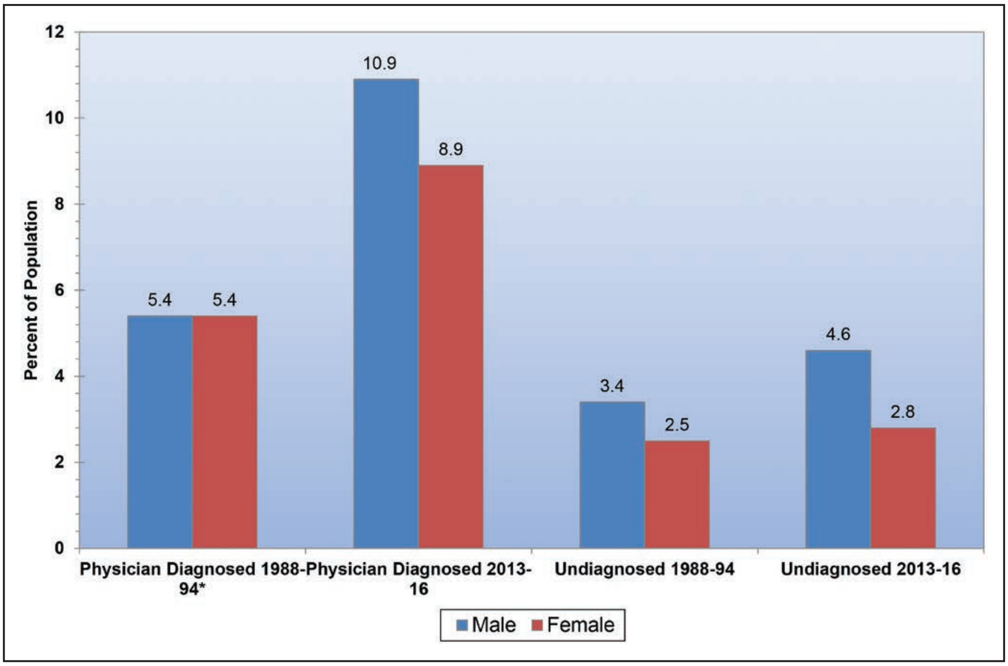

Chart 9-3. Trends in diabetes mellitus prevalence in adults ≥20 years of age by sex (NHANES, 1988–1994, 2011–2014, and 2013–2016).
The definition of diabetes changed in 1997 (from glucose ≥140 mg/dL to ≥126 mg/dL).
NHANES indicates National Health and Nutrition Examination Survey.
Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

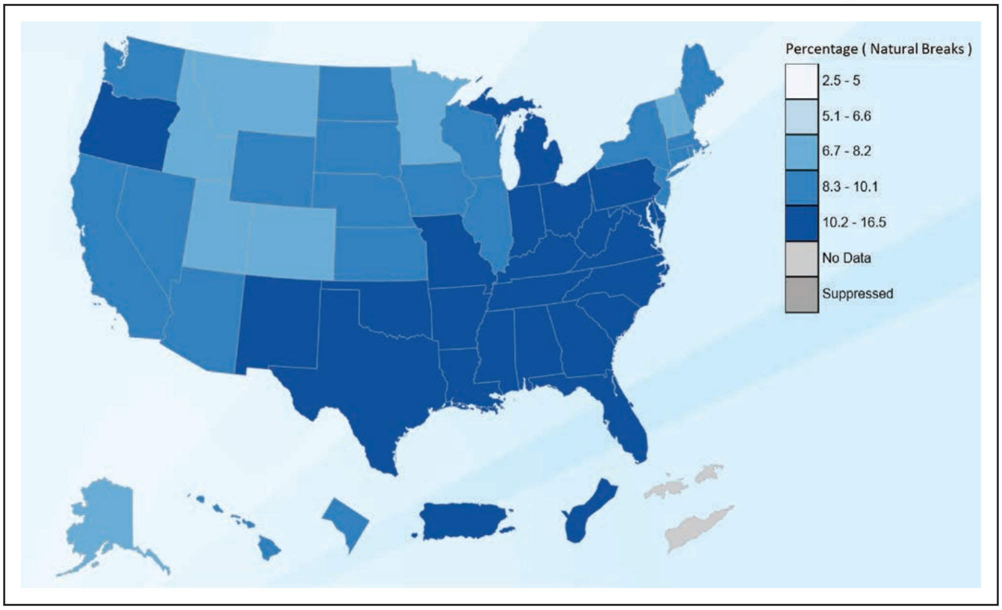

Chart 9-4. Diagnosed diabetes (crude percentage) among adults with diabetes, US states and territories, 2015.
Source: Center for Disease Control and Prevention, Division of Diabetes Translation.

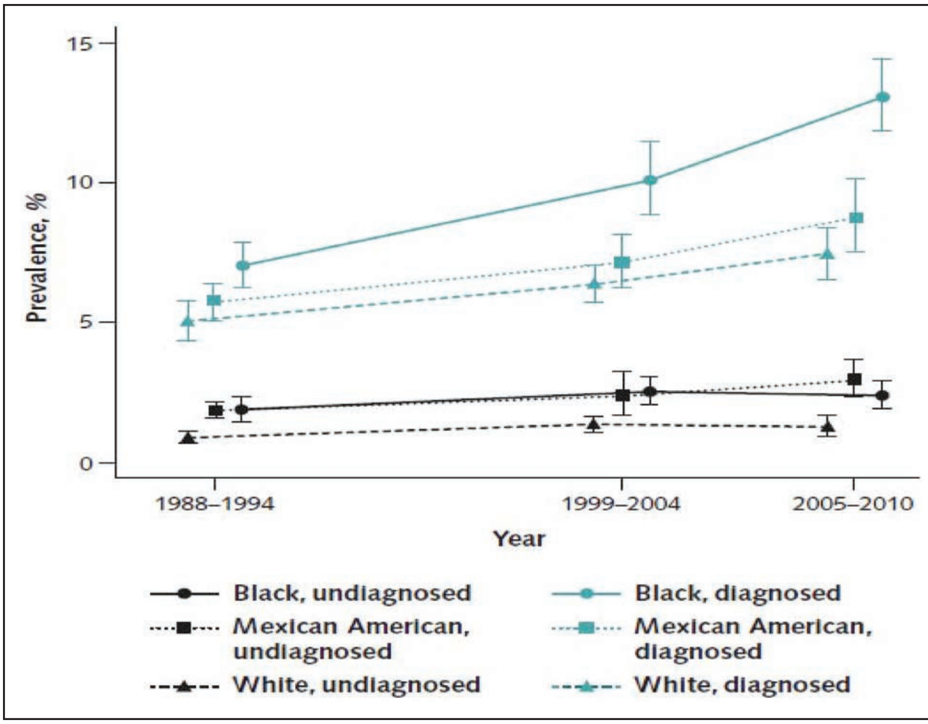

Chart 9-5. Trends in the prevalence of diagnosed and undiagnosed diabetes mellitus (calibrated hemoglobin A_{1c} levels >6.5%), by racial/ethnic group.
Data from US adults aged ≥20 years in NHANES 1988 to 1994, 1999 to 2004, and 2005 to 2010.
NHANES indicates National Health and Nutrition Examination Survey.
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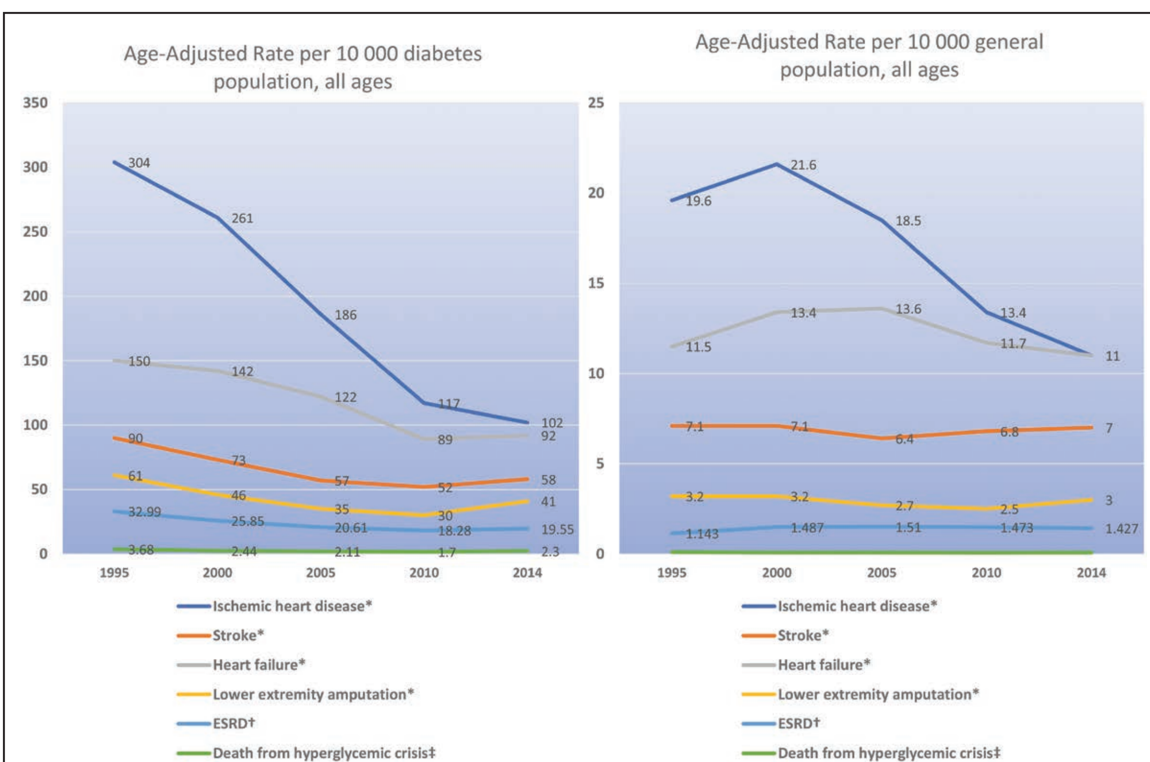

Chart 9-6. Trends in age-standardized rates of complications among US adults with and without diagnosed diabetes, 1995 to 2014.
ESRD indicates end-stage renal disease.
*Hospitalization rates; data from the National Inpatient Sample of the Agency for Healthcare Research and Quality.
†Diabetes-related ESRD; data from the United States Renal Data System.
‡Data from the Centers for Disease Control and Prevention's National Vital Statistics System.

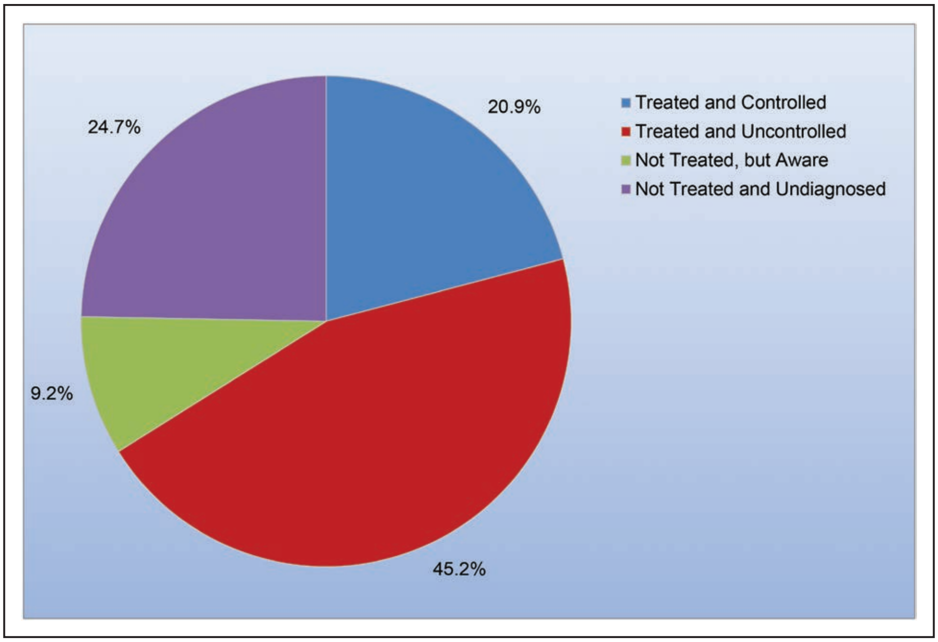

Chart 9-7. Diabetes mellitus awareness, treatment, and control in adults ≥20 years of age (NHANES, 2013–2016).
NHANES indicates National Health and Nutrition Examination Survey.
Source: National Heart, Lung, and Blood Institute.

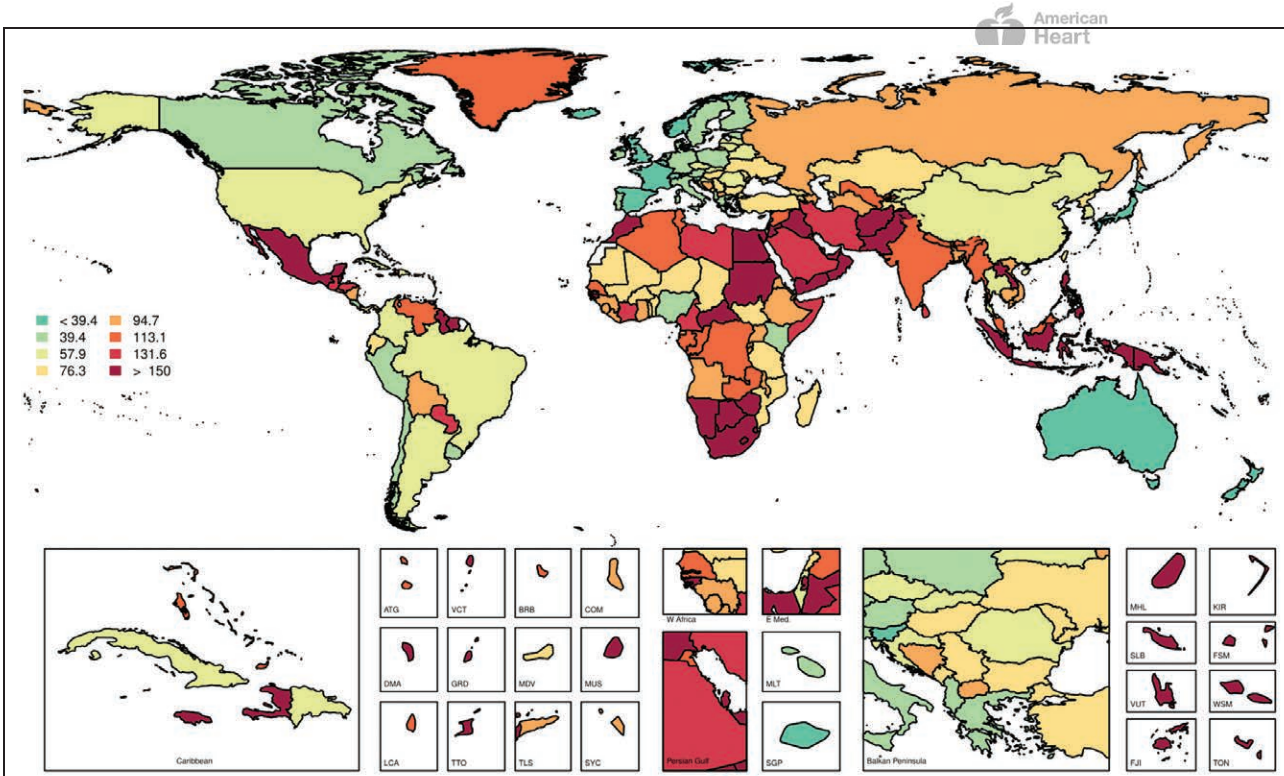

Chart 9-8. Age-standardized global mortality rates attributable to high fasting plasma glucose per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[105] Printed with permission.

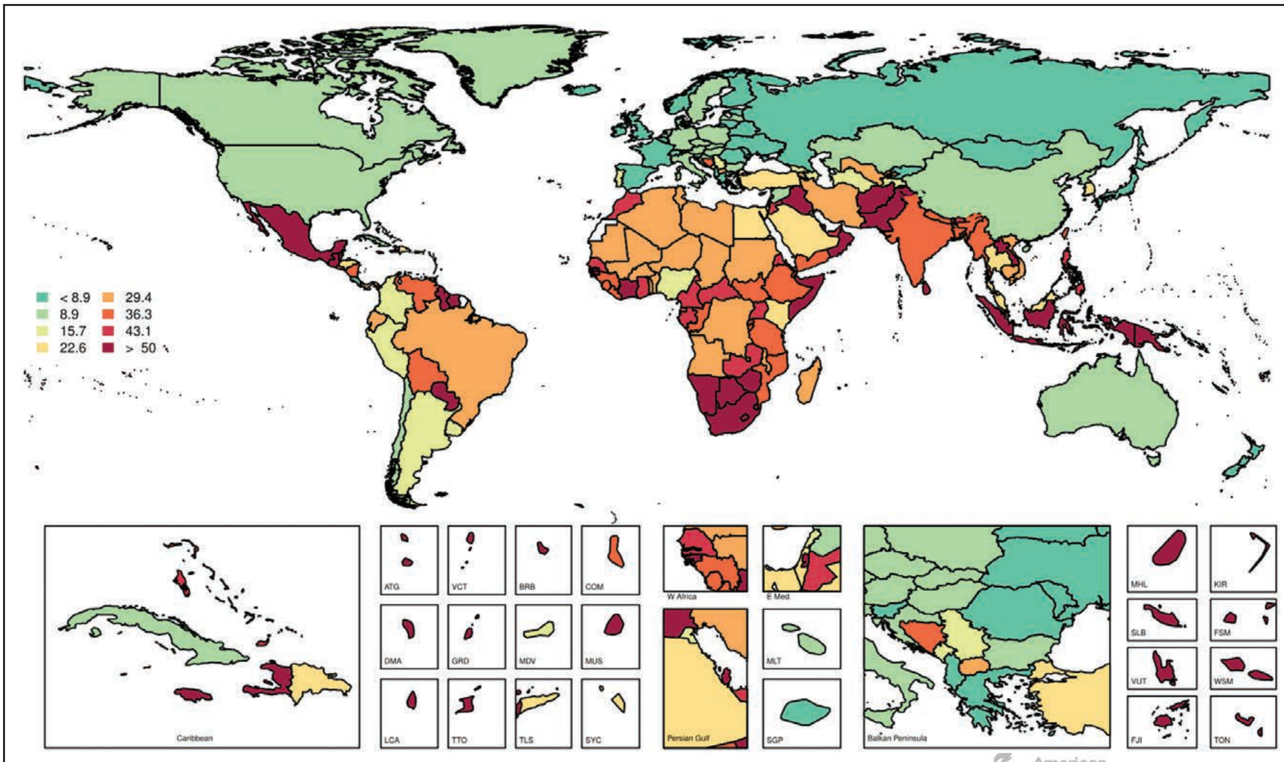

Chart 9-9. Age-standardized global mortality rates attributable to diabetes mellitus per 100 000, both sexes, 2016.

Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.

Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[105] Printed with permission.

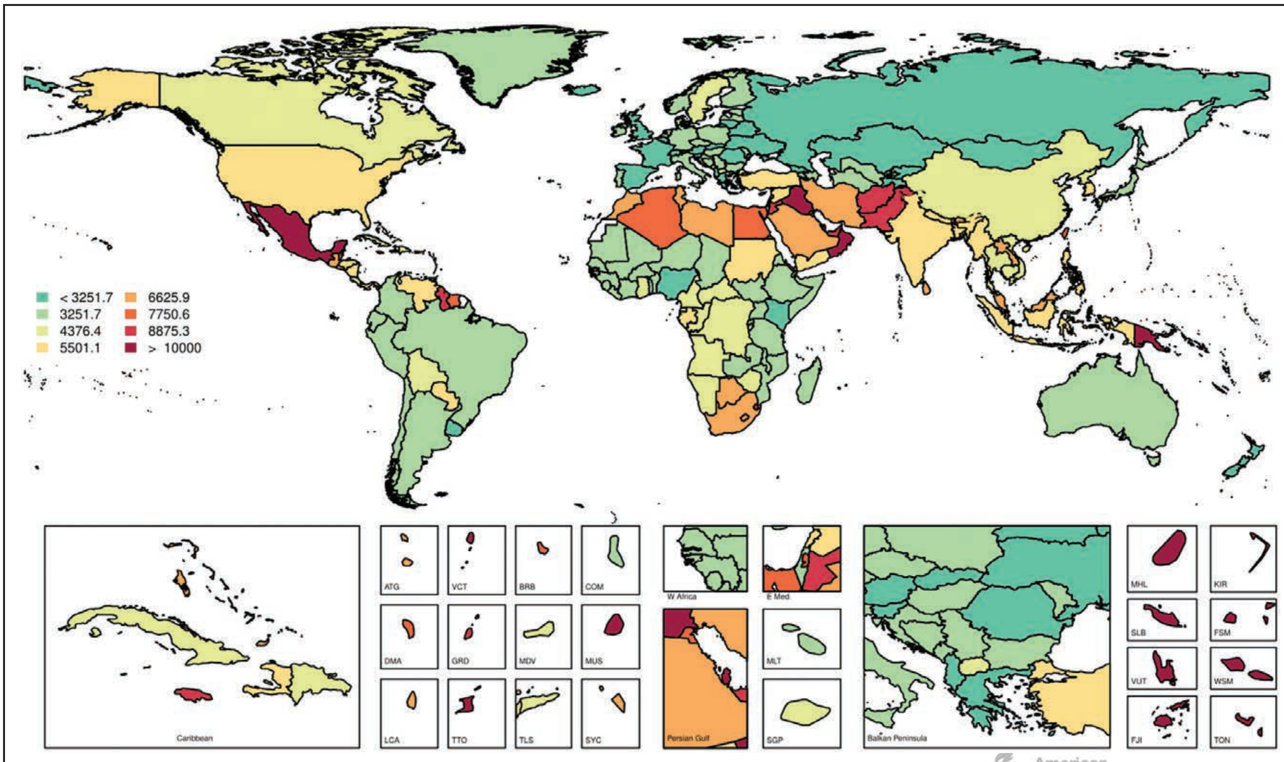

Chart 9-10. Age-standardized global prevalence rates of diabetes mellitus per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[105] Printed with permission. Copyright © 2017, University of Washington.

REFERENCES

1. National Center for Chronic Disease Prevention and Health Promotion, Division of Diabetes Translation. National Diabetes Statistics Report, 2017: Estimates of Diabetes and Its Burden in the United States. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2017.
2. Menke A, Orchard TJ, Imperatore G, Bullard KM, Mayer-Davis E, Cowie CC. The prevalence of type 1 diabetes in the United States. *Epidemiology*. 2013;24:773–774. doi: 10.1097/EDE.0b013e31829ef01a
2a. American Diabetes Association. Standards of medical care in diabetes: 2010 [published correction appears in *Diabetes Care*. 2010;33:692]. *Diabetes Care*. 2010;33(suppl 1):S11–S61.
3. The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies [published correction appears in *Lancet*. 2010;376:958]. *Lancet*. 2010;375:2215–2222. doi: 10.1016/S0140-6736(10)60484-9
4. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson R M, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
5. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, Bell R, Badaru A, Talton JW, Crume T, Liese AD, Merchant AT, Lawrence JM, Reynolds K, Dolan L, Liu LL, Hamman RF; for the SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA*. 2014;311:1778–1786. doi: 10.1001/jama.2014.3201
6. Liu LL, Lawrence JM, Davis C, Liese AD, Pettitt DJ, Pihoker C, Dabelea D, Hamman R, Waitzfelder B, Kahn HS; SEARCH for Diabetes in Youth Study Group. Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for Diabetes in Youth study. *Pediatr Diabetes*. 2010;11:4–11. doi: 10.1111/j.1399-5448.2009.00519.x
7. May AL, Kuklina EV, Yoon PW. Prevalence of cardiovascular disease risk factors among US adolescents, 1999-2008. *Pediatrics*. 2012;129:1035–1041. doi: 10.1542/peds.2011-1082
8. Menke A, Casagrande S, Cowie CC. Prevalence of diabetes in adolescents aged 12 to 19 years in the United States, 2005-2014. *JAMA*. 2016;316:344–345. doi: 10.1001/jama.2016.8544
9. Hummel K, McFann KK, Realsen J, Messer LH, Klingensmith GJ, Chase HP. The increasing onset of type 1 diabetes in children. *J Pediatr*. 2012;161:652–7.e1. doi: 10.1016/j.jpeds.2012.03.061
10. Schneiderman N, Llabre M, Cowie CC, Barnhart J, Carnethon M, Gallo LC, Giachello AL, Heiss G, Kaplan RC, LaVange LM, Teng Y, Villa-Caballero L, Avilés-Santa ML. Prevalence of diabetes among Hispanics/Latinos from diverse backgrounds: the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Diabetes Care*. 2014;37:2233–2239. doi: 10.2337/dc13-2939
11. Tsujimoto T, Kajio H, Sugiyama T. Obesity, diabetes, and length of time in the United States: analysis of National Health and Nutrition Examination Survey 1999 to 2012. *Medicine (Baltimore)*. 2016;95:e4578. doi: 10.1097/MD.0000000000004578
12. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997;20:1183–1197. doi: 10.2337/diacare.20.7.1183
13. Deleted in proof.
14. Dwyer-Lindgren L, Mackenbach JP, van Lenthe FJ, Flaxman AD, Mokdad AH. Diagnosed and undiagnosed diabetes prevalence by county in the U.S., 1999-2012. *Diabetes Care*. 2016;39:1556–1562. doi: 10.2337/dc16-0678

15. Loop MS, Howard G, de Los Campos G, Al-Hamdan MZ, Safford MM, Levitan EB, McClure LA. Heat maps of hypertension, diabetes mellitus, and smoking in the continental United States. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003350. doi: 10.1161/CIRCOUTCOMES.116.003350
16. Zhang N, Yang X, Zhu X, Zhao B, Huang T, Ji Q. Type 2 diabetes mellitus unawareness, prevalence, trends and risk factors: National Health and Nutrition Examination Survey (NHANES) 1999-2010. *J Int Med Res*. 2017;45:594–609. doi: 10.1177/0300060517693178
17. Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, Imperatore G, Linder B, Marcovina S, Pettitt DJ, Pihoker C, Saydah S, Wagenknecht L; SEARCH for Diabetes in Youth Study. Incidence trends of Type 1 and type 2 diabetes among youths, 2002-2012. *N Engl J Med*. 2017;376:1419–1429. doi: 10.1056/NEJMoa1610187
18. Imperatore G, Boyle JP, Thompson TJ, Case D, Dabelea D, Hamman RF, Lawrence JM, Liese AD, Liu LL, Mayer-Davis EJ, Rodriguez BL, Standiford D; SEARCH for Diabetes in Youth Study Group. Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. *Diabetes Care*. 2012;35:2515–2520. doi: 10.2337/dc12-0669
19. Bancks MP, Kershaw K, Carson AP, Gordon-Larsen P, Schreiner PJ, Carnethon MR. Association of modifiable risk factors in young adulthood with racial disparity in incident type 2 diabetes during middle adulthood. *JAMA*. 2017;318:2457–2465. doi: 10.1001/jama.2017.19546
20. National Center for Health Statistics. Centers for Disease Control and Prevention website. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2016. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed May 21, 2018.
21. Stokes A, Preston SH. Deaths attributable to diabetes in the United States: comparison of data sources and estimation approaches. *PLoS One*. 2017;12:e0170219. doi: 10.1371/journal.pone.0170219
22. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, Holme I, Njølstad I, Fletcher A, Nilsson P, Lewington S, Collins R, Gudnason V, Thompson SG, Sattar N, Selvin E, Hu FB, Danesh J; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death [published correction appears in *N Engl J Med*. 2011;364:1281]. *N Engl J Med*. 2011;364:829–841. doi: 10.1056/NEJMoa1008862
23. Liu L, Simon B, Shi J, Mallhi AK, Eisen HJ. Impact of diabetes mellitus on risk of cardiovascular disease and all-cause mortality: evidence on health outcomes and antidiabetic treatment in United States adults. *World J Diabetes*. 2016;7:449–461. doi: 10.4239/wjd.v7.i18.449
24. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson AM, Miftaraj M, McGuire DK, Sattar N, Rosengren A, Gudbjörnsdottir S. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med*. 2017;376:1407–1418. doi: 10.1056/NEJMoa1608664
25. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson AM, Miftaraj M, McGuire DK, Sattar N, Rosengren A, Gudbjörnsdottir S. Range of risk factor levels: control, mortality, and cardiovascular outcomes in type 1 diabetes mellitus. *Circulation*. 2017;135:1522–1531. doi: 10.1161/CIRCULATIONAHA.116.025961
26. Secrest AM, Becker DJ, Kelsey SF, Laporte RE, Orchard TJ. Cause-specific mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes. *Diabetes*. 2010;59:3216–3222. doi: 10.2337/db10-0862
27. Wang SY, Andrews CA, Herman WH, Gardner TW, Stein JD. Incidence and risk factors for developing diabetic retinopathy among youths with type 1 or type 2 diabetes throughout the United States. *Ophthalmology*. 2017;124:424–430. doi: 10.1016/j.ophtha.2016.10.031
28. Wu B, Bell K, Stanford A, Kern DM, Tunceli O, Vupputuri S, Kalsekar I, Willey V. Understanding CKD among patients with T2DM: prevalence, temporal trends, and treatment patterns: NHANES 2007-2012. *BMJ Open Diabetes Res Care*. 2016;4:e000154. doi: 10.1136/bmjdrc-2015-000154
29. Afkarian M, Zelnick LR, Hall YN, Heagerty PJ, Tuttle K, Weiss NS, de Boer IH. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. *JAMA*. 2016;316:602–610. doi: 10.1001/jama.2016.10924
30. Economic costs of diabetes in the US in 2017. American Diabetes Association. *Diabetes Care*. 2018;41:917–928. doi: 10.2337/dci18-0007.
31. Centers for Disease Control and Prevention, Division of Diabetes Translation, US Diabetes Surveillance System. Diabetes Data and Statistics. 2018. https://www.cdc.gov/diabetes/data. Accessed July 30, 2018.
32. Mondesir FL, Brown TM, Muntner P, Durant RW, Carson AP, Safford MM, Levitan EB. Diabetes, diabetes severity, and coronary heart disease risk equivalence: REasons for Geographic and Racial Differences in Stroke (REGARDS). *Am Heart J*. 2016;181:43–51. doi: 10.1016/j.ahj.2016.08.002
33. Bell EJ, Folsom AR, Lutsey PL, Selvin E, Zakai NA, Cushman M, Alonso A. Diabetes mellitus and venous thromboembolism: a systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2016;111:10–18. doi: 10.1016/j.diabres.2015.10.019
34. Loehr LR, Meyer ML, Poon AK, Selvin E, Palta P, Tanaka H, Pankow JS, Wright JD, Griswold ME, Wagenknecht LE, Heiss G. Prediabetes and diabetes are associated with arterial stiffness in older adults: the ARIC study. *Am J Hypertens*. 2016;29:1038–1045. doi: 10.1093/ajh/hpw036
35. Bertoni AG, Kramer H, Watson K, Post WS. Diabetes and clinical and subclinical CVD. *Glob Heart*. 2016;11:337–342. doi: 10.1016/j.gheart.2016.07.005
36. Reis JP, Allen NB, Bancks MP, Carr JJ, Lewis CE, Lima JA, Rana JS, Gidding SS, Schreiner PJ. Duration of diabetes and prediabetes during adulthood and subclinical atherosclerosis and cardiac dysfunction in middle age: the CARDIA study. *Diabetes Care*. 2018;41:731–738. doi: 10.2337/dc17-2233
37. Pallisgaard JL, Schjerning AM, Lindhardt TB, Procida K, Hansen ML, Torp-Pedersen C, Gislason GH. Risk of atrial fibrillation in diabetes mellitus: a nationwide cohort study. *Eur J Prev Cardiol*. 2016;23:621–627. doi: 10.1177/2047487315599892
38. Huxley RR, Filion KB, Konety S, Alonso A. Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. *Am J Cardiol*. 2011;108:56–62. doi: 10.1016/j.amjcard.2011.03.004
39. Hui G, Koch B, Calara F, Wong ND. Angina in coronary artery disease patients with and without diabetes: US National Health and Nutrition Examination Survey 2001-2010. *Clin Cardiol*. 2016;39:30–36. doi: 10.1002/clc.22488
40. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2010;121:e258]. *Circulation*. 2009;119:e391–e479. doi: 10.1161/CIRCULATIONAHA.109.192065
41. Khan H, Kunutsor SK, Kauhanen J, Kurl S, Gorodeski EZ, Adler AI, Butler J, Laukkanen JA. Fasting plasma glucose and incident heart failure risk: a population-based cohort study and new meta-analysis. *J Card Fail*. 2014;20:584–592. doi: 10.1016/j.cardfail.2014.05.011
42. Sarma S, Mentz RJ, Kwasny MJ, Fought AJ, Huffman M, Subacius H, Nodari S, Konstam M, Swedberg K, Maggioni AP, Zannad F, Bonow RO, Gheorghiade M; EVEREST investigators. Association between diabetes mellitus and post-discharge outcomes in patients hospitalized with heart failure: findings from the EVEREST trial. *Eur J Heart Fail*. 2013;15:194–202. doi: 10.1093/eurjhf/hfs153
43. Bozkurt B, Aguilar D, Deswal A, Dunbar SB, Francis GS, Horwich T, Jessup M, Kosiborod M, Pritchett AM, Ramasubbu K, Rosendorff C, Yancy C; on behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular and Stroke Nursing; Council on Hypertension; and Council on Quality and Outcomes Research. Contributory risk and management of comorbidities of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in chronic heart failure: a scientific statement from the American Heart Association. *Circulation*. 2016;134:e535–e578. doi: 10.1161/CIR.0000000000000450
44. Lipska KJ, Ross JS, Wang Y, Inzucchi SE, Minges K, Karter AJ, Huang ES, Desai MM, Gill TM, Krumholz HM. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. *JAMA Intern Med*. 2014;174:1116–1124. doi: 10.1001/jamainternmed.2014.1824
45. Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Billot L, Woodward M, Ninomiya T, Neal B, MacMahon S, Grobbee DE, Kengne AP, Marre M, Heller S; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med*. 2010;363:1410–1418. doi: 10.1056/NEJMoa1003795
46. Lee AK, Warren B, Lee CJ, McEvoy JW, Matsushita K, Huang ES, Sharrett AR, Coresh J, Selvin E. The association of severe hypoglycemia with incident cardiovascular events and mortality in adults with type 2 diabetes. *Diabetes Care*. 2018;41:104–111. doi: 10.2337/dc17-1669
47. Heller SR, Bergenstal RM, White WB, Kupfer S, Bakris GL, Cushman WC, Mehta CR, Nissen SE, Wilson CA, Zannad F, Liu Y, Gourlie NM, Cannon CP; EXAMINE Investigators. Relationship of glycated haemoglobin and

reported hypoglycaemia to cardiovascular outcomes in patients with type 2 diabetes and recent acute coronary syndrome events: the EXAMINE trial. *Diabetes Obes Metab*. 2017;19:664–671. doi: 10.1111/dom.12871
48. Schroeder EB, Xu S, Goodrich GK, Nichols GA, O'Connor PJ, Steiner JF. Predicting the 6-month risk of severe hypoglycemia among adults with diabetes: development and external validation of a prediction model. *J Diabetes Complications*. 2017;31:1158–1163. doi: 10.1016/j.jdiacomp.2017.04.004
49. Lipska KJ, Warton EM, Huang ES, Moffet HH, Inzucchi SE, Krumholz HM, Karter AJ. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the Diabetes and Aging Study. *Diabetes Care*. 2013;36:3535–3542. doi: 10.2337/dc13-0610
50. Karter AJ, Lipska KJ, O'Connor PJ, Liu JY, Moffet HH, Schroeder EB, Lawrence JM, Nichols GA, Newton KM, Pathak RD, Desai J, Waitzfelder B, Butler MG, Thomas A, Steiner JF; SUPREME-DM Study Group. High rates of severe hypoglycemia among African American patients with diabetes: the Surveillance, Prevention, and Management of Diabetes Mellitus (SUPREME-DM) network. *J Diabetes Complications*. 2017;31:869–873. doi: 10.1016/j.jdiacomp.2017.02.009
51. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA*. 2009;301:1565–1572. doi: 10.1001/jama.2009.460
52. Collins J, Abbass IM, Harvey R, Suehs B, Uribe C, Bouchard J, Prewitt T, DeLuzio T, Allen E. Predictors of all-cause-30-day-readmission among Medicare patients with type 2 diabetes. *Curr Med Res Opin*. 2017;33:1517–1523. doi: 10.1080/03007995.2017.1330258
53. Schneider AL, Kalyani RR, Golden S, Stearns SC, Wruck L, Yeh HC, Coresh J, Selvin E. Diabetes and prediabetes and risk of hospitalization: the Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care*. 2016;39:772–779. doi: 10.2337/dc15-1335
54. Joo H, Zhang P, Wang G. Cost of informal care for patients with cardiovascular disease or diabetes: current evidence and research challenges. *Qual Life Res*. 2017;26:1379–1386. doi: 10.1007/s11136-016-1478-0
55. Joseph JJ, Echouffo-Tcheugui JB, Carnethon MR, Bertoni AG, Shay CM, Ahmed HM, Blumenthal RS, Cushman M, Golden SH. The association of ideal cardiovascular health with incident type 2 diabetes mellitus: the Multi-Ethnic Study of Atherosclerosis. *Diabetologia*. 2016;59:1893–1903. doi: 10.1007/s00125-016-4003-7
56. Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. *Obes Rev*. 2016;17:56–67. doi: 10.1111/obr.12316
57. Song Y, Huang YT, Song Y, Hevener AL, Ryckman KK, Qi L, LeBlanc ES, Kazlauskaite R, Brennan KM, Liu S. Birthweight, mediating biomarkers and the development of type 2 diabetes later in life: a prospective study of multi-ethnic women. *Diabetologia*. 2015;58:1220–1230. doi: 10.1007/s00125-014-3479-2
58. Imamura F, O'Connor L, Ye Z, Mursu J, Hayashino Y, Bhupathiraju SN, Forouhi NG. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. *Br J Sports Med*. 2016;50:496–504. doi: 10.1136/bjsports-2016-h3576rep
59. Kyu HH, Bachman VF, Alexander LT, Mumford JE, Afshin A, Estep K, Veerman JL, Delwiche K, Iannarone ML, Moyer ML, Cercy K, Vos T, Murray CJ, Forouzanfar MH. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. *BMJ*. 2016;354:i3857. doi: 10.1136/bmj.i3857
60. Chow LS, Odegaard AO, Bosch TA, Bantle AE, Wang Q, Hughes J, Carnethon M, Ingram KH, Durant N, Lewis CE, Ryder J, Shay CM, Kelly AS, Schreiner PJ. Twenty year fitness trends in young adults and incidence of prediabetes and diabetes: the CARDIA study. *Diabetologia*. 2016;59:1659–1665. doi: 10.1007/s00125-016-3969-5
61. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis [published correction appears in *Ann Intern Med*. 2015;163:400]. *Ann Intern Med*. 2015;162:123–132. doi: 10.7326/M14-1651
62. Henson J, Dunstan DW, Davies MJ, Yates T. Sedentary behaviour as a new behavioural target in the prevention and treatment of type 2 diabetes. *Diabetes Metab Res Rev*. 2016;32(suppl 1):213–220. doi: 10.1002/dmrr.2759
63. Hua S, Loehr LR, Tanaka H, Heiss G, Coresh J, Selvin E, Matsushita K. Ankle-brachial index and incident diabetes mellitus: the Atherosclerosis Risk in Communities (ARIC) study. *Cardiovasc Diabetol*. 2016;15:163. doi: 10.1186/s12933-016-0476-4
64. Sabatine MS, Leiter LA, Wiviott SD, Giugliano RP, Deedwania P, De Ferrari GM, Murphy SA, Kuder JF, Gouni-Berthold I, Lewis BS, Handelsman Y, Pineda AL, Honarpour N, Keech AC, Sever PS, Pedersen TR. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. *Lancet Diabetes Endocrinol*. 2017;5:941–950. doi: 10.1016/S2213-8587(17)30313-3
65. Nichols GA, Horberg M, Koebnick C, Young DR, Waitzfelder B, Sherwood NE, Daley MF, Ferrara A. Cardiometabolic risk factors among 1.3 million adults with overweight or obesity, but not diabetes, in 10 geographically diverse regions of the United States, 2012-2013. *Prev Chronic Dis*. 2017;14:E22. doi: 10.5888/pcd14.160438
66. Herman WH, Pan Q, Edelstein SL, Mather KJ, Perreault L, Barrett-Connor E, Dabelea DM, Horton E, Kahn SE, Knowler WC, Lorenzo C, Pi-Sunyer X, Venditti E, Ye W; Diabetes Prevention Program Research Group. Impact of lifestyle and metformin interventions on the risk of progression to diabetes and regression to normal glucose regulation in overweight or obese people with impaired glucose regulation [published correction appears in *Diabetes Care*. 2018;41:913]. *Diabetes Care*. 2017;40:1668–1677. doi: 10.2337/dc17-1116
67. Zeitler P, Hirst K, Pyle L, Linder B, Copeland K, Arslanian S, Cuttler L, Nathan DM, Tollefsen S, Wilfley D, Kaufman F; TODAY Study Group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med*. 2012;366:2247–2256. doi: 10.1056/NEJMoa1109333
68. Kriska A, Delahanty L, Edelstein S, Amodei N, Chadwick J, Copeland K, Galvin B, El ghormli L, Haymond M, Kelsey M, Lassiter C, Mayer-Davis E, Milaszewski K, Syme A. Sedentary behavior and physical activity in youth with recent onset of type 2 diabetes. *Pediatrics*. 2013;131:e850–e856. doi: 10.1542/peds.2012-0620
69. Wong ND, Zhao Y, Patel R, Patao C, Malik S, Bertoni AG, Correa A, Folsom AR, Kachroo S, Mukherjee J, Taylor H, Selvin E. Cardiovascular risk factor targets and cardiovascular disease event risk in diabetes: a pooling project of the Atherosclerosis Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study. *Diabetes Care*. 2016;39:668–676. doi: 10.2337/dc15-2439
70. Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. *Diabetes Care*. 2013;36:2271–2279. doi: 10.2337/dc12-2258
71. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care, 1999-2010 [published correction appears in *N Engl J Med*. 2013;369:587]. *N Engl J Med*. 2013;368:1613–1624. doi: 10.1056/NEJMsa1213829
72. Casagrande SS, Aviles-Santa L, Corsino L, Daviglus ML, Gallo LC, Espinoza Giacinto RA, Llabre MM, Reina SA, Savage PJ, Schneiderman N, Talavera GA, Cowie CC. Hemoglobin A1c, blood pressure, and LDL-cholesterol control among Hispanic/Latino adults with diabetes: results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Endocr Pract*. 2017;23:1232–1253. doi: 10.4158/EP171765.OR
73. Wang X, Strizich G, Hua S, Sotres-Alvarez D, Buelna C, Gallo LC, Gellman MD, Mossavar-Rahmani Y, O'Brien MJ, Stoutenberg M, Wang T, Avilés-Santa ML, Kaplan RC, Qi Q. Objectively measured sedentary time and cardiovascular risk factor control in US Hispanics/Latinos with diabetes mellitus: results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *J Am Heart Assoc*. 2017;6:e004324. doi: 10.1161/JAHA.116.004324
74. Albertorio-Diaz JR, Eberhardt MS, Oquendo M, Mesa-Frias M, He Y, Jonas B, Kang K. Depressive states among adults with diabetes: findings from the National Health and Nutrition Examination Survey, 2007-2012. *Diabetes Res Clin Pract*. 2017;127:80–88. doi: 10.1016/j.diabres.2017.02.031
75. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PWF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published corrections appear in *Circulation*. 2014;129:S46–S48 and *Circulation*. 2015;132:e396]. *Circulation*. 2014;129(suppl 2):S1–S45. doi: 10.1161/01.cir.0000437738.63853.7a
76. Deedwania P, Acharya T, Kotak K, Fonarow GC, Cannon CP, Laskey WK, Peacock WF, Pan W, Bhatt DL; GWTG Steering Committee and

Investigators. Compliance with guideline-directed therapy in diabetic patients admitted with acute coronary syndrome: findings from the American Heart Association's Get With The Guidelines-Coronary Artery Disease (GWTG-CAD) program. *Am Heart J*. 2017;187:78–87. doi: 10.1016/j.ahj.2017.02.025

77. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in *Hypertension*. 2018;71:e140–e144]. *Hypertension*. 2018;71:e13–e115. doi: 10.1161/HYP0000000000000065
78. Levine DM, Linder JA, Landon BE. The quality of outpatient care delivered to adults in the United States, 2002 to 2013. *JAMA Intern Med*. 2016;176:1778–1790. doi: 10.1001/jamainternmed.2016.6217
79. Tran EMT, Bhattacharya J, Pershing S. Self-reported receipt of dilated fundus examinations among patients with diabetes: Medicare Expenditure Panel Survey, 2002-2013. *Am J Ophthalmol*. 2017;179:18–24. doi: 10.1016/j.ajo.2017.04.009
80. Cefalu WT, Kaul S, Gerstein HC, Holman RR, Zinman B, Skyler JS, Green JB, Buse JB, Inzucchi SE, Leiter LA, Raz I, Rosenstock J, Riddle MC. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a *Diabetes Care* Editors' Expert Forum. *Diabetes Care*. 2018;41:14–31. doi: 10.2337/dci17-0057
81. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311–322. doi: 10.1056/NEJMoa1603827
82. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834–1844. doi: 10.1056/NEJMoa1607141
83. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128. doi: 10.1056/NEJMoa1504720
84. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657. doi: 10.1056/NEJMoa1611925
85. Almgren P, Lehtovirta M, Isomaa B, Sarelin L, Taskinen MR, Lyssenko V, Tuomi T, Groop L; Botnia Study Group. Heritability and familiality of type 2 diabetes and related quantitative traits in the Botnia Study. *Diabetologia*. 2011;54:2811–2819. doi: 10.1007/s00125-011-2267-5
86. Poulsen P, Kyvik KO, Vaag A, Beck-Nielsen H. Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance–a population-based twin study. *Diabetologia*. 1999;42:139–145.
87. Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring Study. *Diabetes*. 2000;49:2201–2207.
88. Kong A, Steinthorsdottir V, Masson G, Thorleifsson G, Sulem P, Besenbacher S, Jonasdottir A, Sigurdsson A, Kristinsson KT, Jonasdottir A, Frigge ML, Gylfason A, Olason PI, Gudjonsson SA, Sverrisson S, Stacey SN, Sigurgeirsson B, Benediktsdottir KR, Sigurdsson H, Jonsson T, Benediktsson R, Olafsson JH, Johannsson OT, Hreidarsson AB, Sigurdsson G, Ferguson-Smith AC, Gudbjartsson DF, Thorsteinsdottir U, Stefansson K; DIAGRAM Consortium. Parental origin of sequence variants associated with complex diseases. *Nature*. 2009;462:868–874. doi: 10.1038/nature08625
89. Bonnefond A, Froguel P. Rare and common genetic events in type 2 diabetes: what should biologists know? *Cell Metab*. 2015;21:357–368. doi: 10.1016/j.cmet.2014.12.020
90. Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S. Maturity-onset diabetes of the young (MODY): how many cases are we missing? *Diabetologia*. 2010;53:2504–2508. doi: 10.1007/s00125-010-1799-4
91. Morris AP, Voight BF, Teslovich TM, Ferreira T, Segrè AV, Steinthorsdottir V, Strawbridge RJ, Khan H, Grallert H, Mahajan A, Prokopenko I, Kang HM, Dina C, Esko T, Fraser RM, Kanoni S, Kumar A, Lagou V, Langenberg C, Luan J, Lindgren CM, Müller-Nurasyid M, Pechlivanis S, Rayner NW, Scott LJ, Wiltshire S, Yengo L, Kinnunen L, Rossin EJ, Raychaudhuri S, Johnson AD, Dimas AS, Loos RJ, Vedantam S, Chen H, Florez JC, Fox C, Liu CT, Rybin D, Couper DJ, Kao WH, Li M, Cornelis MC, Kraft P, Sun Q, van Dam RM, Stringham HM, Chines PS, Fischer K, Fontanillas P, Holmen OL, Hunt SE, Jackson AU, Kong A, Lawrence R, Meyer J, Perry JR, Platou CG, Potter S, Rehnberg E, Robertson N, Sivapalaratnam S, Stančáková A, Stirrups K, Thorleifsson G, Tikkanen E, Wood AR, Almgren P, Atalay M, Benediktsson R, Bonnycastle LL, Burtt N, Carey J, Charpentier G, Crenshaw AT, Doney AS, Dorkhan M, Edkins S, Emilsson V, Eury E, Forsen T, Gertow K, Gigante B, Grant GB, Groves CJ, Guiducci C, Herder C, Hreidarsson AB, Hui J, James A, Jonsson A, Rathmann W, Klopp N, Kravic J, Krjutškov K, Langford C, Leander K, Lindholm E, Lobbens S, Männistö S, Mirza G, Mühleisen TW, Musk B, Parkin M, Rallidis L, Saramies J, Sennblad B, Shah S, Sigurðsson G, Silveira A, Steinbach G, Thorand B, Trakalo J, Veglia F, Wennauer R, Winckler W, Zabaneh D, Campbell H, van Duijn C, Uitterlinden AG, Hofman A, Sijbrands E, Abecasis GR, Owen KR, Zeggini E, Trip MD, Forouhi NG, Syvänen AC, Eriksson JG, Peltonen L, Nöthen MM, Balkau B, Palmer CN, Lyssenko V, Tuomi T, Isomaa B, Hunter DJ, Qi L, Shuldiner AR, Roden M, Barroso I, Wilsgaard T, Beilby J, Hovingh K, Price JF, Wilson JF, Rauramaa R, Lakka TA, Lind L, Dedoussis G, Njølstad I, Pedersen NL, Khaw KT, Wareham NJ, Keinanen-Kiukaanniemi SM, Saaristo TE, Korpi-Hyövälti E, Saltevo J, Laakso M, Kuusisto J, Metspalu A, Collins FS, Mohlke KL, Bergman RN, Tuomilehto J, Boehm BO, Gieger C, Hveem K, Cauchi S, Froguel P, Baldassarre D, Tremoli E, Humphries SE, Saleheen D, Danesh J, Ingelsson E, Ripatti S, Salomaa V, Erbel R, Jöckel KH, Moebus S, Peters A, Illig T, de Faire U, Hamsten A, Morris AD, Donnelly PJ, Frayling TM, Hattersley AT, Boerwinkle E, Melander O, Kathiresan S, Nilsson PM, Deloukas P, Thorsteinsdottir U, Groop LC, Stefansson K, Hu F, Pankow JS, Dupuis J, Meigs JB, Altshuler D, Boehnke M, McCarthy MI; Wellcome Trust Case Control Consortium; Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) Investigators; Genetic Investigation of ANthropometric Traits (GIANT) Consortium; Asian Genetic Epidemiology Network–Type 2 Diabetes (AGEN-T2D) Consortium; South Asian Type 2 Diabetes (SAT2D) Consortium; DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat Genet*. 2012;44:981–990. doi: 10.1038/ng.2383
92. DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium, Asian Genetic Epidemiology Network Type 2 Diabetes (AGEN-T2D) Consortium, South Asian Type 2 Diabetes (SAT2D) Consortium, Mexican American Type 2 Diabetes (MAT2D) Consortium, Type 2 Diabetes Genetic Exploration by Next-generation sequencing in multi-Ethnic Samples (T2D-GENES) Consortium. Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. *Nat Genet*. 2014;46:234–244. doi: 10.1038/ng.2897
93. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, Boutin P, Vincent D, Belisle A, Hadjadj S, Balkau B, Heude B, Charpentier G, Hudson TJ, Montpetit A, Pshezhetsky AV, Prentki M, Posner BI, Balding DJ, Meyre D, Polychronakos C, Froguel P. A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature*. 2007;445:881–885. doi: 10.1038/nature05616
94. Knowles JW, Xie W, Zhang Z, Chennamsetty I, Assimes TL, Paananen J, Hansson O, Pankow J, Goodarzi MO, Carcamo-Orive I, Morris AP, Chen YD, Mäkinen VP, Ganna A, Mahajan A, Guo X, Abbasi F, Greenawalt DM, Lum P, Molony C, Lind L, Lindgren C, Raffel LJ, Tsao PS, Schadt EE, Rotter JI, Sinaiko A, Reaven G, Yang X, Hsiung CA, Groop L, Cordell HJ, Laakso M, Hao K, Ingelsson E, Frayling TM, Weedon MN, Walker M, Quertermous T; RISC (Relationship between Insulin Sensitivity and Cardiovascular Disease) Consortium; EUGENE (European Network on Functional Genomics of Type Diabetes) Study; GUARDIAN (Genetics UndeRlying DIAbetes in HispaNics) Consortium; SAPPHIRe (Stanford Asian and Pacific Program for Hypertension and Insulin Resistance) Study. Identification and validation of N-acetyltransferase 2 as an insulin sensitivity gene [published correction appears in *J Clin Invest*. 2016;126:403]. *J Clin Invest*. 2015;125:1739–1751. doi: 10.1172/JCI74692
95. Yasuda K, Miyake K, Horikawa Y, Hara K, Osawa H, Furuta H, Hirota Y, Mori H, Jonsson A, Sato Y, Yamagata K, Hinokio Y, Wang HY, Tanahashi T, Nakamura N, Oka Y, Iwasaki N, Iwamoto Y, Yamada Y, Seino Y, Maegawa H, Kashiwagi A, Takeda J, Maeda E, Shin HD, Cho YM, Park KS, Lee HK, Ng MC, Ma RC, So WY, Chan JC, Lyssenko V, Tuomi T, Nilsson P, Groop L, Kamatani N, Sekine A, Nakamura Y, Yamamoto K, Yoshida T, Tokunaga K, Itakura M, Makino H, Nanjo K, Kadowaki T, Kasuga M. Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. *Nat Genet*. 2008;40:1092–1097. doi: 10.1038/ng.207

96. Said MA, Verweij N, van der Harst P. Associations of combined genetic and lifestyle risks with incident cardiovascular disease and diabetes in the UK Biobank Study. *JAMA Cardiol*. 2018;3:693–702. doi: 10.1001/jamacardio.2018.1717
97. Zhou K, Donnelly L, Yang J, Li M, Deshmukh H, Van Zuydam N, Ahlqvist E, Spencer CC, Groop L, Morris AD, Colhoun HM, Sham PC, McCarthy MI, Palmer CN, Pearson ER; Wellcome Trust Case Control Consortium 2. Heritability of variation in glycaemic response to metformin: a genome-wide complex trait analysis. *Lancet Diabetes Endocrinol*. 2014;2:481–487. doi: 10.1016/S2213-8587(14)70050-6
98. The GoDARTS and UKPDS Diabetes Pharmacogenetics Study Group; Zhou K, Bellenguez C, Spencer CC, Bennett AJ, Coleman RL, Tavendale R, Hawley SA, Donnelly LA, Schofield C, Groves CJ, Burch L, Carr F, Strange A, Freeman C, Blackwell JM, Bramon E, Brown MA, Casas JP, Corvin A, Craddock N, Deloukas P, Dronov S, Duncanson A, Edkins S, Gray E, Hunt S, Jankowski J, Langford C, Markus HS, Mathew CG, Plomin R, Rautanen A, Sawcer SJ, Samani NJ, Trembath R, Viswanathan AC, Wood NW; Harries LW, Hattersley AT, Doney AS, Colhoun H, Morris AD, Sutherland C, Hardie DG, Peltonen L, McCarthy MI, Holman RR, Palmer CN, Donnelly P, Pearson ER; Wellcome Trust Case Control Consortium 2. Common variants near ATM are associated with glycemic response to metformin in type 2 diabetes. *Nat Genet*. 2011;43:117–120. doi: 10.1038/ng.735
99. Steinthorsdottir V, Thorleifsson G, Sulem P, Helgason H, Grarup N, Sigurdsson A, Helgadottir HT, Johannsdottir H, Magnusson OT, Gudjonsson SA, Justesen JM, Harder MN, Jørgensen ME, Christensen C, Brandslund I, Sandbæk A, Lauritzen T, Vestergaard H, Linneberg A, Jørgensen T, Hansen T, Daneshpour MS, Fallah MS, Hreidarsson AB, Sigurdsson G, Azizi F, Benediktsson R, Masson G, Helgason A, Kong A, Gudbjartsson DF, Pedersen O, Thorsteinsdottir U, Stefansson K. Identification of low-frequency and rare sequence variants associated with elevated or reduced risk of type 2 diabetes. *Nat Genet*. 2014;46:294–298. doi: 10.1038/ng.2882
100. Gusarova V, O'Dushlaine C, Teslovich TM, Benotti PN, Mirshahi T, Gottesman O, Van Hout CV, Murray MF, Mahajan A, Nielsen JB, Fritsche L, Wulff AB, Gudbjartsson DF, Sjögren M, Emdin CA, Scott RA, Lee WJ, Small A, Kwee LC, Dwivedi OP, Prasad RB, Bruse S, Lopez AE, Penn J, Marcketta A, Leader JB, Still CD, Kirchner HL, Mirshahi UL, Wardeh AH, Hartle CM, Habegger L, Fetterolf SN, Tusie-Luna T, Morris AP, Holm H, Steinthorsdottir V, Sulem P, Thorsteinsdottir U, Rotter JI, Chuang LM, Damrauer S, Birtwell D, Brummett CM, Khera AV, Natarajan P, Orho-Melander M, Flannick J, Lotta LA, Willer CJ, Holmen OL, Ritchie MD, Ledbetter DH, Murphy AJ, Borecki IB, Reid JG, Overton JD, Hansson O, Groop L, Shah SH, Kraus WE, Rader DJ, Chen YI, Hveem K, Wareham NJ, Kathiresan S, Melander O, Stefansson K, Nordestgaard BG, Tybjærg-Hansen A, Abecasis GR, Altshuler D, Florez JC, Boehnke M, McCarthy MI, Yancopoulos GD, Carey DJ, Shuldiner AR, Baras A, Dewey FE, Gromada J. Genetic inactivation of ANGPTL4 improves glucose homeostasis and is associated with reduced risk of diabetes. *Nat Commun*. 2018;9:2252. doi: 10.1038/s41467-018-04611-z
101. Pociot F, Lernmark Å. Genetic risk factors for type 1 diabetes. *Lancet*. 2016;387:2331–2339. doi: 10.1016/S0140-6736(16)30582-7
102. Oram RA, Patel K, Hill A, Shields B, McDonald TJ, Jones A, Hattersley AT, Weedon MN. A type 1 diabetes genetic risk score can aid discrimination between type 1 and type 2 diabetes in young adults. *Diabetes Care*. 2016;39:337–344. doi: 10.2337/dc15-1111
103. Langefeld CD, Beck SR, Bowden DW, Rich SS, Wagenknecht LE, Freedman BI. Heritability of GFR and albuminuria in Caucasians with type 2 diabetes mellitus. *Am J Kidney Dis*. 2004;43:796–800.
104. Qi L, Qi Q, Prudente S, Mendonca C, Andreozzi F, di Pietro N, Sturma M, Novelli V, Mannino GC, Formoso G, Gervino EV, Hauser TH, Muehlschlegel JD, Niewczas MA, Krolewski AS, Biolo G, Pandolfi A, Rimm E, Sesti G, Trischitta V, Hu F, Doria A. Association between a genetic variant related to glutamic acid metabolism and coronary heart disease in individuals with type 2 diabetes. *JAMA*. 2013;310:821–828. doi: 10.1001/jama.2013.276305
105. Global Burden of Disease Study 2016. Global Burden of Disease Study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed May 1, 2018.
106. Bommer C, Sagalova V, Heesemann E, Manne-Goehler J, Atun R, Bärnighausen T, Davies J, Vollmer S. Global economic burden of diabetes in adults: projections from 2015 to 2030. *Diabetes Care*. 2018;41:963–970. doi: 10.2337/dc17-1962
107. Deleted in proof.
108. Selvin E, Parrinello CM, Sacks DB, Coresh J. Trends in prevalence and control of diabetes in the United States, 1988-1994 and 1999-2010. *Ann Intern Med*. 2014;160:517–525. doi: 10.7326/M13-2411

10. METABOLIC SYNDROME

See Charts 10-1 through 10-10

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Definition

- Metabolic syndrome is a multicomponent risk factor for CVD and type 2 DM that reflects the clustering of individual cardiometabolic risk factors related to abdominal obesity and insulin resistance. Clinically, metabolic syndrome is a useful entity for communicating the nature of lifestyle-related cardiometabolic risk to both patients and clinicians. Although several different clinical definitions for metabolic syndrome have been proposed, the International Diabetes Federation, NHLBI, AHA, and others proposed a harmonized definition for metabolic syndrome. By this definition, metabolic syndrome is diagnosed when any 3 of the following 5 risk factors are present:
  - — Fasting plasma glucose ≥100 mg/dL or undergoing drug treatment for elevated glucose
  - — HDL-C <40 mg/dL in males or <50 mg/dL in females or undergoing drug treatment for reduced HDL-C
  - — Triglycerides ≥150 mg/dL or undergoing drug treatment for elevated triglycerides
  - — WC >102 cm in males or >88 cm in females for people of most ancestries living in the United States. Ethnicity and country-specific thresholds can be used for diagnosis in other groups, particularly Asians and

Abbreviations Used in Chapter 10

AF	atrial fibrillation
AHA	American Heart Association
AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes
AMP	adenosine monophosphate
ARIC	Atherosclerosis Risk in Communities Study
ATP III	Adult Treatment Panel III
BioSHaRE	Biobank Standardization and Harmonization for Research Excellence in the European Union
BMI	body mass index
BP	blood pressure
CAC	coronary artery calcification
CAD	coronary artery disease
Carbs	carbohydrates
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CHRIS	Collaborative Health Research in South Tyrol Study
CI	confidence interval
CRP	C-reactive protein
CT	computed tomography
CVD	cardiovascular disease
DBP	diastolic blood pressure
DESIR	Data from an Epidemiological Study on the Insulin Resistance Syndrome
DILGOM	Dietary, Lifestyle, and Genetics Determinants of Obesity and Metabolic Syndrome
DM	diabetes mellitus
EGCUT	Estonian Genome Center of the University of Tartu
GFR	glomerular filtration rate
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
HCUP-NIS	Healthcare Cost and Utilization Project Nationwide Inpatient Sample
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HIV	human immunodeficiency virus
HR	hazard ratio
HUNT2	Nord-Trøndelag Health Study
IMT	intima-media thickness
JHS	Jackson Heart Study
KORA	Cooperative Health Research in the Region of Augsburg
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LV	left ventricular
MESA	Multi-Ethnic Study of Atherosclerosis
MET	metabolic equivalent
MetS	metabolic syndrome
Mex-Am	Mexican American

(*Continued*)

Abbreviations Used in Chapter 10 Continued

MHO	metabolically healthy obesity
MI	myocardial infarction
MICROS	Microisolates in South Tyrol Study
MORGAM	MONICA [Monitoring Trends and Determinants in Cardiovascular Disease], Risk, Genetics, Archiving and Monograph Project
MRI	magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease
NCDS	National Child Development Study
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIPPON DATA	National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in Aged
OR	odds ratio
OSA	obstructive sleep apnea
PA	physical activity
PAD	peripheral artery disease
PAR	population attributable risk
PREMA	Prediction of Metabolic Syndrome in Adolescence
PREVEND	Prevention of Renal and Vascular End-Stage Disease
PUFA	polyunsaturated fatty acid
RCT	randomized controlled trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
RV	right ventricular
SBP	systolic blood pressure
SCD	sudden cardiac death
SES	socioeconomic status
SNP	single-nucleotide polymorphism
SSB	sugar-sweetened beverage
VTE	venous thromboembolism
Waist circumf	waist circumference
WC	waist circumference
WHO	World Health Organization

individuals of non-European ancestry who have predominantly resided outside the United States.
— SBP ≥130 mm Hg or DBP ≥85 mm Hg or undergoing drug treatment for hypertension, or antihypertensive drug treatment in a patient with a history of hypertension

- The harmonized metabolic syndrome definition identifies a comparable risk group and predicts CVD risk similarly to the prior metabolic syndrome definitions.[1]
- There are many adverse health conditions that are related to metabolic syndrome but are not part of its clinical definition. These include NAFLD, sexual/reproductive dysfunction (erectile dysfunction in males and polycystic ovarian syndrome in females), OSA, certain forms of cancer, and possibly osteoarthritis, as well as a general proinflammatory and prothrombotic state.[2]
- Those with a fasting blood glucose ≥126 mg/dL, random or 2-hour postchallenge glucose ≥200 mg/dL, HbA_{1c} ≥6.5%, or taking hypoglycemic medication will normally be classified separately as having DM; many of these people will also have metabolic syndrome because of the presence of ≥2 of the additional risk factors noted above.
- Identification and treatment of metabolic syndrome fits closely with the current AHA 2020 Impact Goal, including emphasis on PA, healthy diet, and healthy weight for attainment of ideal BP, serum cholesterol, and fasting blood glucose. Monitoring the prevalence of metabolic syndrome is a secondary metric in the 2020 Impact Goals. Identification of metabolic syndrome represents a call to action for the healthcare provider and patient to address the underlying lifestyle-related risk factors. A multidisciplinary team of healthcare professionals is desirable to adequately address these multiple issues in patients with metabolic syndrome.[3]
- Despite its high prevalence (see Prevalence of Metabolic Syndrome), the public's recognition of metabolic syndrome is limited.[4] Making a diagnosis of metabolic syndrome and communicating with the patient about it may increase risk perception and motivation toward a healthier behavior.[5]

Prevalence of Metabolic Syndrome

Youth

- Metabolic syndrome should be diagnosed with caution in children and adolescents, because its categorization is not stable in these age groups.[6]
- Approximately half of the 1098 adolescent participants in the Princeton School District Study diagnosed with pediatric Adult Treatment Panel III metabolic syndrome lost the diagnosis over 3 years of follow-up.[7]
- In children 6 to 17 years of age participating in research studies in a single clinical research hospital, the diagnosis of metabolic syndrome was unstable in 46% of cases after a mean of 5.6 years of follow-up.[8]
- In the HCHS/SOL Youth, the prevalence of metabolic syndrome among children 10 to 16 years of age varied according to the clinical definition used, with only 1 participant being classified as having metabolic syndrome by all 3 clinical definitions.[9]
- Although metabolic syndrome categorization is generally unstable at younger ages, a single grouping of cardiometabolic risk factors was identified in a confirmatory factor analysis and shown to be present across the spectrum from children to adults.[10] However, a separate confirmatory factor analysis in HCHS/SOL Youth showed that SBP and fasting glucose did not cluster with other metabolic syndrome components.[9]
- Uncertainty remains concerning the definition of the obesity component of metabolic syndrome in the pediatric population because it is age dependent. Therefore, use of BMI percentiles[11] and waist-height ratio[12] has been recommended. Using standard CDC and FitnessGram standards for pediatric obesity, the prevalence of metabolic syndrome in obese youth ranges from 19% to 35%.[11]

Adults (See Charts 10-1 and 10-2)

The following estimates include many who also have DM, in addition to those with metabolic syndrome without DM:

- Prevalence of metabolic syndrome varies by the definition used, with definitions such as that from the International Diabetes Federation and the harmonized definition suggesting lower thresholds for defining central obesity in European whites, Asians (in particular, South Asians), Middle Easterners, sub-Saharan Africans, and Hispanics, which results in higher prevalence estimates.[13]
- On the basis of NHANES 2007 to 2014, the overall prevalence of metabolic syndrome was 34.3% and was similar for males (35.3%) and females (33.3%).[14] The prevalence of metabolic syndrome increased with age, from 19.3% among people 20 to 39 years of age to 37.7% for people 40 to

59 years of age and 54.9% among people ≥60 years of age.

- In a recent meta-analysis of 26 609 young adults (aged 18–30 years) across 34 studies, the prevalence of metabolic syndrome was 4.8% to 7% depending on the definition used.[15]
- Using data from HCHS/SOL 2008 to 2011, the overall prevalence of metabolic syndrome among Hispanics/Latinos living in the United States was 34% among males and 36% among females (Chart 10-1); it increased with age, with the highest prevalence in females 70 to 74 years of age (Chart 10-2). In males and females, the lowest prevalence of metabolic syndrome was observed among South Americans (27%). In males, the highest prevalence was observed in Cubans (35%), and in females, the highest prevalence was observed among Puerto Ricans (41%). Some differences in individual components existed by specific Hispanic/Latino background (Chart 10-1).[16]
- Among African Americans in the JHS, the overall prevalence of metabolic syndrome was 34%, and it was higher in females than in males (40% versus 27%, respectively).[17]
- Filipinos in the United States are at high risk for metabolic syndrome at lower BMI levels.[18]
- The prevalence of metabolic syndrome has been noted to be high among select special populations, including those with schizophrenia spectrum disorders[19]; those taking atypical antipsychotic drugs[20]; those receiving prior solid organ transplants[21]; those receiving prior hematopoietic cell transplantation[22]; HIV-infected individuals[23]; those previously treated for blood cancers[24]; those with systemic inflammatory disorders such as psoriasis,[25] systemic lupus erythematosus,[26] and rheumatoid arthritis[27]; those with multiple sclerosis[28]; individuals with well-controlled type 1 DM[29]; those with hypopituitarism[30]; those with prior gestational DM[31]; those with prior pregnancy-induced hypertension[32]; veterans with war-related bilateral lower-limb amputation[33] or spinal cord injury[34]; and individuals in select professions, including law enforcement[35] and firefighters.[36]
- Perhaps most important with respect to meeting the 2020 goals, the prevalence of metabolic syndrome increases with greater cumulative life-course exposure to sedentary behavior and physical inactivity[37]; screen time, including television viewing[38]; fast food intake[39]; short sleep duration[40]; and intake of SSBs.[41,42] Each of these risk factors is reversible with lifestyle change.[37–42]

Secular Trends of Metabolic Syndrome

Youth
(See Chart 10-3)

- Data from NHANES 2009 to 2012 suggest that the prevalence of metabolic syndrome is decreasing in 12- to 19-year-olds. This appears to be correlated with increases in HDL-C and decreases in levels of triglycerides despite a persistently increasing level of obesity. The lifestyle factors that correlate with decreasing metabolic syndrome are less carbohydrate intake and more unsaturated fat intake (Chart 10-3).[43]

Adults
(See Charts 10-4 through 10-8)

- On the basis of data from NHANES 2001 to 2010, after declining from NHANES 2001 to 2002 to NHANES 2005 to 2006, the age-adjusted prevalence of metabolic syndrome in the United States went up in the 2007 to 2008 cycle and then declined again in the 2009 to 2010 cycle (Chart 10-4).[44]
- In a recent updated analysis of NHANES 2007 to 2014, the prevalence of metabolic syndrome was stable for males and females (Chart 10-5).[14] The prevalence remained stable for all age and racial/ethnic subgroups (P>0.10).
- Prevalence of metabolic syndrome was lower in NH black males than white males and Mexican American males in the NHANES cycle 1999 to 2010 (Chart 10-6).[45]
- Prevalence of metabolic syndrome was higher in Mexican American females than white and black females in the NHANES cycle 1999 to 2010 (Chart 10-7).[45]
- The changing trends in the age-adjusted prevalence of metabolic syndrome are attributable to changes in the prevalence of its individual components. From NHANES data cycles 1999 through 2010, hypertriglyceridemia and elevated BP were lower in the total population, whereas hyperglycemia and elevated WC were higher in the total population; however, these trends varied significantly by sex and race/ethnicity (Chart 10-8). Differences in the prevalence statistics are the result of different handling of age adjustment as the prevalence of metabolic syndrome increases with age and handling of medication therapy for its component conditions.[45]

Natural History and Progression of Metabolic Syndrome

(See Chart 10-9)

- Preclinical forms of metabolic syndrome are commonly progressive and precede the development of overt metabolic syndrome. In the ARIC study, a sex- and race/ethnicity-specific metabolic syndrome severity score increased in 76% of participants, with faster progression observed in younger participants and in females. The metabolic syndrome severity score predicted time to development of incident metabolic syndrome over a mean 10-year follow-up (1987–1989 to 1996–1998). In ARIC, prevalence of metabolic syndrome increased from 33% to 50% over the mean 10-year follow-up, with differences by age and sex. The prevalence of metabolic syndrome was lower in African American males than in white males at all time points and for all ages across the study. African American females had higher prevalence of metabolic syndrome than white females at baseline and subsequent time points for all ages except for those >60 years of age (Chart 10-9).[46]

- Isolated metabolic syndrome, which could be considered an earlier form of metabolic syndrome, has been defined as those with ≥3 metabolic syndrome components but without overt hypertension and DM. In a population-based random sample of 2042 residents of Olmsted County, MN, those with isolated metabolic syndrome were found to be at increased risk of incident hypertension, DM, diastolic dysfunction, and reduced renal function (GFR <60 mL/min) compared with healthy control subjects ($P<0.05$). However, isolated metabolic syndrome was not significantly associated with higher rates of mortality ($P=0.12$) or development of HF ($P=0.64$) over the 8-year follow-up.[47]

Cost and Healthcare Utilization in Metabolic Syndrome

- Metabolic syndrome is associated with increased healthcare use and healthcare-related costs among individuals with and without DM. Overall, healthcare costs increase by ≈24% for each additional metabolic syndrome component present.[48]
- The presence of metabolic syndrome increases the risk for postoperative complications, including prolonged hospital stay and risk for blood transfusion, surgical site infection, and respiratory failure, across various surgical populations.[49–51]

Complications of Metabolic Syndrome

Youth

- Few prospective pediatric studies have examined the future risk for CVD or DM according to baseline metabolic syndrome status. Data from 771 participants 6 to 19 years of age from the NHLBI's Lipid Research Clinics Princeton Prevalence Study and the Princeton Follow-up Study showed that the risk of developing CVD was substantially higher among those with metabolic syndrome than among those without this syndrome (OR, 14.6 [95% CI, 4.8–45.3]) who were followed up for 25 years.[52]
- In an international childhood cardiovascular cohort consortium that included 5803 participants in 4 cohort studies (Cardiovascular Risk in Young Finns, Bogalusa Heart Study, Princeton Lipid Research Study, and Insulin Study) with a mean follow-up period of 22.3 years, childhood metabolic syndrome and overweight were associated with a >2.4-fold risk for adult metabolic syndrome from the age of 5 years onward.[53] The risk for type 2 DM was increased beginning at the age of 8 years (RR, 2.6 [95% CI, 1.4–6.8]) onward based on international cutoff values for definition of childhood metabolic syndrome. Risk of carotid IMT was increased beginning at age 11 years (RR, 2.44 [95% CI, 1.55–3.55]) using the same definition. Notably, BMI measurement alone at the same age points provided similar findings for type 2 DM and subclinical atherosclerosis.
- In a study of 6328 subjects from 4 prospective studies, compared with people with normal BMI as children and as adults, those with consistently high adiposity from childhood to adulthood had an increased risk of the following metabolic syndrome components: hypertension (RR, 2.7 [95% CI, 2.2–3.3]), low HDL-C (RR, 2.1 [95% CI, 1.8–2.5]), elevated triglycerides (RR, 3.0 [95% CI, 2.4–3.8]), and type 2 DM (RR, 5.4 [95% CI, 3.4–8.5]). Individuals who were overweight or had obesity during childhood but did not have obesity as adults had no increased risk compared with those with consistently normal BMI.[54]
- Among 1757 youths from the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study, those with metabolic syndrome in youth and adulthood were at 3.4 times increased risk of high carotid IMT and 12.2 times increased risk of type 2 DM in adulthood as those without metabolic syndrome at either time. Adults whose metabolic syndrome had resolved after their youth were at no increased risk of having high IMT or type 2 DM.[55]
- In the Princeton Lipid Research Cohort Study, metabolic syndrome severity scores during childhood were lowest among those who never developed CVD and were proportionally higher progressing

from those who developed early CVD (mean 38 years old) to those who developed CVD later in life (mean 50 years old).[56] Metabolic syndrome severity score was also strongly associated with early onset of DM.[57] Similarly, metabolic syndrome score, based on the number of components of metabolic syndrome, was associated with biomarkers of inflammation, endothelial damage, and CVD risk in a separate cohort of 677 prepubertal children.[58]

Adults

Metabolic Syndrome and CVD Morbidity and Mortality

- A meta-analysis of prospective studies concluded that metabolic syndrome increased the risk of developing CVD (summary RR, 1.78 [95% CI, 1.58–2.00]).[59] The RR of CVD tended to be higher in females (summary RR, 2.63) than in males (summary RR, 1.98; *P*=0.09). On the basis of results from 3 studies, metabolic syndrome was associated with an increased risk of cardiovascular events after adjustment for the individual components of the syndrome (summary RR, 1.54 [95% CI, 1.32–1.79]). Metabolic syndrome is also associated with incident CVD independent of the baseline subclinical CVD.[60] A meta-analysis among 87 studies comprising 951 083 subjects showed an even higher risk of CVD associated with metabolic syndrome (summary RR, 2.35 [95% CI, 2.02–2.73]), with significant increased risks (RRs ranging from 1.6 to 2.9) for all-cause mortality, CVD mortality, MI, and stroke, as well as for those with metabolic syndrome without DM.[61]
- The cardiovascular risk associated with metabolic syndrome varies on the basis of the combination of metabolic syndrome components present. Of all possible ways to have 3 metabolic syndrome components, the combination of central obesity, elevated BP, and hyperglycemia conferred the greatest risk for CVD (HR, 2.36 [95% CI, 1.54–3.61]) and mortality (HR, 3.09 [95% CI, 1.93–4.94]) in the Framingham Offspring Study.[62]
- Data from the Aerobics Center Longitudinal Study indicate that risk for CVD mortality is increased in males without DM who have metabolic syndrome (HR, 1.8 [95% CI, 1.5–2.0]); however, among those with metabolic syndrome, the presence of DM is associated with even greater risk for CVD mortality (HR, 2.1 [95% CI, 1.7–2.6]).[63]
- In a recent meta-analysis of 20 prospective cohort studies that included 57 202 adults aged ≥60 years, metabolic syndrome was associated with increased risk of all-cause mortality (RR, 1.20 [95% CI, 1.05–1.38] for males and 1.22 [95% CI, 1.02–1.44] for females) and CVD mortality (RR, 1.29 [95% CI, 1.09–1.53] for males and 1.20 [95%, 0.91–1.60] for females).[64] There was significant heterogeneity across the studies (all-cause mortality, I^2=55.9%, *P*=0.001; CVD mortality, I^2=58.1%, *P*=0.008). In subgroup analyses, the association of metabolic syndrome with CVD and all-cause mortality varied by geographic location, sample size, definition of metabolic syndrome, and adjustment for frailty.
- The impact of the metabolic syndrome on mortality has been shown to be modified by objective sleep duration.[65] In data from the Penn State Adult Cohort, a prospective population-based study of sleep disorders, objectively measured short sleep duration (<6 hours) was associated with increased all-cause (HR, 1.99 [95% CI, 1.53–2.59]) and CVD mortality (HR, 2.10 [95% CI, 1.39–3.16]), whereas sleep ≥6 hours was not associated with increased all-cause (HR, 1.29 [95% CI, 0.89–1.87]) or CVD (HR, 1.49 [95% CI, 0.75–2.97]) mortality among participants with metabolic syndrome.
- In the INTERHEART case-control study of 26 903 subjects from 52 countries, metabolic syndrome was associated with an increased risk of MI, both according to the WHO (OR, 2.69 [95% CI, 2.45–2.95]) and the International Diabetes Federation (OR, 2.20 [95% CI, 2.03–2.38]) definitions, with a PAR of 14.5% (95% CI, 12.7%–16.3%) and 16.8% (95% CI, 14.8%–18.8%), respectively, and associations that were similar across all regions and ethnic groups. In addition, the presence of ≥3 risk factors with subthreshold values was associated with increased risk of MI (OR, 1.50 [95% CI, 1.24–1.81]) compared with having "normal" values. Similar results were observed when the International Diabetes Federation definition was used.[66]
- In the Three-City Study, among 7612 participants aged ≥65 years who were followed up for 5.2 years, metabolic syndrome was associated with increased total CHD (HR, 1.78 [95% CI, 1.39–2.28]) and fatal CHD (HR, 2.40 [95% CI, 1.41–4.09]); however, metabolic syndrome was not associated with CHD beyond its individual risk components.[67]
- Among 3414 patients with stable CVD and atherogenic dyslipidemia who were treated intensively with statins in the AIM-HIGH trial, neither the presence of metabolic syndrome or the number of metabolic syndrome components was associated with cardiovascular outcomes, including

coronary events, ischemic stroke, nonfatal MI, CAD death, or the composite end point.[68]

- Metabolic syndrome is also associated with risk of incident stroke.[69] In a recent meta-analysis of 16 studies including 116 496 participants who were initially free of CVD, those with metabolic syndrome had a significantly high risk of incident stroke (pooled RR, 1.70 [95% CI, 1.49–1.95]) compared with those without metabolic syndrome. This effect was most notable among females (RR, 1.83 [95% CI, 1.31–2.56]) compared with males (RR, 1.47 [95% CI, 1.22–1.78]). Finally, those with metabolic syndrome had the highest risk for ischemic stroke (RR, 2.12 [95% CI, 1.46–3.08]) rather than hemorrhagic stroke (RR, 1.48 [95% CI, 0.98–2.24]).
- It is estimated that 13.3% to 44% of the excess CVD mortality in the United States, compared with other countries such as Japan, is explained by metabolic syndrome or metabolic syndrome–related existing CVD.[70]
- In the ARIC study, among 13 168 participants with a median follow-up of 23.6 years, metabolic syndrome was independently associated with an increased risk of SCD (adjusted HR, 1.70 [95% CI, 1.37–2.12]; *P*<0.001).[71] In addition, the risk of SCD varied according to the number of metabolic syndrome components (HR=1.31 per additional component of the metabolic syndrome [95% CI, 1.19–1.44]; *P*<0.001), independent of race or sex.
- Metabolic syndrome has also been associated with incident AF,[72] recurrent AF after ablation,[73] HF,[74] and PAD.[75]
- Using the 36 cohorts represented in the MORGAM Project, the association between metabolic syndrome and CVD varied by age for females but not males.[76]

Metabolic Syndrome and Subclinical CVD

- In MESA, among 6603 people aged 45 to 84 years (1686 [25%] with metabolic syndrome without DM and 881 [13%] with DM), subclinical atherosclerosis assessed by CAC was more severe in people with metabolic syndrome and DM than in those without these conditions, and the extent of CAC was a strong predictor of CHD and CVD events in these groups.[77] There appears to be a synergistic relationship between metabolic syndrome, NAFLD, and prevalence of CAC,[78,79] as well as a synergistic relationship with smoking.[80] Furthermore, the progression of CAC was greater in people with metabolic syndrome and DM than in those without, and progression of CAC predicted future CVD event risk both in those with metabolic syndrome and in those with DM.[81] In MESA, the prevalence of thoracic calcification was 33% for people with metabolic syndrome compared with 38% for those with DM (with and without metabolic syndrome) and 24% of those with neither DM nor metabolic syndrome.[82]
- In the DESIR cohort, metabolic syndrome was associated with an unfavorable hemodynamic profile, including increased brachial central pulse pressure and increased pulse-pressure amplification, compared with similar individuals with isolated hypertension but without metabolic syndrome.[83] In MESA, metabolic syndrome was associated with major and minor electrocardiographic abnormalities, although this varied by sex.[84] Metabolic syndrome is associated with reduced heart rate variability and altered cardiac autonomic modulation in adolescents.[85]
- Individuals with metabolic syndrome have a higher degree of endothelial dysfunction than individuals with a similar burden of traditional cardiovascular risk factors.[86] Furthermore, individuals with both metabolic syndrome and DM have demonstrated increased microvascular and macrovascular dysfunction.[87] Metabolic syndrome is associated with increased thrombosis, including increased resistance to aspirin[88] and clopidogrel loading.[89]
- In a recent meta-analysis of 8 population-based studies that included 19 696 patients (22.2% with metabolic syndrome), metabolic syndrome was associated with higher carotid IMT (standard mean difference 0.28±0.06 [95% CI, 0.16–0.40]; *P*=0.00003) and higher prevalence of carotid plaques than in individuals without metabolic syndrome (pooled OR, 1.61 [95% CI, 1.29–2.01]; *P*<0.0001).[90]
- In modern imaging studies using echocardiography, MRI, cardiac CT, and positron emission tomography, metabolic syndrome has been shown to be closely related to increased epicardial adipose tissues,[91] regional neck fat distribution,[92] increased visceral fat in other locations,[93] increased ascending aortic diameter,[94] high-risk coronary plaque features including increased necrotic core,[95] impaired coronary flow reserve,[96] abnormal indices of LV strain,[97] LV diastolic dysfunction,[98] LV dysynchrony,[99] and subclinical RV dysfunction.[100]

Metabolic Syndrome and Non-CVD Complications

- Metabolic syndrome has been associated with erectile dysfunction,[101] DM,[102] cancer[103,104] (in particular, breast, endometrial, prostate, pancreatic, hepatic, colorectal, and renal), cirrhosis,[105] and cognitive decline.[106] Data from case-control studies, but not prospective studies, support an association with

VTE.[107] There may be an association with increased incident asthma.[108] In MESA, the prevalence of erectile dysfunction among participants aged 55 to 65 years with metabolic syndrome was 16% compared with 10% in their counterparts without metabolic syndrome (*P*<0.001).[101]

- In data from ARIC and JHS, metabolic syndrome was associated with an increased risk of DM (HR, 4.36 [95% CI, 3.83–4.97]), although the association was attenuated after adjustment for the individual components of the metabolic syndrome.[102] However, use of a continuous sex- and race-specific metabolic severity *Z* score was associated with increased risk of DM independent of individual metabolic syndrome components, and increases in this score over time conferred additional risk for DM independent of confounders.
- Metabolic syndrome is linked to poorer cancer outcomes, including increased risk of recurrence and overall mortality.[104] For example, in a retrospective study of 3662 males with low-risk prostate cancer who were treated with radical prostatectomy, metabolic syndrome was associated with higher perioperative complications (OR, 1.24 [95% CI, 1.04–1.49]; *P*=0.018).[109] In addition, a recent meta-analysis of 24 studies that included 132 589 males (17.4% with metabolic syndrome) showed that metabolic syndrome was associated with worse oncologic outcomes including biochemical recurrence and more aggressive tumor features in prostate cancer.[110]
- In data obtained from HCUP-NIS, hospitalized patients with a diagnosis of metabolic syndrome and cancer had significantly increased odds of adverse health outcomes, including increased postsurgical complications (OR, 1.20 [95% CI, 1.03–1.39] and 1.22 [95% CI, 1.09–1.37] for breast and prostate cancer, respectively).[49]
- In 25 038 black and white participants from the REGARDS study, metabolic syndrome was associated with increased risk of cancer-related mortality (HR, 1.22 [95% CI, 1.03–1.45]).[103] In race-stratified analysis, black participants with metabolic syndrome had significantly increased risk of cancer mortality compared with those without metabolic syndrome (HR, 1.32 [95% CI, 1.01–1.72]). The risk of cancer mortality increased more than 2-fold among those with 5 metabolic syndrome components (HR, 2.35 [95% CI, 1.01–5.51]).
- In data from NHANES III, metabolic syndrome was associated with total cancer mortality (HR, 1.33 [95% CI, 1.04–1.70]) and breast cancer mortality (HR, 2.1 [95% CI, 1.09–4.11]).[111]
- For some cancers, the risk estimate differs between sexes, populations, and the definitions of the metabolic syndrome used.[112]
- NAFLD, a spectrum of liver disease that ranges from isolated fatty liver to fatty liver plus inflammation (nonalcoholic steatohepatitis), is hypothesized to represent the hepatic manifestation of the metabolic syndrome. On the basis of data from NHANES 2011 to 2014, the overall prevalence of NAFLD among US adults was 21.9%.[113] In a prospective study of 4401 Japanese adults aged 21 to 80 years free of NAFLD at baseline, the presence of metabolic syndrome increased the risk for NAFLD in both males (adjusted OR, 4.00 [95% CI, 2.63–6.08]) and females (adjusted OR, 11.20 [95% CI, 4.85–25.87]).[114] In cross-sectional studies, an increase in the number of components of the metabolic syndrome was associated with underlying nonalcoholic steatohepatitis and advanced fibrosis in NAFLD.[113,115]

Risk Factors for Metabolic Syndrome

Genetics and Family History

- Investigation of genetic factors related to metabolic syndrome has shed some light on the underlying pathways and mediators. Several pleiotropic variants of genes of apolipoproteins (*APOE*, *APOC1*, *APOC3*, and *APOA5*), Wnt signaling pathway (*TCF7L2*), lipoproteins (*LPL, CETP*), mitochondrial proteins (*TOMM40*), gene transcription regulation (*PROX1*), cell proliferation (*DUSP9*), cyclic AMP signaling (*ADCY5*), oxidative LDL metabolism (*COLEC12*), and expression of liver-specific genes (*HNF1A*) have been identified across various racial/ethnic populations that could explain some of the correlated architecture of metabolic syndrome traits.[116–119]
- The minor G allele of the atrial natriuretic peptide genetic variant rs5068, which is associated with higher circulating atrial natriuretic peptide levels, has been associated with lower prevalence of metabolic syndrome in whites and African Americans.[120]
- SNPs of inflammatory genes (encoding interleukin 6, interleukin 1β, and interleukin 10) and plasma fatty acids, as well as interactions among these SNPs, are differentially associated with odds of metabolic syndrome.[121]

In Youth

- Risk of metabolic syndrome probably begins before birth. The PREMA Study showed that the coexistence of low birth weight, small head circumference, and parental history of overweight or obesity places children at the highest risk for metabolic syndrome in adolescence. Other risk factors identified included parental history of DM, gestational hypertension in the mother, and lack of breastfeeding.[122] However, a recent RCT that tested a breastfeeding promotion intervention did not lead to reduced childhood metabolic syndrome among healthy term infants.[123]

- In NHANES, adolescents 12 to 19 years old were at greater risk of metabolic syndrome if they had concurrent exposure to secondhand smoke and low exposure to certain nutrients (vitamin E and omega-3 polyunsaturated fatty acids)[124] and if they consumed more sugar in their diet.[125]

In Adults

- There is a bidirectional relationship between metabolic syndrome and depression. In prospective studies, the presence of depression increases the risk of metabolic syndrome (OR, 1.49 [95% CI, 1.19–1.87]), whereas metabolic syndrome increases the risk of depression (OR, 1.52 [95% CI, 1.20–1.91]).[126]
- In prospective or retrospective cohort studies, the following factors have been reported as being directly associated with incident metabolic syndrome, defined by 1 of the major definitions: age,[45] low educational attainment,[127,128] low SES,[129] not being able to understand or read food labels,[130] everyday discrimination,[131] urbanization,[132] smoking,[127,129,133] parental smoking,[134] low levels of PA,[127,129,133] low levels of physical fitness,[135,136] intake of soft drinks,[137] intake of diet soda,[138] fructose intake,[139] magnesium intake,[140,141] energy intake,[142] carbohydrate intake,[128,133,143] total fat intake,[144] meat intake (red but not white meat),[145] intake of fried foods,[138] skipping breakfast,[146] heavy alcohol consumption,[147] abstention from alcohol use,[128] parental history of DM,[144] long-term stress at work,[148] pediatric metabolic syndrome,[144] obesity or BMI,[55,62] childhood obesity,[149] intra-abdominal fat,[150] gain in weight or BMI,[142] weight fluctuation,[151] heart rate,[152] homeostasis model assessment,[153] fasting insulin,[153] 2-hour insulin,[153] proinsulin,[153] oxidized LDL-C,[154,155] HDL particle concentration,[156] LDL particle concentration,[156,157] lipoprotein-associated phospholipase A2,[158] uric acid,[159,160] γ-glutamyltransferase,[161,162] alanine transaminase,[161] plasminogen activator inhibitor-1,[163] fibroblast growth factor 21,[164] aldosterone,[163] leptin,[165] ferritin,[166] CRP,[167,168] adipocyte–fatty acid binding protein,[169] testosterone and sex hormone–binding globulin,[170,171] matrix metalloproteinase 9,[172] active periodontitis,[173] and urinary bisphenol A levels.[174] In cross-sectional studies, a high-salt diet,[175] stress,[176] low cardiorespiratory fitness,[177] cancer antigen 19-9,[177,178] erythrocyte parameters[179] such as hemoglobin level and red blood cell distribution width, excessive dietary calcium (>1200 mg/d) in males,[180] and OSA[181] were significant predictors of metabolic syndrome.
- The following factors have been reported as being inversely associated with incident metabolic syndrome, defined by 1 of the major definitions, in prospective or retrospective cohort studies: muscular strength,[182] increased PA or physical fitness,[133,183] aerobic training,[184] moderate alcohol intake,[185] fiber intake,[186,187] fruits and vegetables,[188] white fish intake,[189] Mediterranean diet,[190] dairy consumption[138] (particularly yogurt and low-fat dairy products),[191] consumption of fermented milk with *Lactobacillus plantarum*,[192] animal or fat protein,[193] hot tea consumption (but not sugar-sweetened iced tea),[194] coffee consumption,[195] vitamin D intake,[196] intake of tree nuts,[197] walnut intake,[198] avocado intake,[199] intake of long-chain omega-3 PUFA,[200] potassium intake,[201] ability to interpret nutrition labels,[130] living at geographically higher elevation,[202] insulin sensitivity,[153] ratio of aspartate aminotransferase to alanine transaminase,[203] total testosterone,[150,153,204] serum 25-hydroxyvitamin D,[205] sex hormone–binding globulin,[150,153,204] and Δ5-desaturase activity.[206] In cross-sectional studies, increased standing,[207] a vegetarian diet,[208] subclinical hypothyroidism in males,[209] marijuana use,[210] total antioxidant capacity from diet and dietary supplements,[211] and organic food consumption[212] were inversely associated with metabolic syndrome.
- In a pooled population of 117 020 patients (from 20 studies) with NAFLD diagnosed by serum liver enzymes (aminotransferases or γ-glutamyltransferase) or ultrasonography who were followed up for a median of 5 years (range, 3–14.7 years), NAFLD was associated with an increased risk of incident metabolic syndrome with a pooled RR of 1.80 (95% CI, 1.72–1.89) for alanine aminotransferase (last versus first quartile or quintile), 1.98 (95% CI, 1.89–2.07) for γ-glutamyltransferase, and 3.22 (95% CI, 3.05–3.41) for ultrasonography, respectively.[161]
- During >6 years of follow-up in the ARIC study, 1970 individuals (25%) developed metabolic syndrome, and compared with the normal-weight group (BMI <25 kg/m^2), the ORs of developing metabolic syndrome were 2.81 (95% CI, 2.50–3.17) and 5.24 (95% CI, 4.50–6.12) for the overweight (BMI 25–30 kg/m^2) and obese (BMI ≥30 kg/m^2) groups, respectively.[213]
- In a meta-analysis that included 76 699 participants and 13 871 incident cases of metabolic syndrome, there was a negative linear relationship between leisure-time PA and development of metabolic syndrome.[214] For every increase in 10 MET-hours per week (approximately equal to 150 minutes of moderate PA per week), risk of

metabolic syndrome was reduced by 10% (RR, 0.90 [95% CI, 0.86–0.94]).

Global Burden of Metabolic Syndrome (See Chart 10-10)

- Metabolic syndrome is becoming hyperendemic around the world. Recent evidence has described the prevalence of metabolic syndrome in Canada,[215] Latin America,[216] India,[217–219] Bangladesh,[220] Iran,[221] Nigeria,[222] South Africa,[223] Ecuador,[224] Nigeria,[225] and Vietnam,[226] as well as many other countries.
- On the basis of data from NIPPON DATA (1990–2005), the age-adjusted prevalence of metabolic syndrome in a Japanese population was 19.3%.[70] In a partially representative Chinese population, the 2009 age-adjusted prevalence of metabolic syndrome in China was 21.3%,[132] whereas in northwest China, the prevalence for 2010 was 15.1%.[227]
- In a report from BioSHaRE, which harmonizes modern data from 10 different population-based cohorts in 7 European countries, the age-adjusted prevalence of metabolic syndrome in obese subjects ranged from 24% to 65% in females and from ≈43% to ≈78% in males. In the obese population, the prevalence of metabolic syndrome far exceeded the prevalence of MHO, which had a prevalence of 7% to 28% in females and 2% to 19% in males. The prevalence of metabolic syndrome varied considerably by European country in the BioSHaRE consortium (Chart 10-10).[228]
- The prevalence of metabolic syndrome has been reported to be low (14.6%) in a population-representative study in France (the French Nutrition and Health Survey, 2006–2007) compared with other industrialized countries.[229]
- In a recent systematic review of 10 Brazilian studies, the weighted mean prevalence of metabolic syndrome in Brazil was 29.6%.[230]
- In a report from a representative survey of the northern state of Nuevo León, Mexico, the prevalence of metabolic syndrome in adults (≥16 years old) for 2011 to 2012 was 54.8%. In obese adults, the prevalence reached 73.8%. The prevalence in adult North Mexican females (60.4%) was higher than in adult North Mexican males (48.9%).[231]
- Metabolic syndrome is highly prevalent in modern indigenous populations, notably in Brazil and Australia. The prevalence of metabolic syndrome was estimated to be 41.5% in indigenous groups in Brazil,[230,231] 33.0% in Australian Aborigines, and 50.3% in Torres Strait Islanders.[232]

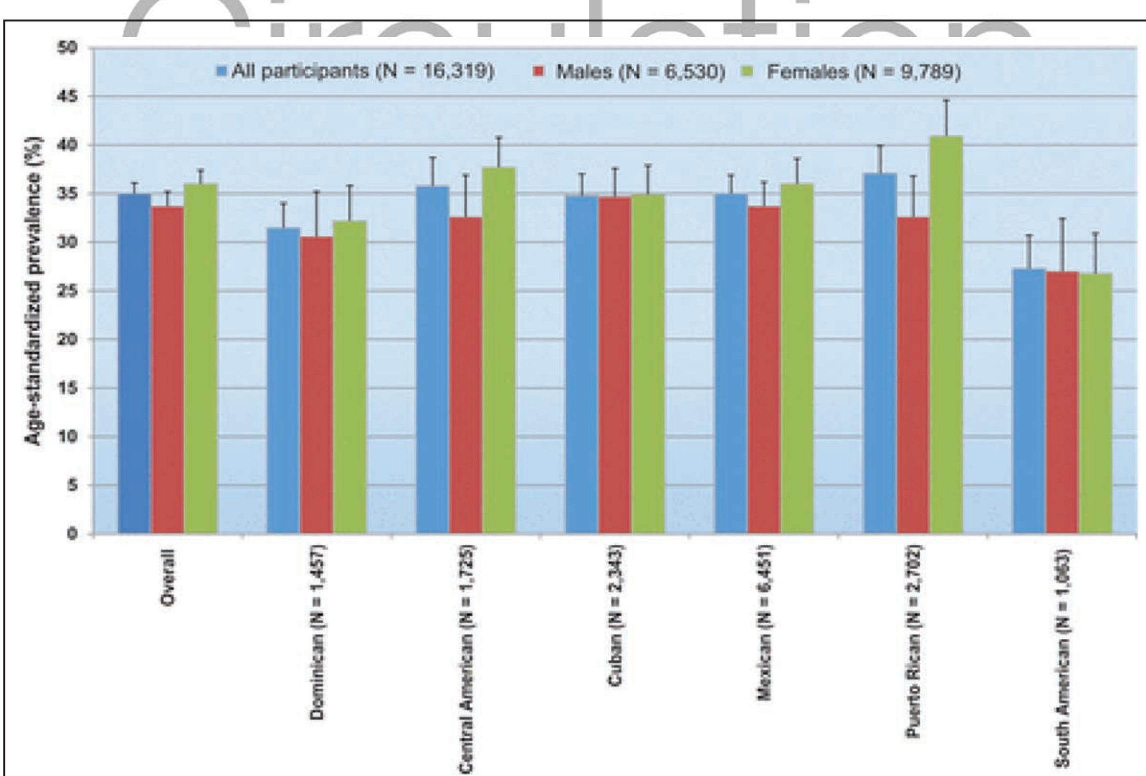

Chart 10-1. Age-standardized prevalence of metabolic syndrome by sex and Hispanic/Latino background, 2008 to 2011.
Values were weighted for survey design and nonresponse and were age standardized to the population described by the 2010 US census.
Source: Hispanic Community Health Study/Study of Latinos.[16]

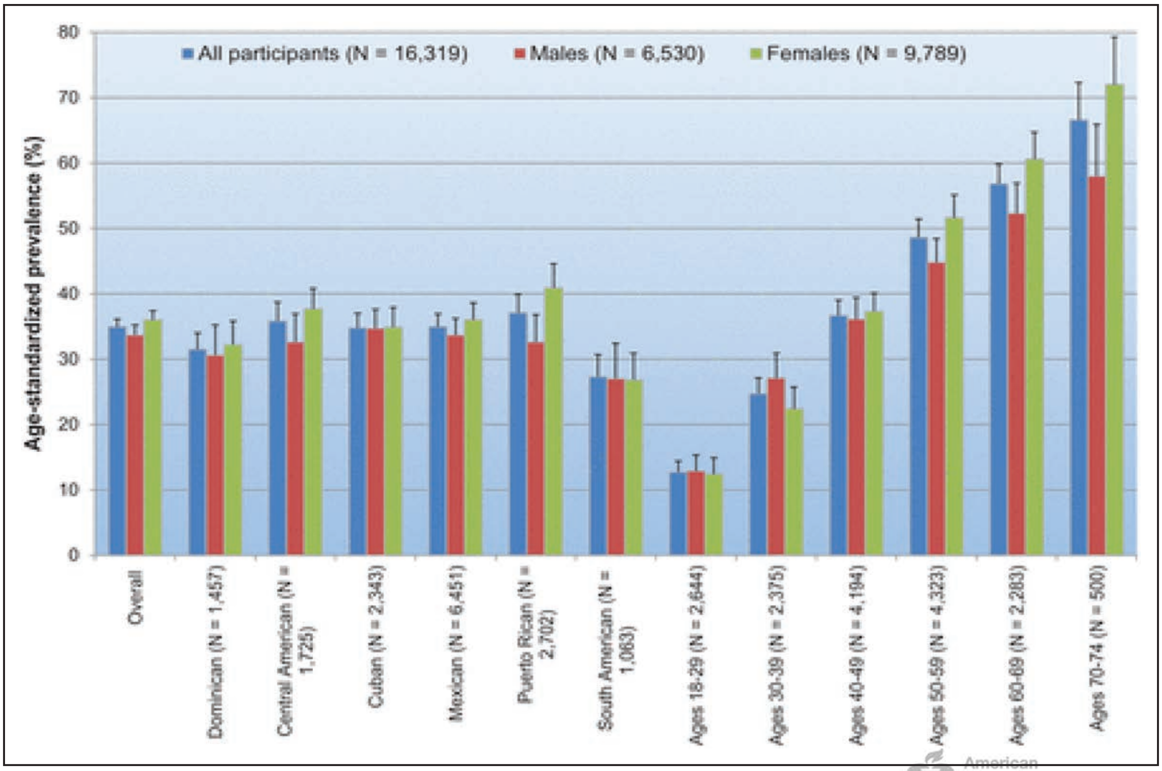

Chart 10-2. Age-standardized prevalence of metabolic syndrome by age and sex in Hispanics/Latinos, 2008 to 2011.
Values were weighted for survey design and nonresponse and were age standardized to the population described by the 2010 US census.
Source: Hispanic Community Health Study/Study of Latinos.[16]

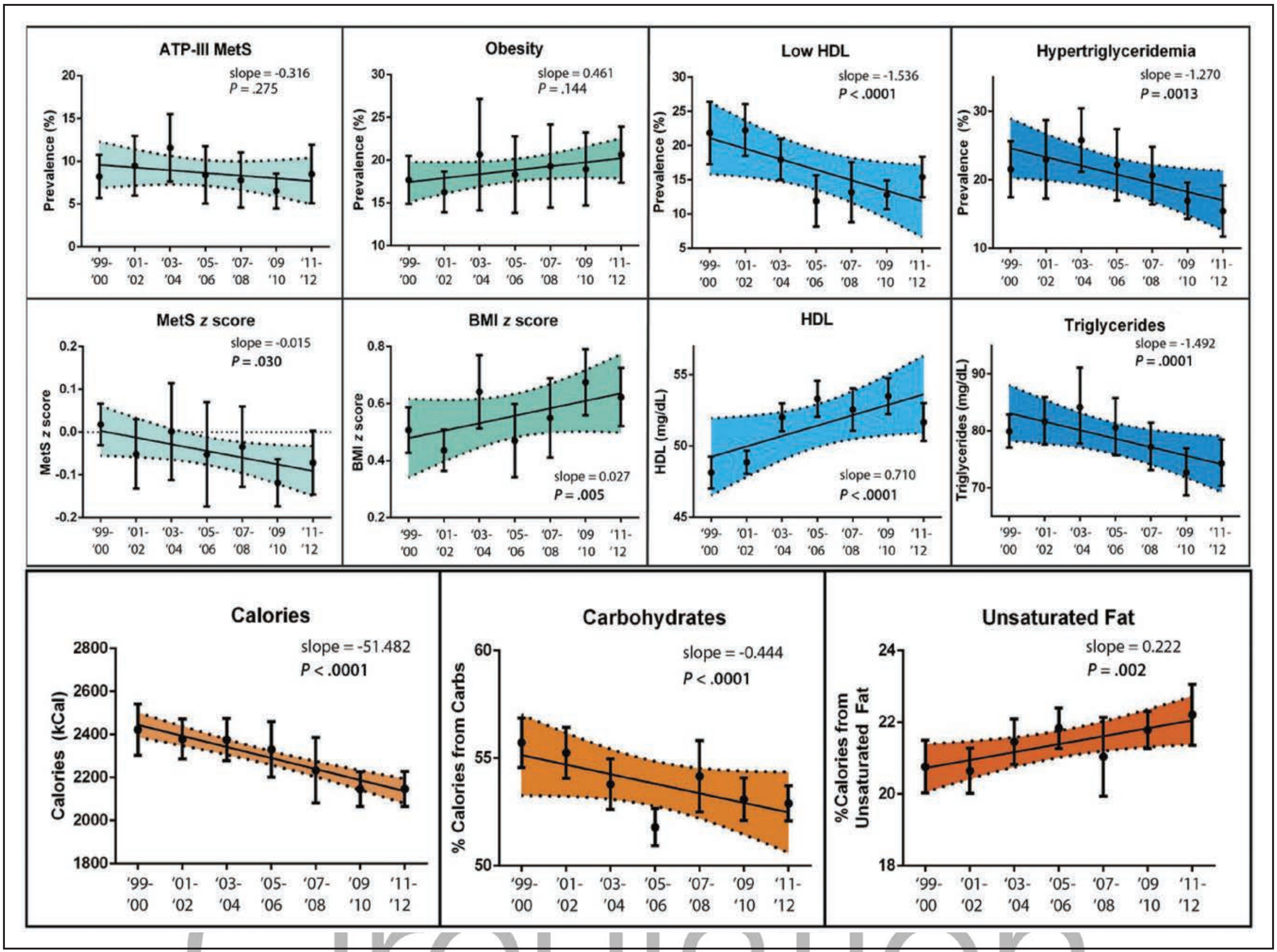

Chart 10-3. Prevalence of metabolic syndrome in youth.
ATP III indicates Adult Treatment Panel III; BMI, body mass index; Carbs, carbohydrates; HDL, high-density lipoprotein; and MetS, metabolic syndrome.
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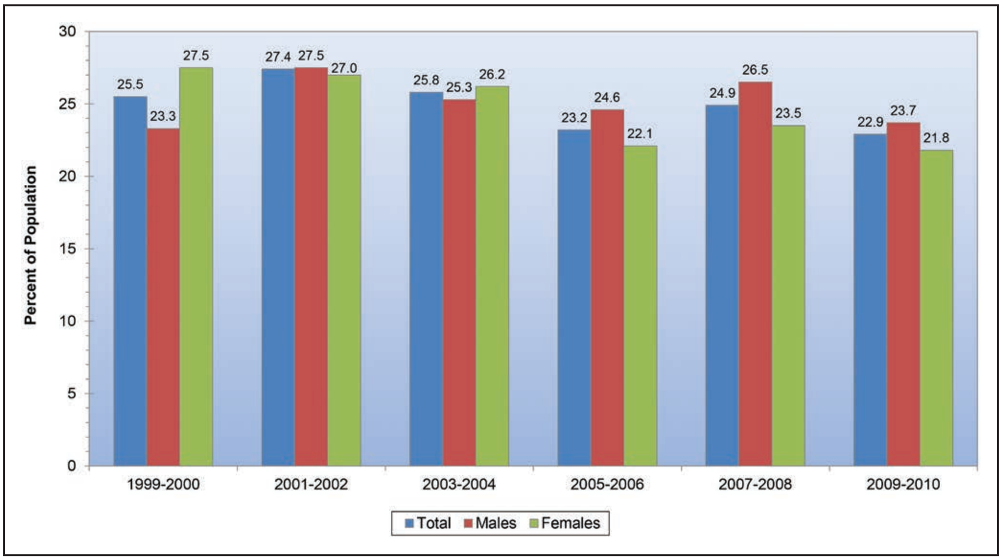

Chart 10-4. Age-adjusted prevalence of metabolic syndrome in the United States, NHANES, 1999 to 2010.
NHANES indicates National Health and Nutrition Examination Survey.
Data derived from Beltrán-Sánchez et al.[45]

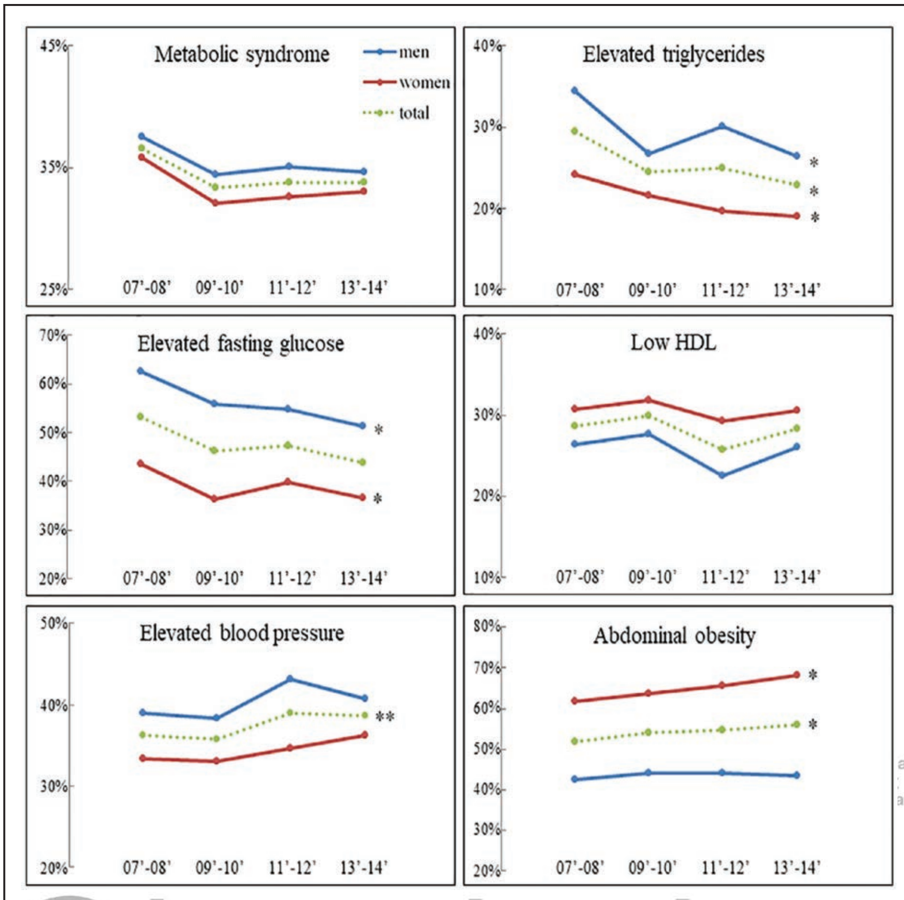

Chart 10-5. Sex-stratified trends in the age-adjusted weighted prevalence of metabolic syndrome and its components among US adults in 2007 to 2014, NHANES.
HDL indicates high-density lipoprotein; and NHANES, National Health and Nutrition Examination Survey.
Data derived from Shin et al.[14]

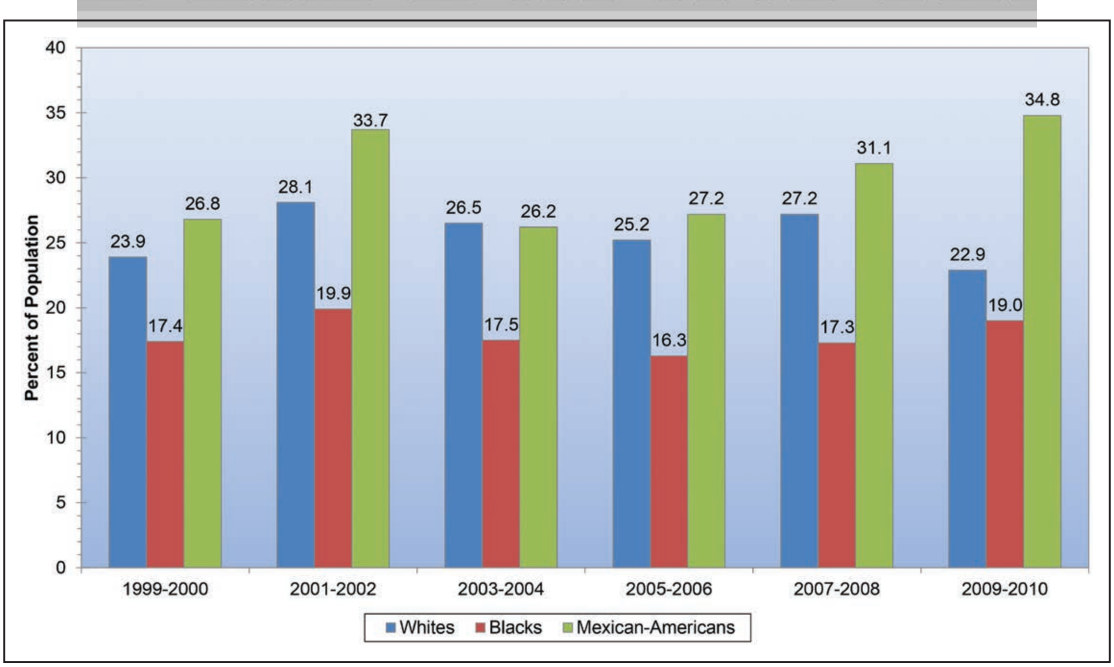

Chart 10-6. Age-adjusted prevalence of metabolic syndrome among males by race, NHANES, 1999 to 2010.
NHANES indicates National Health and Nutrition Examination Survey.
Data derived from Beltrán-Sánchez et al.[45]

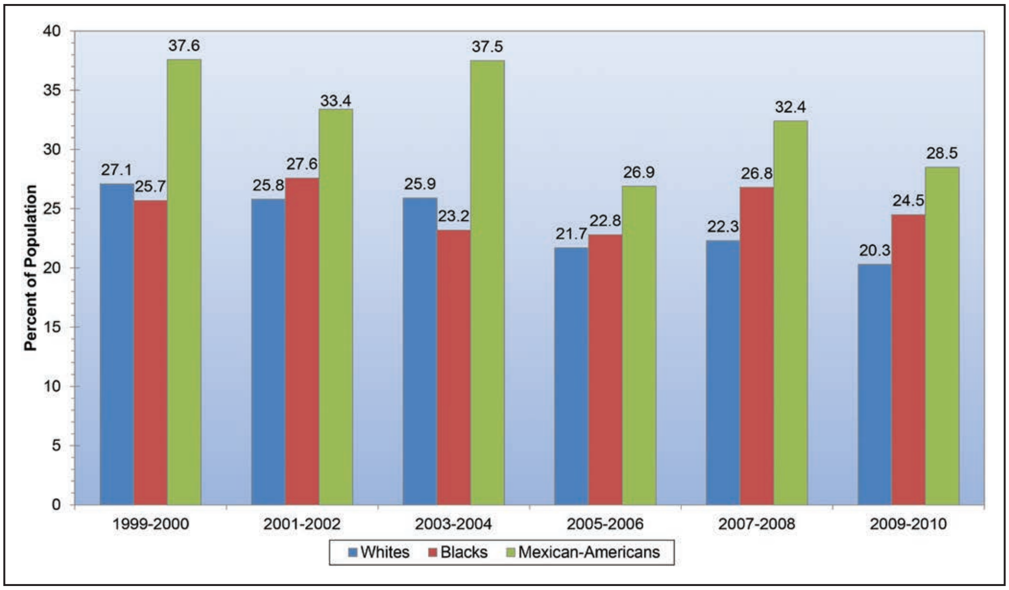

Chart 10-7. Age-adjusted prevalence of metabolic syndrome among females by race, NHANES, 1999 to 2010.
NHANES indicates National Health and Nutrition Examination Survey.
Data derived from Beltrán-Sánchez et al.[45]

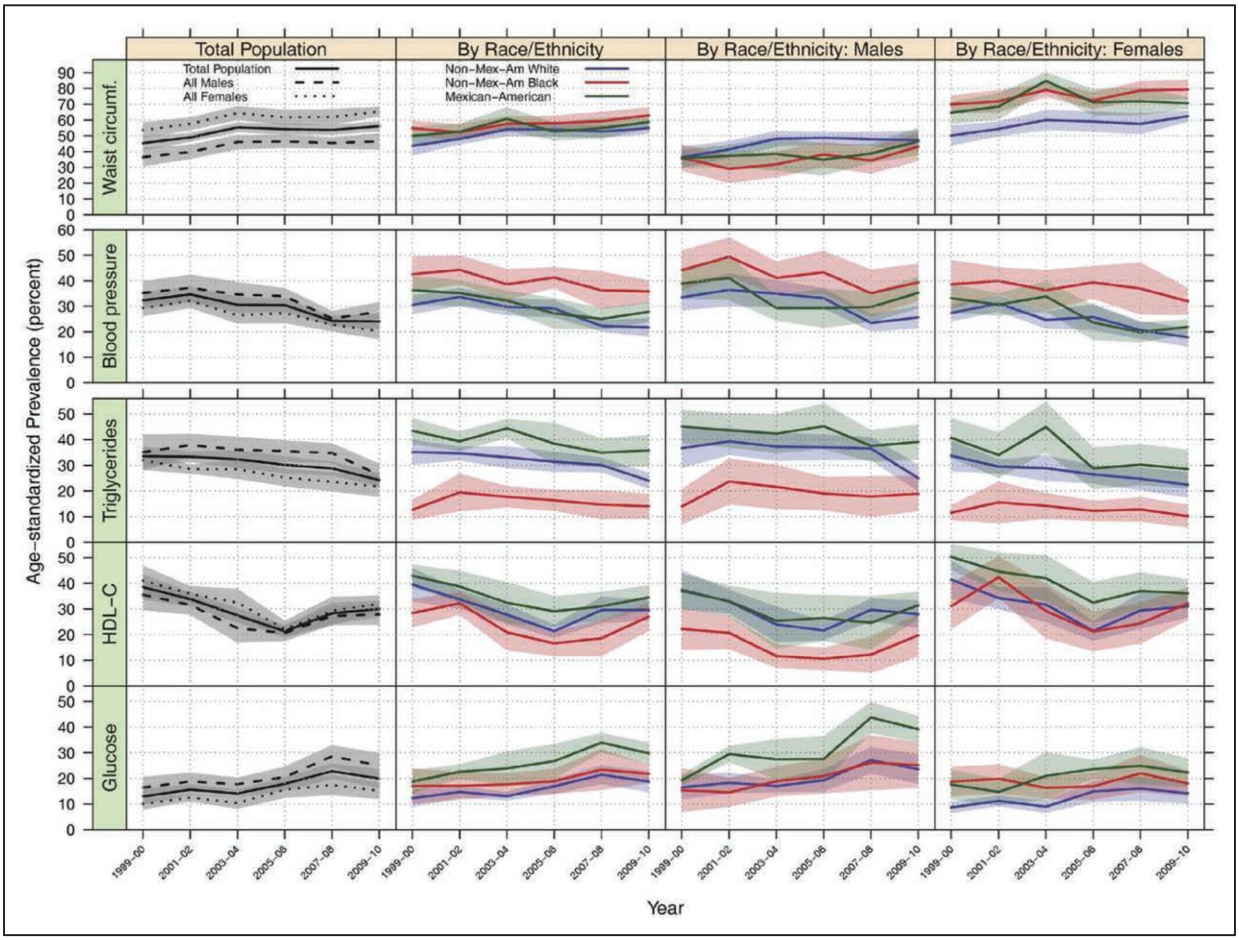

Chart 10-8. Prevalence and trends of the 5 components of metabolic syndrome in the adult US population (≥20 years old), 1999 to 2010, by sex (first column), race/ethnicity (second column), and race/ethnicity and sex (third and fourth columns).
Shaded areas represent 95% CIs.
HDL-C indicates high-density lipoprotein cholesterol; Mex-Am, Mexican American; and Waist circumf, waist circumference.
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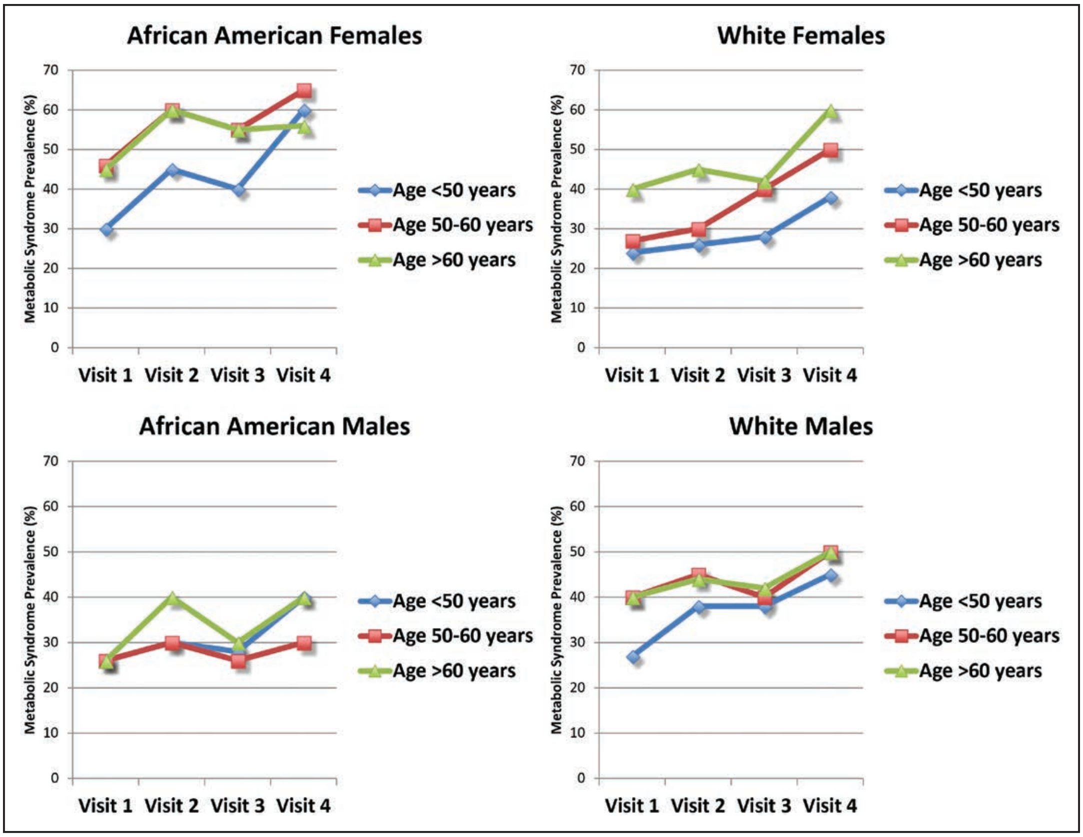

Chart 10-9. Ten-year progression of metabolic syndrome in the ARIC study, stratified by age, sex, and race/ethnicity.
ARIC indicates Atherosclerosis Risk in Communities Study.
Adapted from Vishnu et al[46] with permission from Elsevier. Copyright © 2015, Elsevier Ireland Ltd.

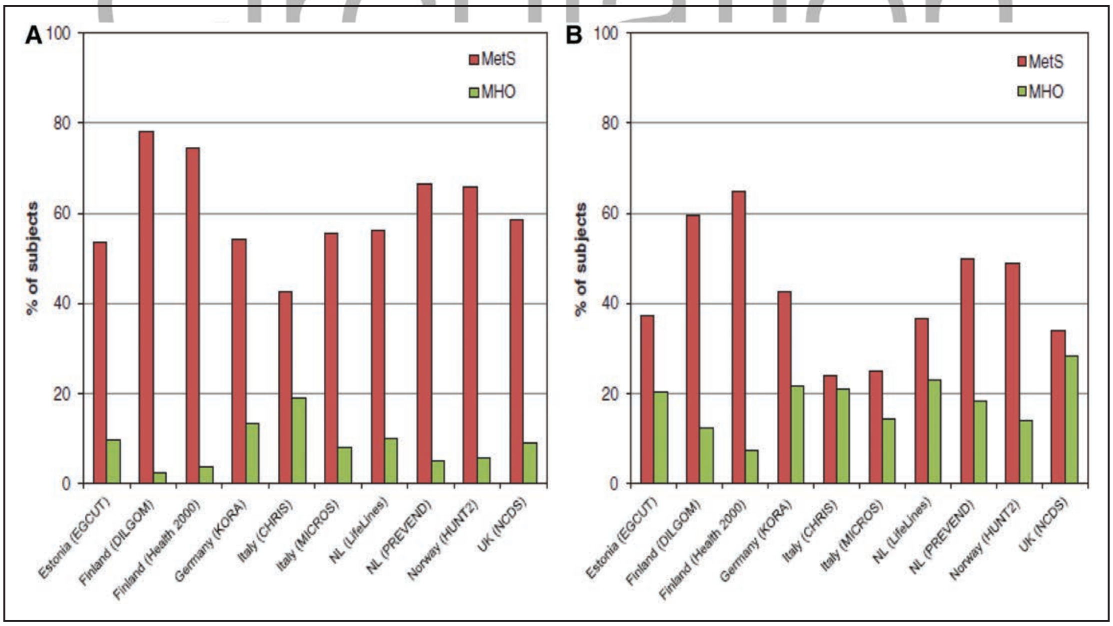

Chart 10-10. Age-standardized prevalence of MetS and MHO among obese (body mass index ≥30 kg/m²) males (A) and females (B) in different cohorts.
CHRIS indicates Collaborative Health Research in South Tyrol Study; DILGOM, Dietary, Lifestyle, and Genetics Determinants of Obesity and Metabolic Syndrome; EGCUT, Estonian Genome Center of the University of Tartu; HUNT2, Nord-Trøndelag Health Study; KORA, Cooperative Health Research in the Region of Augsburg; MetS, metabolic syndrome; MHO, metabolically healthy obesity; MICROS, Microisolates in South Tyrol Study; NCDS, National Child Development Study; NL, the Netherlands; and PREVEND, Prevention of Renal and Vascular End-Stage Disease.
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REFERENCES

1. Hari P, Nerusu K, Veeranna V, Sudhakar R, Zalawadiya S, Ramesh K, Afonso L. A gender-stratified comparative analysis of various definitions of metabolic syndrome and cardiovascular risk in a multiethnic U.S. population. *Metab Syndr Relat Disord*. 2012;10:47–55. doi: 10.1089/met.2011.0087
2. Tota-Maharaj R, Defilippis AP, Blumenthal RS, Blaha MJ. A practical approach to the metabolic syndrome: review of current concepts and management. *Curr Opin Cardiol*. 2010;25:502–512. doi: 10.1097/HCO.0b013e32833cd474
3. Bischoff SC, Boirie Y, Cederholm T, Chourdakis M, Cuerda C, Delzenne NM, Deutz NE, Fouque D, Genton L, Gil C, Koletzko B, Leon-Sanz M, Shamir R, Singer J, Singer P, Stroebele-Benschop N, Thorell A, Weimann A, Barazzoni R. Towards a multidisciplinary approach to understand and manage obesity and related diseases. *Clin Nutr*. 2017;36:917–938. doi: 10.1016/j.clnu.2016.11.007
4. Lewis SJ, Rodbard HW, Fox KM, Grandy S; SHIELD Study Group. Self-reported prevalence and awareness of metabolic syndrome: findings from SHIELD. *Int J Clin Pract*. 2008;62:1168–1176. doi: 10.1111/j.1742-1241.2008.01770.x
5. Jumean MF, Korenfeld Y, Somers VK, Vickers KS, Thomas RJ, Lopez-Jimenez F. Impact of diagnosing metabolic syndrome on risk perception. *Am J Health Behav*. 2012;36:522–532. doi: 10.5993/AJHB.36.4.9
6. Steinberger J, Daniels SR, Eckel RH, Hayman L, Lustig RH, McCrindle B, Mietus-Snyder ML. Progress and challenges in metabolic syndrome in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2009;119:628–647. doi: 10.1161/CIRCULATIONAHA.108.191394
7. Goodman E, Daniels SR, Meigs JB, Dolan LM. Instability in the diagnosis of metabolic syndrome in adolescents. *Circulation*. 2007;115:2316–2322. doi: 10.1161/CIRCULATIONAHA.106.669994
8. Gustafson JK, Yanoff LB, Easter BD, Brady SM, Keil MF, Roberts MD, Sebring NG, Han JC, Yanovski SZ, Hubbard VS, Yanovski JA. The stability of metabolic syndrome in children and adolescents. *J Clin Endocrinol Metab*. 2009;94:4828–4834. doi: 10.1210/jc.2008-2665
9. Reina SA, Llabre MM, Vidot DC, Isasi CR, Perreira K, Carnethon M, Parrinello CM, Gallo LC, Ayala GX, Delamater A. Metabolic syndrome in Hispanic Youth: results from the Hispanic Community Children's Health Study/Study of Latino Youth. *Metab Syndr Relat Disord*. 2017;15:400–406. doi: 10.1089/met.2017.0054
10. Viitasalo A, Lakka TA, Laaksonen DE, Savonen K, Lakka HM, Hassinen M, Komulainen P, Tompuri T, Kurl S, Laukkanen JA, Rauramaa R. Validation of metabolic syndrome score by confirmatory factor analysis in children and adults and prediction of cardiometabolic outcomes in adults. *Diabetologia*. 2014;57:940–949. doi: 10.1007/s00125-014-3172-5
11. Laurson KR, Welk GJ, Eisenmann JC. Diagnostic performance of BMI percentiles to identify adolescents with metabolic syndrome. *Pediatrics*. 2014;133:e330–e338. doi: 10.1542/peds.2013-1308
12. Khoury M, Manlhiot C, McCrindle BW. Role of the waist/height ratio in the cardiometabolic risk assessment of children classified by body mass index. *J Am Coll Cardiol*. 2013;62:742–751. doi: 10.1016/j.jacc.2013.01.026
13. Brown TM, Voeks JH, Bittner V, Safford MM. Variations in prevalent cardiovascular disease and future risk by metabolic syndrome classification in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Am Heart J*. 2010;159:385–391. doi: 10.1016/j.ahj.2009.12.022
14. Shin D, Kongpakpaisarn K, Bohra C. Trends in the prevalence of metabolic syndrome and its components in the United States 2007-2014. *Int J Cardiol*. 2018;259:216–219. doi: 10.1016/j.ijcard.2018.01.139
15. Nolan PB, Carrick-Ranson G, Stinear JW, Reading SA, Dalleck LC. Prevalence of metabolic syndrome and metabolic syndrome components in young adults: a pooled analysis. *Prev Med Rep*. 2017;7:211–215. doi: 10.1016/j.pmedr.2017.07.004
16. Heiss G, Snyder ML, Teng Y, Schneiderman N, Llabre MM, Cowie C, Carnethon M, Kaplan R, Giachello A, Gallo L, Loehr L, Avilés-Santa L. Prevalence of metabolic syndrome among Hispanics/Latinos of diverse background: the Hispanic Community Health Study/Study of Latinos. *Diabetes Care*. 2014;37:2391–2399. doi: 10.2337/dc13-2505
17. Khan RJ, Gebreab SY, Sims M, Riestra P, Xu R, Davis SK. Prevalence, associated factors and heritabilities of metabolic syndrome and its individual components in African Americans: the Jackson Heart Study. *BMJ Open*. 2015;5:e008675. doi: 10.1136/bmjopen-2015-008675
18. Abesamis CJ, Fruh S, Hall H, Lemley T, Zlomke KR. Cardiovascular health of Filipinos in the United States: a review of the literature. *J Transcult Nurs*. 2016;27:518–528. doi: 10.1177/1043659615597040
19. Correll CU, Robinson DG, Schooler NR, Brunette MF, Mueser KT, Rosenheck RA, Marcy P, Addington J, Estroff SE, Robinson J, Penn DL, Azrin S, Goldstein A, Severe J, Heinssen R, Kane JM. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. *JAMA Psychiatry*. 2014;71:1350–1363. doi: 10.1001/jamapsychiatry.2014.1314
20. Rojo LE, Gaspar PA, Silva H, Risco L, Arena P, Cubillos-Robles K, Jara B. Metabolic syndrome and obesity among users of second generation antipsychotics: a global challenge for modern psychopharmacology. *Pharmacol Res*. 2015;101:74–85. doi: 10.1016/j.phrs.2015.07.022
21. Sorice GP, Di Pizio L, Sun VA, Schirò T, Muscogiuri G, Mezza T, Cefalo CM, Prioletta A, Pontecorvi A, Giaccari A. Metabolic syndrome in transplant patients: an updating point of view. *Minerva Endocrinol*. 2012;37:211–220.
22. DeFilipp Z, Duarte RF, Snowden JA, Majhail NS, Greenfield DM, Miranda JL, Arat M, Baker KS, Burns LJ, Duncan CN, Gilleece M, Hale GA, Hamadani M, Hamilton BK, Hogan WJ, Hsu JW, Inamoto Y, Kamble RT, Lupo-Stanghellini MT, Malone AK, McCarthy P, Mohty M, Norkin M, Paplham P, Ramanathan M, Richart JM, Salooja N, Schouten HC, Schoemans H, Seber A, Steinberg A, Wirk BM, Wood WA, Battiwalla M, Flowers ME, Savani BN, Shaw BE. Metabolic syndrome and cardiovascular disease following hematopoietic cell transplantation: screening and preventive practice recommendations from CIBMTR and EBMT. *Bone Marrow Transplant*. 2017;52:173–182. doi: 10.1038/bmt.2016.203
23. Calza L, Colangeli V, Magistrelli E, Rossi N, Rosselli Del Turco E, Bussini L, Borderi M, Viale P. Prevalence of metabolic syndrome in HIV-infected patients naive to antiretroviral therapy or receiving a first-line treatment. *HIV Clin Trials*. 2017;18:110–117. doi: 10.1080/15284336.2017.1311502
24. Nottage KA, Ness KK, Li C, Srivastava D, Robison LL, Hudson MM. Metabolic syndrome and cardiovascular risk among long-term survivors of acute lymphoblastic leukaemia: from the St. Jude Lifetime Cohort. *Br J Haematol*. 2014;165:364–374. doi: 10.1111/bjh.12754
25. Rodríguez-Zúñiga MJM, García-Perdomo HA. Systematic review and meta-analysis of the association between psoriasis and metabolic syndrome. *J Am Acad Dermatol*. 2017;77:657–666.e8. doi: 10.1016/j.jaad.2017.04.1133
26. Sun C, Qin W, Zhang YH, Wu Y, Li Q, Liu M, He CD. Prevalence and risk of metabolic syndrome in patients with systemic lupus erythematosus: a meta-analysis. *Int J Rheum Dis*. 2017;20:917–928. doi: 10.1111/1756-185X.13153
27. Gomes KWP, Luz AJP, Felipe MRB, Beltrão LA, Sampaio AXC, Rodrigues CEM. Prevalence of metabolic syndrome in rheumatoid arthritis patients from Northeastern Brazil: association with disease activity. *Mod Rheumatol*. 2018;28:258–263. doi: 10.1080/14397595.2017.1316813
28. Sicras-Mainar A, Ruíz-Beato E, Navarro-Artieda R, Maurino J. Comorbidity and metabolic syndrome in patients with multiple sclerosis from Asturias and Catalonia, Spain. *BMC Neurol*. 2017;17:134. doi: 10.1186/s12883-017-0914-2
29. Chillarón JJ, Flores Le-Roux JA, Benaiges D, Pedro-Botet J. Type 1 diabetes, metabolic syndrome and cardiovascular risk. *Metabolism*. 2014;63:181–187. doi: 10.1016/j.metabol.2013.10.002
30. Verhelst J, Mattsson AF, Luger A, Thunander M, Góth MI, Koltowska-Häggström M, Abs R. Prevalence and characteristics of the metabolic syndrome in 2479 hypopituitary patients with adult-onset GH deficiency before GH replacement: a KIMS analysis. *Eur J Endocrinol*. 2011;165:881–889. doi: 10.1530/EJE-11-0599
31. Noctor E, Crowe C, Carmody LA, Kirwan B, O'Dea A, Glynn LG, McGuire BE, O'Shea PM, Dunne FP. ATLANTIC-DIP: prevalence of metabolic syndrome and insulin resistance in women with previous gestational diabetes mellitus by International Association of Diabetes in Pregnancy Study Groups criteria. *Acta Diabetol*. 2015;52:153–160. doi: 10.1007/s00592-014-0621-z
32. Facca TA, Mastroianni-Kirsztajn G, Sabino ARP, Passos MT, Dos Santos LF, Famá EAB, Nishida SK, Sass N. Pregnancy as an early stress test for cardiovascular and kidney disease diagnosis. *Pregnancy Hypertens*. 2018;12:169–173. doi: 10.1016/j.preghy.2017.11.008
33. Ejtahed HS, Soroush MR, Hasani-Ranjbar S, Angoorani P, Mousavi B, Masumi M, Edjtehadi F, Soveid M. Prevalence of metabolic syndrome and health-related quality of life in war-related bilateral lower limb amputees. *J Diabetes Metab Disord*. 2017;16:17. doi: 10.1186j/s40200-017-0298-2

34. Gater DR Jr, Farkas GJ, Berg AS, Castillo C. Prevalence of metabolic syndrome in veterans with spinal cord injury. *J Spinal Cord Med*. 2018:1–8. doi: 10.1080/10790268.2017
35. Zimmerman FH. Cardiovascular disease and risk factors in law enforcement personnel: a comprehensive review. *Cardiol Rev*. 2012;20:159–166. doi: 10.1097/CRD.0b013e318248d631
36. Li K, Lipsey T, Leach HJ, Nelson TL. Cardiac health and fitness of Colorado male/female firefighters. *Occup Med (Lond)*. 2017;67:268–273. doi: 10.1093/occmed/kqx033
37. Bankoski A, Harris TB, McClain JJ, Brychta RJ, Caserotti P, Chen KY, Berrigan D, Troiano RP, Koster A. Sedentary activity associated with metabolic syndrome independent of physical activity. *Diabetes Care*. 2011;34:497–503. doi: 10.2337/dc10-0987
38. Wennberg P, Gustafsson PE, Howard B, Wennberg M, Hammarström A. Television viewing over the life course and the metabolic syndrome in mid-adulthood: a longitudinal population-based study. *J Epidemiol Community Health*. 2014;68:928–933. doi: 10.1136/jech-2013-203504
39. Bahadoran Z, Mirmiran P, Hosseini-Esfahani F, Azizi F. Fast food consumption and the risk of metabolic syndrome after 3-years of follow-up: Tehran Lipid and Glucose Study. *Eur J Clin Nutr*. 2013;67:1303–1309. doi: 10.1038/ejcn.2013.217
40. Xi B, He D, Zhang M, Xue J, Zhou D. Short sleep duration predicts risk of metabolic syndrome: a systematic review and meta-analysis. *Sleep Med Rev*. 2014;18:293–297. doi: 10.1016/j.smrv.2013.06.001
41. Barrio-Lopez MT, Martinez-Gonzalez MA, Fernandez-Montero A, Beunza JJ, Zazpe I, Bes-Rastrollo M. Prospective study of changes in sugar-sweetened beverage consumption and the incidence of the metabolic syndrome and its components: the SUN cohort. *Br J Nutr*. 2013;110:1722–1731. doi: 10.1017/S0007114513000822
42. Malik VS, Popkin BM, Bray GA, Després JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. *Diabetes Care*. 2010;33:2477–2483. doi: 10.2337/dc10-1079
43. Lee AM, Gurka MJ, DeBoer MD. Trends in metabolic syndrome severity and lifestyle factors among adolescents [published correction appears in *Pediatrics*. 2016;137:e20161255]. *Pediatrics*. 2016;137:e20153177. doi: 10.1542/peds.2015-3177
44. Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic syndrome in the United States, 2003-2012. *JAMA*. 2015;313:1973–1974. doi: 10.1001/jama.2015.4260
45. Beltrán-Sánchez H, Harhay MO, Harhay MM, McElligott S. Prevalence and trends of metabolic syndrome in the adult U.S. population, 1999-2010. *J Am Coll Cardiol*. 2013;62:697–703. doi: 10.1016/j.jacc.2013.05.064
46. Vishnu A, Gurka MJ, DeBoer MD. The severity of the metabolic syndrome increases over time within individuals, independent of baseline metabolic syndrome status and medication use: the Atherosclerosis Risk in Communities Study. *Atherosclerosis*. 2015;243:278–285. doi: 10.1016/j.atherosclerosis.2015.09.025
47. Patel PA, Scott CG, Rodeheffer RJ, Chen HH. The natural history of patients with isolated metabolic syndrome. *Mayo Clin Proc*. 2016;91:623–633. doi: 10.1016/j.mayocp.2016.02.026
48. Boudreau DM, Malone DC, Raebel MA, Fishman PA, Nichols GA, Feldstein AC, Boscoe AN, Ben-Joseph RH, Magid DJ, Okamoto LJ. Health care utilization and costs by metabolic syndrome risk factors. *Metab Syndr Relat Disord*. 2009;7:305–314. doi: 10.1089/met.2008.0070
49. Akinyemiju T, Sakhuja S, Vin-Raviv N. In-hospital mortality and post-surgical complications among cancer patients with metabolic syndrome. *Obes Surg*. 2018;28:683–692. doi: 10.1007/s11695-017-2900-6
50. Shariq OA, Fruth KM, Hanson KT, Cronin PA, Richards ML, Farley DR, Thompson GB, Habermann EB, McKenzie TJ. Metabolic syndrome is associated with increased postoperative complications and use of hospital resources in patients undergoing laparoscopic adrenalectomy. *Surgery*. 2018;163:167–175. doi: 10.1016/j.surg.2017.06.023
51. Tee MC, Ubl DS, Habermann EB, Nagorney DM, Kendrick ML, Sarr MG, Truty MJ, Que FG, Reid-Lombardo K, Smoot RL, Farnell MB. Metabolic syndrome is associated with increased postoperative morbidity and hospital resource utilization in patients undergoing elective pancreatectomy. *J Gastrointest Surg*. 2016;20:189–98; discussion 198. doi: 10.1007/s11605-015-3007-9
52. Morrison JA, Friedman LA, Gray-McGuire C. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton Lipid Research Clinics Follow-up Study. *Pediatrics*. 2007;120:340–345. doi: 10.1542/peds.2006-1699
53. Koskinen J, Magnussen CG, Sinaiko A, Woo J, Urbina E, Jacobs DR Jr, Steinberger J, Prineas R Sabin MA, Burns T, Berenson G, Bazzano L, Venn A, Viikari JSA, Hutri-Kähönen N, Raitakari O, Dwyer T, Juonala M. Childhood age and associations between childhood metabolic syndrome and adult risk for metabolic syndrome, type 2 diabetes mellitus and carotid intima media thickness: the International Childhood Cardiovascular Cohort Consortium. *J Am Heart Assoc*. 2017;6:e005632. doi: 10.1161/JAHA.117.005632
54. Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, Srinivasan SR, Daniels SR, Davis PH, Chen W, Sun C, Cheung M, Viikari JS, Dwyer T, Raitakari OT. Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med*. 2011;365:1876–1885. doi: 10.1056/NEJMoa1010112
55. Magnussen CG, Koskinen J, Juonala M, Chen W, Srinivasan SR, Sabin MA, Thomson R, Schmidt MD, Nguyen QM, Xu JH, Skilton MR, Kähönen M, Laitinen T, Taittonen L, Lehtimäki T, Rönnemaa T, Viikari JS, Berenson GS, Raitakari OT. A diagnosis of the metabolic syndrome in youth that resolves by adult life is associated with a normalization of high carotid intima-media thickness and type 2 diabetes mellitus risk: the Bogalusa Heart and Cardiovascular Risk in Young Finns studies. *J Am Coll Cardiol*. 2012;60:1631–1639. doi: 10.1016/j.jacc.2012.05.056
56. DeBoer MD, Gurka MJ, Woo JG, Morrison JA. Severity of metabolic syndrome as a predictor of cardiovascular disease between childhood and adulthood: the Princeton Lipid Research Cohort Study. *J Am Coll Cardiol*. 2015;66:755–757. doi: 10.1016/j.jacc.2015.05.061
57. DeBoer MD, Gurka MJ, Woo JG, Morrison JA. Severity of the metabolic syndrome as a predictor of type 2 diabetes between childhood and adulthood: the Princeton Lipid Research Cohort Study. *Diabetologia*. 2015;58:2745–2752. doi: 10.1007/s00125-015-3759-5
58. Olza J, Aguilera CM, Gil-Campos M, Leis R, Bueno G, Valle M, Cañete R, Tojo R, Moreno LA, Gil Á. A continuous metabolic syndrome score is associated with specific biomarkers of inflammation and CVD risk in prepubertal children. *Ann Nutr Metab*. 2015;66:72–79. doi: 10.1159/000369981
59. Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, Montori VM. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol*. 2007;49:403–414. doi: 10.1016/j.jacc.2006.09.032
60. Xanthakis V, Sung JH, Samdarshi TE, Hill AN, Musani SK, Sims M, Ghraibeh KA, Liebson PR, Taylor HA, Vasan RS, Fox ER. Relations between subclinical disease markers and type 2 diabetes, metabolic syndrome, and incident cardiovascular disease: the Jackson Heart Study. *Diabetes Care*. 2015;38:1082–1088. doi: 10.2337/dc14-2460
61. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, Rinfret S, Schiffrin EL, Eisenberg MJ. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;56:1113–1132. doi: 10.1016/j.jacc.2010.05.034
62. Franco OH, Massaro JM, Civil J, Cobain MR, O'Malley B, D'Agostino RB Sr. Trajectories of entering the metabolic syndrome: the Framingham Heart Study. *Circulation*. 2009;120:1943–1950. doi: 10.1161/CIRCULATIONAHA.109.855817
63. Church TS, Thompson AM, Katzmarzyk PT, Sui X, Johannsen N, Earnest CP, Blair SN. Metabolic syndrome and diabetes, alone and in combination, as predictors of cardiovascular disease mortality among men. *Diabetes Care*. 2009;32:1289–1294. doi: 10.2337/dc08-1871
64. Ju SY, Lee JY, Kim DH. Association of metabolic syndrome and its components with all-cause and cardiovascular mortality in the elderly: a meta-analysis of prospective cohort studies. *Medicine (Baltimore)*. 2017;96:e8491. doi: 10.1097/MD.0000000000008491
65. Fernandez-Mendoza J, He F, LaGrotte C, Vgontzas AN, Liao D, Bixler EO. Impact of the metabolic syndrome on mortality is modified by objective short sleep duration [published correction appears in *J Am Heart Assoc*. 2017;6:e002182]. *J Am Heart Assoc*. 2017;6:e005479. doi: 10.1161/JAHA.117.005479
66. Mente A, Yusuf S, Islam S, McQueen MJ, Tanomsup S, Onen CL, Rangarajan S, Gerstein HC, Anand SS; INTERHEART Investigators. Metabolic syndrome and risk of acute myocardial infarction a case-control study of 26,903 subjects from 52 countries. *J Am Coll Cardiol*. 2010;55:2390–2398. doi: 10.1016/j.jacc.2009.12.053
67. Rachas A, Raffaitin C, Barberger-Gateau P, Helmer C, Ritchie K, Tzourio C, Amouyel P, Ducimetière P, Empana JP. Clinical usefulness of the metabolic syndrome for the risk of coronary heart disease does not exceed the sum of its individual components in older men and women: the Three-City (3C) Study. *Heart*. 2012;98:650–655. doi: 10.1136/heartjnl-2011-301185

68. Lyubarova R, Robinson JG, Miller M, Simmons DL, Xu P, Abramson BL, Elam MB, Brown TM, McBride R, Fleg JL, Desvigne-Nickens P, Ayenew W, Boden WE; Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) Investigators. Metabolic syndrome cluster does not provide incremental prognostic information in patients with stable cardiovascular disease: a post hoc analysis of the AIM-HIGH trial. *J Clin Lipidol*. 2017;11:1201–1211. doi: 10.1016/j.jacl.2017.06.017
69. Li X, Li X, Lin H, Fu X, Lin W, Li M, Zeng X, Gao Q. Metabolic syndrome and stroke: a meta-analysis of prospective cohort studies. *J Clin Neurosci*. 2017;40:34–38. doi: 10.1016/j.jocn.2017.01.018
70. Liu L, Miura K, Fujiyoshi A, Kadota A, Miyagawa N, Nakamura Y, Ohkubo T, Okayama A, Okamura T, Ueshima H. Impact of metabolic syndrome on the risk of cardiovascular disease mortality in the United States and in Japan. *Am J Cardiol*. 2014;113:84–89. doi: 10.1016/j.amjcard.2013.08.042
71. Hess PL, Al-Khalidi HR, Friedman DJ, Mulder H, Kucharska-Newton A, Rosamond WR, Lopes RD, Gersh BJ, Mark DB, Curtis LH, Post WS, Prineas RJ, Sotoodehnia N, Al-Khatib SM. The metabolic syndrome and risk of sudden cardiac death: the Atherosclerosis Risk in Communities Study. *J Am Heart Assoc*. 2017;6:e006103. doi: 10.1161/JAHA.117.006103
72. Chamberlain AM, Agarwal SK, Ambrose M, Folsom AR, Soliman EZ, Alonso A. Metabolic syndrome and incidence of atrial fibrillation among blacks and whites in the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J*. 2010;159:850–856. doi: 10.1016/j.ahj.2010.02.005
73. Lin KJ, Cho SI, Tiwari N, Bergman M, Kizer JR, Palma EC, Taub CC. Impact of metabolic syndrome on the risk of atrial fibrillation recurrence after catheter ablation: systematic review and meta-analysis. *J Interv Card Electrophysiol*. 2014;39:211–223. doi: 10.1007/s10840-013-9863-x
74. Perrone-Filardi P, Paolillo S, Costanzo P, Savarese G, Trimarco B, Bonow RO. The role of metabolic syndrome in heart failure. *Eur Heart J*. 2015;36:2630–2634. doi: 10.1093/eurheartj/ehv350
75. Vidula H, Liu K, Criqui MH, Szklo M, Allison M, Sibley C, Ouyang P, Tracy RP, Chan C, McDermott MM. Metabolic syndrome and incident peripheral artery disease: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2015;243:198–203. doi: 10.1016/j.atherosclerosis.2015.08.044
76. Vishram JK, Borglykke A, Andreasen AH, Jeppesen J, Ibsen H, Jørgensen T, Palmieri L, Giampaoli S, Donfrancesco C, Kee F, Mancia G, Cesana G, Kuulasmaa K, Salomaa V, Sans S, Ferrieres J, Dallongeville J, Söderberg S, Arveiler D, Wagner A, Tunstall-Pedoe H, Drygas W, Olsen MH; MORGAM Project. Impact of age and gender on the prevalence and prognostic importance of the metabolic syndrome and its components in Europeans: the MORGAM Prospective Cohort Project [published correct appears in *PLoS One*. 2015;10:e0128848]. *PLoS One*. 2014;9:e107294. doi: 10.1371/journal.pone.0107294
77. Malik S, Budoff MJ, Katz R, Blumenthal RS, Bertoni AG, Nasir K, Szklo M, Barr RG, Wong ND. Impact of subclinical atherosclerosis on cardiovascular disease events in individuals with metabolic syndrome and diabetes: the Multi-Ethnic Study of Atherosclerosis. *Diabetes Care*. 2011;34:2285–2290. doi: 10.2337/dc11-0816
78. Hong HC, Hwang SY, Ryu JY, Yoo HJ, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM. The synergistic impact of nonalcoholic fatty liver disease and metabolic syndrome on subclinical atherosclerosis. *Clin Endocrinol (Oxf)*. 2016;84:203–209. doi: 10.1111/cen.12940
79. Al Rifai M, Silverman MG, Nasir K, Budoff MJ, Blankstein R, Szklo M, Katz R, Blumenthal RS, Blaha MJ. The association of nonalcoholic fatty liver disease, obesity, and metabolic syndrome, with systemic inflammation and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2015;239:629–633. doi: 10.1016/j.atherosclerosis.2015.02.011
80. Lee YA, Kang SG, Song SW, Rho JS, Kim EK. Association between metabolic syndrome, smoking status and coronary artery calcification. *PLoS One*. 2015;10:e0122430. doi: 10.1371/journal.pone.0122430
81. Wong ND, Nelson JC, Granston T, Bertoni AG, Blumenthal RS, Carr JJ, Guerci A, Jacobs DR Jr, Kronmal R, Liu K, Saad M, Selvin E, Tracy R, Detrano R. Metabolic syndrome, diabetes, and incidence and progression of coronary calcium: the Multiethnic Study of Atherosclerosis study. *JACC Cardiovasc Imaging*. 2012;5:358–366. doi: 10.1016/j.jcmg.2011.12.015
82. Katz R, Budoff MJ, O'Brien KD, Wong ND, Nasir K. The metabolic syndrome and diabetes mellitus as predictors of thoracic aortic calcification as detected by non-contrast computed tomography in the Multi-Ethnic Study of Atherosclerosis. *Diabet Med*. 2016;33:912–919. doi: 10.1111/dme.12958
83. Safar ME, Balkau B, Lange C, Protogerou AD, Czernichow S, Blacher J, Levy BI, Smulyan H. Hypertension and vascular dynamics in men and women with metabolic syndrome. *J Am Coll Cardiol*. 2013;61:12–19. doi: 10.1016/j.jacc.2012.01.088
84. Ebong IA, Bertoni AG, Soliman EZ, Guo M, Sibley CT, Chen YD, Rotter JI, Chen YC, Goff DC Jr. Electrocardiographic abnormalities associated with the metabolic syndrome and its components: the Multi-Ethnic Study of Atherosclerosis. *Metab Syndr Relat Disord*. 2012;10:92–97. doi: 10.1089/met.2011.0090
85. Rodríguez-Colón SM, He F, Bixler EO, Fernandez-Mendoza J, Vgontzas AN, Calhoun S, Zheng ZJ, Liao D. Metabolic syndrome burden in apparently healthy adolescents is adversely associated with cardiac autonomic modulation–Penn State Children Cohort. *Metabolism*. 2015;64:626–632. doi: 10.1016/j.metabol.2015.01.018
86. Li J, Flammer AJ, Lennon RJ, Nelson RE, Gulati R, Friedman PA, Thomas RJ, Sandhu NP, Hua Q, Lerman LO, Lerman A. Comparison of the effect of the metabolic syndrome and multiple traditional cardiovascular risk factors on vascular function. *Mayo Clin Proc*. 2012;87:968–975. doi: 10.1016/j.mayocp.2012.07.004
87. Walther G, Obert P, Dutheil F, Chapier R, Lesourd B, Naughton G, Courteix D, Vinet A. Metabolic syndrome individuals with and without type 2 diabetes mellitus present generalized vascular dysfunction: cross-sectional study. *Arterioscler Thromb Vasc Biol*. 2015;35:1022–1029. doi: 10.1161/ATVBAHA.114.304591
88. Smith JP, Haddad EV, Taylor MB, Oram D, Blakemore D, Chen Q, Boutaud O, Oates JA. Suboptimal inhibition of platelet cyclooxygenase-1 by aspirin in metabolic syndrome. *Hypertension*. 2012;59:719–725. doi: 10.1161/HYPERTENSIONAHA.111.181404
89. Feldman L, Tubach F, Juliard JM, Himbert D, Ducrocq G, Sorbets E, Triantafyllou K, Kerner A, Abergel H, Huisse MG, Roussel R, Esposito-Farèse M, Steg PG, Ajzenberg N. Impact of diabetes mellitus and metabolic syndrome on acute and chronic on-clopidogrel platelet reactivity in patients with stable coronary artery disease undergoing drug-eluting stent placement. *Am Heart J*. 2014;168:940–7.e5. doi: 10.1016/j.ahj.2014.08.014
90. Cuspidi C, Sala C, Tadic M, Gherbesi E, Grassi G, Mancia G. Association of metabolic syndrome with carotid thickening and plaque in the general population: a meta-analysis. *J Clin Hypertens (Greenwich)*. 2018;20:4–10. doi: 10.1111/jch.13138
91. Pierdomenico SD, Pierdomenico AM, Cuccurullo F, Iacobellis G. Meta-analysis of the relation of echocardiographic epicardial adipose tissue thickness and the metabolic syndrome. *Am J Cardiol*. 2013;111:73–78. doi: 10.1016/j.amjcard.2012.08.044
92. Torriani M, Gill CM, Daley S, Oliveira AL, Azevedo DC, Bredella MA. Compartmental neck fat accumulation and its relation to cardiovascular risk and metabolic syndrome. *Am J Clin Nutr*. 2014;100:1244–1251. doi: 10.3945/ajcn.114.088450
93. van der Meer RW, Lamb HJ, Smit JW, de Roos A. MR imaging evaluation of cardiovascular risk in metabolic syndrome. *Radiology*. 2012;264:21–37. doi: 10.1148/radiol.12110772
94. Chun H. Ascending aortic diameter and metabolic syndrome in Korean men. *J Investig Med*. 2017;65:1125–1130. doi: 10.1136/jim-2016-000367
95. Marso SP, Mercado N, Maehara A, Weisz G, Mintz GS, McPherson J, Schiele F, Dudek D, Fahy M, Xu K, Lansky A, Templin B, Zhang Z, de Bruyne B, Serruys PW, Stone GW. Plaque composition and clinical outcomes in acute coronary syndrome patients with metabolic syndrome or diabetes. *JACC Cardiovasc Imaging*. 2012;5(suppl):S42–S52. doi: 10.1016/j.jcmg.2012.01.008
96. Di Carli MF, Charytan D, McMahon GT, Ganz P, Dorbala S, Schelbert HR. Coronary circulatory function in patients with the metabolic syndrome. *J Nucl Med*. 2011;52:1369–1377. doi: 10.2967/jnumed.110.082883
97. Almeida AL, Teixido-Tura G, Choi EY, Opdahl A, Fernandes VR, Wu CO, Bluemke DA, Lima JA. Metabolic syndrome, strain, and reduced myocardial function: Multi-Ethnic Study of Atherosclerosis. *Arq Bras Cardiol*. 2014;102:327–335.
98. Aksoy S, Durmuş G, Özcan S, Toprak E, Gurkan U, Oz D, Canga Y, Karatas B, Duman D. Is left ventricular diastolic dysfunction independent from presence of hypertension in metabolic syndrome? An echocardiographic study. *J Cardiol*. 2014;64:194–198. doi: 10.1016/j.jjcc.2014.01.002
99. Crendal E, Walther G, Dutheil F, Courteix D, Lesourd B, Chapier R, Naughton G, Vinet A, Obert P. Left ventricular myocardial dyssynchrony is already present in nondiabetic patients with metabolic syndrome. *Can J Cardiol*. 2014;30:320–324. doi: 10.1016/j.cjca.2013.10.019

100. Tadic M, Cuspidi C, Sljivic A, Andric A, Ivanovic B, Scepanovic R, Ilic I, Jozika L, Marjanovic T, Celic V. Effects of the metabolic syndrome on right heart mechanics and function. *Can J Cardiol*. 2014;30:325–331. doi: 10.1016/j.cjca.2013.12.006
101. Besiroglu H, Otunctemur A, Ozbek E. The relationship between metabolic syndrome, its components, and erectile dysfunction: a systematic review and a meta-analysis of observational studies. *J Sex Med*. 2015;12:1309–1318. doi: 10.1111/jsm.12885
102. Gurka MJ, Golden SH, Musani SK, Sims M, Vishnu A, Guo Y, Cardel M, Pearson TA, DeBoer MD. Independent associations between a metabolic syndrome severity score and future diabetes by sex and race: the Atherosclerosis Risk In Communities Study and Jackson Heart Study. *Diabetologia*. 2017;60:1261–1270. doi: 10.1007/s00125-017-4267-6
103. Akinyemiju T, Moore JX, Judd S, Lakoski S, Goodman M, Safford MM, Pisu M. Metabolic dysregulation and cancer mortality in a national cohort of blacks and whites. *BMC Cancer*. 2017;17:856. doi: 10.1186/s12885-017-3807-2
104. Micucci C, Valli D, Matacchione G, Catalano A. Current perspectives between metabolic syndrome and cancer. *Oncotarget*. 2016;7:38959–38972. doi: 10.18632/oncotarget.8341
105. Åberg F, Helenius-Hietala J, Puukka P, Färkkilä M, Jula A. Interaction between alcohol consumption and metabolic syndrome in predicting severe liver disease in the general population. *Hepatology*. 2018;67:2141–2149. doi: 10.1002/hep.29631
106. Raffaitin C, Féart C, Le Goff M, Amieva H, Helmer C, Akbaraly TN, Tzourio C, Gin H, Barberger-Gateau P. Metabolic syndrome and cognitive decline in French elders: the Three-City Study. *Neurology*. 2011;76:518–525. doi: 10.1212/WNL.0b013e31820b7656
107. Ageno W, Di Minno MN, Ay C, Jang MJ, Hansen JB, Steffen LM, Vayà A, Rattazzi M, Pabinger I, Oh D, Di Minno G, Braekkan SK, Cushman M, Bonet E, Pauletto P, Squizzato A, Dentali F. Association between the metabolic syndrome, its individual components, and unprovoked venous thromboembolism: results of a patient-level meta-analysis. *Arterioscler Thromb Vasc Biol*. 2014;34:2478–2485. doi: 10.1161/ATVBAHA.114.304085
108. Brumpton BM, Camargo CA Jr, Romundstad PR, Langhammer A, Chen Y, Mai XM. Metabolic syndrome and incidence of asthma in adults: the HUNT study. *Eur Respir J*. 2013;42:1495–1502. doi: 10.1183/09031936.00046013
109. Colicchia M, Morlacco A, Rangel LJ, Carlson RE, Dal Moro F, Karnes RJ. Role of metabolic syndrome on perioperative and oncological outcomes at radical prostatectomy in a low-risk prostate cancer cohort potentially eligible for active surveillance [published online January 3, 2018]. *Eur Urol Focus*. doi: 10.1016/j.euf.2017.12.005. https://www.eu-focus.europeanurology.com/article/S2405-4569(17)30292-4/fulltext.
110. Gacci M, Russo GI, De Nunzio C, Sebastianelli A, Salvi M, Vignozzi L, Tubaro A, Morgia G, Serni S. Meta-analysis of metabolic syndrome and prostate cancer. *Prostate Cancer Prostatic Dis*. 2017;20:146–155. doi: 10.1038/pcan.2017.1
111. Gathirua-Mwangi WG, Song Y, Monahan PO, Champion VL, Zollinger TW. Associations of metabolic syndrome and C-reactive protein with mortality from total cancer, obesity-linked cancers and breast cancer among women in NHANES III. *Int J Cancer*. 2018;143:535–542. doi: 10.1002/ijc.31344
112. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. *Diabetes Care*. 2012;35:2402–2411. doi: 10.2337/dc12-0336
113. Wong RJ, Liu B, Bhuket T. Significant burden of nonalcoholic fatty liver disease with advanced fibrosis in the US: a cross-sectional analysis of 2011-2014 National Health and Nutrition Examination Survey. *Aliment Pharmacol Ther*. 2017;46:974–980. doi: 10.1111/apt.14327
114. Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, Omatsu T, Nakajima T, Sarui H, Shimazaki M, Kato T, Okuda J, Ida K. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med*. 2005;143:722–728.
115. Xu ZJ, Shi JP, Yu DR, Zhu LJ, Jia JD, Fan JG. Evaluating the relationship between metabolic syndrome and liver biopsy-proven non-alcoholic steatohepatitis in China: a multicenter cross-sectional study design. *Adv Ther*. 2016;33:2069–2081. doi: 10.1007/s12325-016-0416-4
116. Lin E, Kuo PH, Liu YL, Yang AC, Tsai SJ. Detection of susceptibility loci on *APOA5* and *COLEC12* associated with metabolic syndrome using a genome-wide association study in a Taiwanese population. *Oncotarget*. 2017;8:93349–93359. doi: 10.18632/oncotarget.20967
117. Morjane I, Kefi R, Charoute H, Lakbakbi El Yaagoubi F, Hechmi M, Saile R, Abdelhak S, Barakat A. Association study of HNF1A polymorphisms with metabolic syndrome in the Moroccan population. *Diabetes Metab Syndr*. 2017;11 Suppl 2:S853–S857. doi: 10.1016/j.dsx.2017.07.005
118. Lakbakbi El Yaagoubi F, Charoute H, Morjane I, et al. Association analysis of genetic variants with metabolic syndrome components in the Moroccan population. *Curr Res Transl Med*. 2017;65:121–125. doi: 10.1016/j.retram.2017.08.001
119. Carty CL, Bhattacharjee S, Haessler J, Cheng I, Hindorff LA, Aroda V, Carlson CS, Hsu CN, Wilkens L, Liu S, Selvin E, Jackson R, North KE, Peters U, Pankow JS, Chatterjee N, Kooperberg C. Analysis of metabolic syndrome components in >15 000 African Americans identifies pleiotropic variants: results from the Population Architecture using Genomics and Epidemiology study. *Circ Cardiovasc Genet*. 2014;7:505–513. doi: 10.1161/CIRCGENETICS.113.000386
120. Cannone V, Cefalu' AB, Noto D, Scott CG, Bailey KR, Cavera G, Pagano M, Sapienza M, Averna MR, Burnett JC Jr. The atrial natriuretic peptide genetic variant rs5068 is associated with a favorable cardiometabolic phenotype in a Mediterranean population. *Diabetes Care*. 2013;36:2850–2856. doi: 10.2337/dc12-2337
121. Maintinguer Norde M, Oki E, Ferreira Carioca AA, Teixeira Damasceno NR, Fisberg RM, Lobo Marchioni DM, Rogero MM. Influence of IL1B, IL6 and IL10 gene variants and plasma fatty acid interaction on metabolic syndrome risk in a cross-sectional population-based study. *Clin Nutr*. 2018;37:659–666. doi: 10.1016/j.clnu.2017.02.009
122. Efstathiou SP, Skeva II, Zorbala E, Georgiou E, Mountokalakis TD. Metabolic syndrome in adolescence: can it be predicted from natal and parental profile? The Prediction of Metabolic Syndrome in Adolescence (PREMA) study. *Circulation*. 2012;125:902–910. doi: 10.1161/CIRCULATIONAHA.111.034546
123. Martin RM, Patel R, Kramer MS, Vilchuck K, Bogdanovich N, Sergeichick N, Gusina N, Foo Y, Palmer T, Thompson J, Gillman MW, Smith GD, Oken E. Effects of promoting longer-term and exclusive breastfeeding on cardiometabolic risk factors at age 11.5 years: a cluster-randomized, controlled trial. *Circulation*. 2014;129:321–329. doi: 10.1161/CIRCULATIONAHA.113.005160
124. Moore BF, Clark ML, Bachand A, Reynolds SJ, Nelson TL, Peel JL. Interactions between diet and exposure to secondhand smoke on metabolic syndrome among children: NHANES 2007-2010. *J Clin Endocrinol Metab*. 2016;101:52–58. doi: 10.1210/jc.2015-2477
125. Rodriguez LA, Madsen KA, Cotterman C, Lustig RH. Added sugar intake and metabolic syndrome in US adolescents: cross-sectional analysis of the National Health and Nutrition Examination Survey 2005–2012. *Public Health Nutr*. 2016;19:2424–2434. doi: 10.1017/S1368980016000057
126. Pan A, Keum N, Okereke OI, Sun Q, Kivimaki M, Rubin RR, Hu FB. Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. *Diabetes Care*. 2012;35:1171–1180. doi: 10.2337/dc11-2055
127. Wilsgaard T, Jacobsen BK. Lifestyle factors and incident metabolic syndrome: the Tromsø Study 1979-2001. *Diabetes Res Clin Pract*. 2007;78:217–224. doi: 10.1016/j.diabres.2007.03.006
128. Carnethon MR, Loria CM, Hill JO, Sidney S, Savage PJ, Liu K; Coronary Artery Risk Development in Young Adults study. Risk factors for the metabolic syndrome: the Coronary Artery Risk Development in Young Adults (CARDIA) study, 1985-2001. *Diabetes Care*. 2004;27:2707–2715.
129. Chichlowska KL, Rose KM, Diez-Roux AV, Golden SH, McNeill AM, Heiss G. Life course socioeconomic conditions and metabolic syndrome in adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol*. 2009;19:875–883. doi: 10.1016/j.annepidem.2009.07.094
130. Kang HT, Shim JY, Lee YJ, Linton JA, Park BJ, Lee HR. Reading nutrition labels is associated with a lower risk of metabolic syndrome in Korean adults: the 2007-2008 Korean NHANES. *Nutr Metab Cardiovasc Dis*. 2013;23:876–882. doi: 10.1016/j.numecd.2012.06.007
131. Beatty Moody DL, Chang Y, Brown C, Bromberger JT, Matthews KA. Everyday discrimination and metabolic syndrome incidence in a racially/ethnically diverse sample: Study of Women's Health Across the Nation. *Psychosom Med*. 2018;80:114–121. doi: 10.1097/PSY.0000000000000516
132. Xi B, He D, Hu Y, Zhou D. Prevalence of metabolic syndrome and its influencing factors among the Chinese adults: the China Health and Nutrition Survey in 2009. *Prev Med*. 2013;57:867–871. doi: 10.1016/j.ypmed.2013.09.023
133. Wannamethee SG, Shaper AG, Whincup PH. Modifiable lifestyle factors and the metabolic syndrome in older men: effects of lifestyle changes. *J Am Geriatr Soc*. 2006;54:1909–1914. doi: 10.1111/j.1532-5415.2006.00974.x

134. Juonala M, Magnussen CG, Venn A, Gall S, Kähönen M, Laitinen T, Taittonen L, Lehtimäki T, Jokinen E, Sun C, Viikari JS, Dwyer T, Raitakari OT. Parental smoking in childhood and brachial artery flow-mediated dilatation in young adults: the Cardiovascular Risk in Young Finns study and the Childhood Determinants of Adult Health study. *Arterioscler Thromb Vasc Biol*. 2012;32:1024–1031. doi: 10.1161/ATVBAHA.111.243261
135. Ferreira I, Henry RM, Twisk JW, van Mechelen W, Kemper HC, Stehouwer CD; Amsterdam Growth and Health Longitudinal Study. The metabolic syndrome, cardiopulmonary fitness, and subcutaneous trunk fat as independent determinants of arterial stiffness: the Amsterdam Growth and Health Longitudinal Study. *Arch Intern Med*. 2005;165:875–882. doi: 10.1001/archinte.165.8.875
136. LaMonte MJ, Barlow CE, Jurca R, Kampert JB, Church TS, Blair SN. Cardiorespiratory fitness is inversely associated with the incidence of metabolic syndrome: a prospective study of men and women. *Circulation*. 2005;112:505–512. doi: 10.1161/CIRCULATIONAHA.104.503805
137. Narain A, Kwok CS, Mamas MA. Soft drink intake and the risk of metabolic syndrome: a systematic review and meta-analysis [published online January 10, 2017]. *Int J Clin Pract*. doi: 10.1111/ijcp.12927. https://onlinelibrary.wiley.com/doi/abs/10.1111/ijcp.12927.
138. Lutsey PL, Steffen LM, Stevens J. Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. *Circulation*. 2008;117:754–761. doi: 10.1161/CIRCULATIONAHA.107.716159
139. Kelishadi R, Mansourian M, Heidari-Beni M. Association of fructose consumption and components of metabolic syndrome in human studies: a systematic review and meta-analysis. *Nutrition*. 2014;30:503–510. doi: 10.1016/j.nut.2013.08.014
140. He K, Liu K, Daviglus ML, Morris SJ, Loria CM, Van Horn L, Jacobs DR Jr, Savage PJ. Magnesium intake and incidence of metabolic syndrome among young adults. *Circulation*. 2006;113:1675–1682. doi: 10.1161/CIRCULATIONAHA.105.588327
141. Song Y, Ridker PM, Manson JE, Cook NR, Buring JE, Liu S. Magnesium intake, C-reactive protein, and the prevalence of metabolic syndrome in middle-aged and older U.S. women. *Diabetes Care*. 2005;28:1438–1444.
142. Ferreira I, Twisk JW, van Mechelen W, Kemper HC, Stehouwer CD. Development of fatness, fitness, and lifestyle from adolescence to the age of 36 years: determinants of the metabolic syndrome in young adults: the Amsterdam Growth and Health Longitudinal Study. *Arch Intern Med*. 2005;165:42–48. doi: 10.1001/archinte.165.1.42
143. Kwon YJ, Lee HS, Lee JW. Association of carbohydrate and fat intake with metabolic syndrome. *Clin Nutr*. 2018;37:746–751. doi: 10.1016/j.clnu.2017.06.022
144. Morrison JA, Friedman LA, Wang P, Glueck CJ. Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. *J Pediatr*. 2008;152:201–206. doi: 10.1016/j.jpeds.2007.09.010
145. Cocate PG, Natali AJ, de Oliveira A, Alfenas Rde C, Peluzio Mdo C, Longo GZ, dos Santos EC, Buthers JM, de Oliveira LL, Hermsdorff HH. Red but not white meat consumption is associated with metabolic syndrome, insulin resistance and lipid peroxidation in Brazilian middle-aged men. *Eur J Prev Cardiol*. 2015;22:223–230. doi: 10.1177/2047487313507684
146. Deshmukh-Taskar P, Nicklas TA, Radcliffe JD, O'Neil CE, Liu Y. The relationship of breakfast skipping and type of breakfast consumed with overweight/obesity, abdominal obesity, other cardiometabolic risk factors and the metabolic syndrome in young adults: the National Health and Nutrition Examination Survey (NHANES): 1999–2006. *Public Health Nutr*. 2013;16:2073–2082. doi: 10.1017/S1368980012004296
147. Baik I, Shin C. Prospective study of alcohol consumption and metabolic syndrome. *Am J Clin Nutr*. 2008;87:1455–1463. doi: 10.1093/ajcn/87.5.1455
148. Chandola T, Brunner E, Marmot M. Chronic stress at work and the metabolic syndrome: prospective study. *BMJ*. 2006;332:521–525. doi: 10.1136/bmj.38693.435301.80
149. Sun SS, Liang R, Huang TT, Daniels SR, Arslanian S, Liu K, Grave GD, Siervogel RM. Childhood obesity predicts adult metabolic syndrome: the Fels Longitudinal Study. *J Pediatr*. 2008;152:191–200. doi: 10.1016/j.jpeds.2007.07.055
150. Tong J, Boyko EJ, Utzschneider KM, McNeely MJ, Hayashi T, Carr DB, Wallace TM, Zraika S, Gerchman F, Leonetti DL, Fujimoto WY, Kahn SE. Intra-abdominal fat accumulation predicts the development of the metabolic syndrome in non-diabetic Japanese-Americans. *Diabetologia*. 2007;50:1156–1160. doi: 10.1007/s00125-007-0651-y
151. Vergnaud AC, Bertrais S, Oppert JM, Maillard-Teyssier L, Galan P, Hercberg S, Czernichow S. Weight fluctuations and risk for metabolic syndrome in an adult cohort. *Int J Obes (Lond)*. 2008;32:315–321. doi: 10.1038/sj.ijo.0803739
152. Tomiyama H, Yamada J, Koji Y, Yambe M, Motobe K, Shiina K, Yamamoto Y, Yamashina A. Heart rate elevation precedes the development of metabolic syndrome in Japanese men: a prospective study. *Hypertens Res*. 2007;30:417–426. doi: 10.1291/hypres.30.417
153. Palaniappan L, Carnethon MR, Wang Y, Hanley AJ, Fortmann SP, Haffner SM, Wagenknecht L; Insulin Resistance Atherosclerosis Study. Predictors of the incident metabolic syndrome in adults: the Insulin Resistance Atherosclerosis Study. *Diabetes Care*. 2004;27:788–793.
154. Koskinen J, Magnussen CG, Würtz P, Soininen P, Kangas AJ, Viikari JS, Kähönen M, Loo BM, Jula A, Ahotupa M, Lehtimäki T, Ala-Korpela M, Juonala M, Raitakari OT. Apolipoprotein B, oxidized low-density lipoprotein, and LDL particle size in predicting the incidence of metabolic syndrome: the Cardiovascular Risk in Young Finns study. *Eur J Prev Cardiol*. 2012;19:1296–1303. doi: 10.1177/1741826711425343
155. Calcaterra V, De Giuseppe R, Biino G, Mantelli M, Marchini S, Bendotti G, Madè A, Avanzini MA, Montalbano C, Cossellu G, Larizza D, Cena H. Relation between circulating oxidized-LDL and metabolic syndrome in children with obesity: the role of hypertriglyceridemic waist phenotype. *J Pediatr Endocrinol Metab*. 2017;30:1257–1263. doi: 10.1515/jpem-2017-0239
156. Mani P, Ren HY, Neeland IJ, McGuire DK, Ayers CR, Khera A, Rohatgi A. The association between HDL particle concentration and incident metabolic syndrome in the multi-ethnic Dallas Heart Study. *Diabetes Metab Syndr*. 2017;11 Suppl 1:S175–S179. doi: 10.1016/j.dsx.2016.12.028
157. Tehrani DM, Zhao Y, Blaha MJ, Mora S, Mackey RH, Michos ED, Budoff MJ, Cromwell W, Otvos JD, Rosenblit PD, Wong ND. Discordance of low-density lipoprotein and high-density lipoprotein cholesterol particle versus cholesterol concentration for the prediction of cardiovascular disease in patients with metabolic syndrome and diabetes mellitus (from the Multi-Ethnic Study of Atherosclerosis [MESA]). *Am J Cardiol*. 2016;117:1921–1927. doi: 10.1016/j.amjcard.2016.03.040
158. Acevedo M, Varleta P, Kramer V, Valentino G, Quiroga T, Prieto C, Parada J, Adasme M, Briones L, Navarrete C. Comparison of lipoprotein-associated phospholipase A2 and high sensitive C-reactive protein as determinants of metabolic syndrome in subjects without coronary heart disease: in search of the best predictor. *Int J Endocrinol*. 2015;2015:934681. doi: 10.1155/2015/934681
159. Ryu S, Song J, Choi BY, Lee SJ, Kim WS, Chang Y, Kim DI, Suh BS, Sung KC. Incidence and risk factors for metabolic syndrome in Korean male workers, ages 30 to 39. *Ann Epidemiol*. 2007;17:245–252. doi: 10.1016/j.annepidem.2006.10.001
160. Sui X, Church TS, Meriwether RA, Lobelo F, Blair SN. Uric acid and the development of metabolic syndrome in women and men. *Metabolism*. 2008;57:845–852. doi: 10.1016/j.metabol.2008.01.030
161. Ballestri S, Zona S, Targher G, Romagnoli D, Baldelli E, Nascimbeni F, Roverato A, Guaraldi G, Lonardo A. Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome: evidence from a systematic review and meta-analysis. *J Gastroenterol Hepatol*. 2016;31:936–944. doi: 10.1111/jgh.13264
162. Lin CM, Hsieh CH, Lee CH, Pei D, Lin JD, Wu CZ, Liang YJ, Hung YJ, Chen YL. Predictive value of serum gamma-glutamyltranspeptidase for future cardiometabolic dysregulation in adolescents: a 10-year longitudinal study. *Sci Rep*. 2017;7:9636. doi: 10.1038/s41598-017-09719-8
163. Ingelsson E, Pencina MJ, Tofler GH, Benjamin EJ, Lanier KJ, Jacques PF, Fox CS, Meigs JB, Levy D, Larson MG, Selhub J, D'Agostino RB Sr, Wang TJ, Vasan RS. Multimarker approach to evaluate the incidence of the metabolic syndrome and longitudinal changes in metabolic risk factors: the Framingham Offspring Study. *Circulation*. 2007;116:984–992. doi: 10.1161/CIRCULATIONAHA.107.708537
164. Lakhani I, Gong M, Wong WT, Bazoukis G, Lampropoulos K, Wong SH, Wu WKK, Wong MCS, Ong KL, Liu T, Tse G; International Health Informatics Study (IHIS) Network. Fibroblast growth factor 21 in cardio-metabolic disorders: a systematic review and meta-analysis. *Metabolism*. 2018;83:11–17. doi: 10.1016/j.metabol.2018.01.017
165. Galletti F, Barbato A, Versiero M, Iacone R, Russo O, Barba G, Siani A, Cappuccio FP, Farinaro E, della Valle E, Strazzullo P. Circulating leptin levels predict the development of metabolic syndrome in middle-aged men: an 8-year follow-up study. *J Hypertens*. 2007;25:1671–1677. doi: 10.1097/HJH.0b013e3281afa09e
166. Iwanaga S, Sakano N, Taketa K, Takahashi N, Wang DH, Takahashi H, Kubo M, Miyatake N, Ogino K. Comparison of serum ferritin and

oxidative stress biomarkers between Japanese workers with and without metabolic syndrome. *Obes Res Clin Pract*. 2014;8:e201–e298. doi: 10.1016/j.orcp.2013.01.003

167. Hassinen M, Lakka TA, Komulainen P, Gylling H, Nissinen A, Rauramaa R. C-reactive protein and metabolic syndrome in elderly women: a 12-year follow-up study. *Diabetes Care*. 2006;29:931–932.
168. Laaksonen DE, Niskanen L, Nyyssönen K, Punnonen K, Tuomainen TP, Valkonen VP, Salonen R, Salonen JT. C-reactive protein and the development of the metabolic syndrome and diabetes in middle-aged men. *Diabetologia*. 2004;47:1403–1410. doi: 10.1007/s00125-004-1472-x
169. Xu A, Tso AW, Cheung BM, Wang Y, Wat NM, Fong CH, Yeung DC, Janus ED, Sham PC, Lam KS. Circulating adipocyte-fatty acid binding protein levels predict the development of the metabolic syndrome: a 5-year prospective study. *Circulation*. 2007;115:1537–1543. doi: 10.1161/CIRCULATIONAHA.106.647503
170. Ding EL, Song Y, Manson JE, Hunter DJ, Lee CC, Rifai N, Buring JE, Gaziano JM, Liu S. Sex hormone-binding globulin and risk of type 2 diabetes in women and men. *N Engl J Med*. 2009;361:1152–1163. doi: 10.1056/NEJMoa0804381
171. Li C, Ford ES, Li B, Giles WH, Liu S. Association of testosterone and sex hormone-binding globulin with metabolic syndrome and insulin resistance in men. *Diabetes Care*. 2010;33:1618–1624. doi: 10.2337/dc09-1788
172. Yadav SS, Mandal RK, Singh MK, Verma A, Dwivedi P, Sethi R, Usman K, Khattri S. High serum level of matrix metalloproteinase 9 and promoter polymorphism – 1562 C:T as a new risk factor for metabolic syndrome. *DNA Cell Biol*. 2014;33:816–822. doi: 10.1089/dna.2014.2511
173. Nibali L, Tatarakis N, Needleman I, Tu YK, D'Aiuto F, Rizzo M, Donos N. Clinical review: association between metabolic syndrome and periodontitis: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2013;98:913–920. doi: 10.1210/jc.2012-3552
174. Teppala S, Madhavan S, Shankar A. Bisphenol A and metabolic syndrome: results from NHANES. *Int J Endocrinol*. 2012;2012:598180. doi: 10.1155/2012/598180
175. Oh SW, Han KH, Han SY, Koo HS, Kim S, Chin HJ. Association of sodium excretion with metabolic syndrome, insulin resistance, and body fat. *Medicine (Baltimore)*. 2015;94:e1650. doi: 10.1097/MD.0000000000001650
176. Janczura M, Bochenek G, Nowobilski R, Dropinski J, Kotula-Horowitz K, Laskowicz B, Stanisz A, Lelakowski J, Domagala T. The relationship of metabolic syndrome with stress, coronary heart disease and pulmonary function: an occupational cohort-based study [published correction appears in *PLoS One*. 2015;10:e0139408]. *PLoS One*. 2015;10:e0133750. doi: 10.1371/journal.pone.0133750
177. Edwards MK, Loprinzi PD. High amounts of sitting, low cardiorespiratory fitness, and low physical activity levels: 3 key ingredients in the recipe for influencing metabolic syndrome prevalence. *Am J Health Promot*. 2018;32:587–594. doi: 10.1177/0890117116684889
178. Du R, Cheng D, Lin L, Sun J, Peng K, Xu Y, Xu M, Chen Y, Bi Y, Wang W, Lu J, Ning G. Association between serum CA 19-9 and metabolic syndrome: a cross-sectional study. *J Diabetes*. 2017;9:1040–1047. doi: 10.1111/1753-0407.12523
179. Huang LL, Dou DM, Liu N, Wang XX, Fu LY, Wu X, Wang P. Association of erythrocyte parameters with metabolic syndrome in the Pearl River Delta region of China: a cross sectional study. *BMJ Open*. 2018;8:e019792. doi: 10.1136/bmjopen-2017-019792
180. Kim MK, Chon SJ, Noe EB, Roh YH, Yun BH, Cho S, Choi YS, Lee BS, Seo SK. Associations of dietary calcium intake with metabolic syndrome and bone mineral density among the Korean population: KNHANES 2008-2011. *Osteoporos Int*. 2017;28:299–308. doi: 10.1007/s00198-016-3717-1
181. Xu S, Wan Y, Xu M, Ming J, Xing Y, An F, Ji Q. The association between obstructive sleep apnea and metabolic syndrome: a systematic review and meta-analysis. *BMC Pulm Med*. 2015;15:105. doi: 10.1186/s12890-015-0102-3
182. Jurca R, Lamonte MJ, Barlow CE, Kampert JB, Church TS, Blair SN. Association of muscular strength with incidence of metabolic syndrome in men. *Med Sci Sports Exerc*. 2005;37:1849–1855.
183. Lin X, Zhang X, Guo J, Roberts CK, McKenzie S, Wu WC, Liu S, Song Y. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2015;4:e002014. doi: 10.1161/JAHA.115.002014
184. Bateman LA, Slentz CA, Willis LH, Shields AT, Piner LW, Bales CW, Houmard JA, Kraus WE. Comparison of aerobic versus resistance exercise training effects on metabolic syndrome (from the Studies of a Targeted Risk Reduction Intervention Through Defined Exercise - STRRIDE-AT/RT). *Am J Cardiol*. 2011;108:838–844. doi: 10.1016/j.amjcard.2011.04.037
185. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation*. 2005;112:3066–3072. doi: 10.1161/CIRCULATIONAHA.105.539528
186. Grooms KN, Ommerborn MJ, Pham DQ, Djousse L, Clark CR. Dietary fiber intake and cardiometabolic risks among US adults, NHANES 1999–2010. *Am J Med*. 2013;126:1059–1067.e4. doi: 10.1016/j.amjmed.2013.07.023
187. Wei B, Liu Y, Lin X, Fang Y, Cui J, Wan J. Dietary fiber intake and risk of metabolic syndrome: a meta-analysis of observational studies [published online October 31, 2017]. *Clin Nutr*. doi: 10.1016/j.cinu.2017.10.019. https://www.clinicalnutritionjournal.com/article/S0261-5614(17)31392-4/fulltext.
188. Shin JY, Kim JY, Kang HT, Han KH, Shim JY. Effect of fruits and vegetables on metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials. *Int J Food Sci Nutr*. 2015;66:416–425. doi: 10.3109/09637486.2015.1025716
189. Vázquez C, Botella-Carretero JI, Corella D, Fiol M, Lage M, Lurbe E, Richart C, Fernández-Real JM, Fuentes F, Ordóñez A, de Cos AI, Salas-Salvadó J, Burguera B, Estruch R, Ros E, Pastor O, Casanueva FF; WISH-CARE Study Investigators. White fish reduces cardiovascular risk factors in patients with metabolic syndrome: the WISH-CARE study, a multicenter randomized clinical trial. *Nutr Metab Cardiovasc Dis*. 2014;24:328–335. doi: 10.1016/j.numecd.2013.09.018
190. Echeverria G, McGee EE, Urquiaga I, Jiménez P, D'Acuña S, Villarroel L, Velasco N, Leighton F, Rigotti A. Inverse associations between a locally validated Mediterranean diet index, overweight/obesity, and metabolic syndrome in Chilean adults. *Nutrients*. 2017;9:E862. doi: 10.3390/nu9080862
191. Babio N, Becerra-Tomás N, Martínez-González MÁ, Corella D, Estruch R, Ros E, Sayón-Orea C, Fitó M, Serra-Majem L, Arós F, Lamuela-Raventós RM, Lapetra J, Gómez-Gracia E, Fiol M, Díaz-López A, Sorlí JV, Martínez JA, Salas-Salvadó J; PREDIMED Investigators. Consumption of yogurt, low-fat milk, and other low-fat dairy products is associated with lower risk of metabolic syndrome incidence in an elderly Mediterranean population. *J Nutr*. 2015;145:2308–2316. doi: 10.3945/jn.115.214593
192. Barreto FM, Colado Simão AN, Morimoto HK, Batisti Lozovoy MA, Dichi I, Helena da Silva Miglioranza L. Beneficial effects of *Lactobacillus plantarum* on glycemia and homocysteine levels in postmenopausal women with metabolic syndrome. *Nutrition*. 2014;30:939–942. doi: 10.1016/j.nut.2013.12.004
193. Hill AM, Harris Jackson KA, Roussell MA, West SG, Kris-Etherton PM. Type and amount of dietary protein in the treatment of metabolic syndrome: a randomized controlled trial. *Am J Clin Nutr*. 2015;102:757–770. doi: 10.3945/ajcn.114.104026
194. Vernarelli JA, Lambert JD. Tea consumption is inversely associated with weight status and other markers for metabolic syndrome in US adults. *Eur J Nutr*. 2013;52:1039–1048. doi: 10.1007/s00394-012-0410-9
195. Shang F, Li X, Jiang X. Coffee consumption and risk of the metabolic syndrome: a meta-analysis. *Diabetes Metab*. 2016;42:80–87. doi: 10.1016/j.diabet.2015.09.001
196. Maki KC, Fulgoni VL 3rd, Keast DR, Rains TM, Park KM, Rubin MR. Vitamin D intake and status are associated with lower prevalence of metabolic syndrome in U.S. adults: National Health and Nutrition Examination Surveys 2003-2006. *Metab Syndr Relat Disord*. 2012;10:363–372. doi: 10.1089/met.2012.0020
197. O'Neil CE, Fulgoni VL 3rd, Nicklas TA. Tree nut consumption is associated with better adiposity measures and cardiovascular and metabolic syndrome health risk factors in U.S. adults: NHANES 2005-2010. *Nutr J*. 2015;14:64. doi: 10.1186/s12937-015-0052-x
198. Hosseinpour-Niazi S, Hosseini S, Mirmiran P, Azizi F. Prospective study of nut consumption and incidence of metabolic syndrome: Tehran Lipid and Glucose Study. *Nutrients*. 2017;9(10):E1056. doi: 10.3390/nu9101056
199. Fulgoni VL 3rd, Dreher M, Davenport AJ. Avocado consumption is associated with better diet quality and nutrient intake, and lower metabolic syndrome risk in US adults: results from the National Health and Nutrition Examination Survey (NHANES) 2001-2008. *Nutr J*. 2013;12:1. doi: 10.1186/1475-2891-12-1
200. Kim YS, Xun P, He K. Fish consumption, long-chain omega-3 polyunsaturated fatty acid intake and risk of metabolic syndrome: a meta-analysis. *Nutrients*. 2015;7:2085–2100. doi: 10.3390/nu7042085

201. Shin D, Joh HK, Kim KH, Park SM. Benefits of potassium intake on metabolic syndrome: the fourth Korean National Health and Nutrition Examination Survey (KNHANES IV). *Atherosclerosis*. 2013;230:80–85. doi: 10.1016/j.atherosclerosis.2013.06.025
202. Lopez-Pascual A, Bes-Rastrollo M, Sayón-Orea C, Perez-Cornago A, Díaz-Gutiérrez J, Pons JJ, Martínez-González MA, González-Muniesa P, Martínez JA. Living at a geographically higher elevation is associated with lower risk of metabolic syndrome: prospective analysis of the SUN cohort. *Front Physiol*. 2016;7:658. doi: 10.3389/fphys.2016.00658
203. Hanley AJ, Williams K, Festa A, Wagenknecht LE, D'Agostino RB Jr, Haffner SM. Liver markers and development of the metabolic syndrome: the Insulin Resistance Atherosclerosis Study. *Diabetes*. 2005;54:3140–3147.
204. Liu S, Sun Q. Sex differences, endogenous sex-hormone hormones, sex-hormone binding globulin, and exogenous disruptors in diabetes and related metabolic outcomes. *J Diabetes*. 2018;10:428–441. doi: 10.1111/1753-0407.12517
205. Al-Khalidi B, Kimball SM, Rotondi MA, Ardern CI. Standardized serum 25-hydroxyvitamin D concentrations are inversely associated with cardiometabolic disease in U.S. adults: a cross-sectional analysis of NHANES, 2001-2010 [published correction appears in *Nutr J*. 2017;16:32]. *Nutr J*. 2017;16:16. doi: 10.1186/s12937-017-0237-6
206. Mayneris-Perxachs J, Guerendiain M, Castellote AI, Estruch R, Covas MI, Fitó M, Salas-Salvadó J, Martínez-González MA, Aros F, Lamuela-Raventós RM, López-Sabater MC; for PREDIMED Study Investigators. Plasma fatty acid composition, estimated desaturase activities, and their relation with the metabolic syndrome in a population at high risk of cardiovascular disease. *Clin Nutr*. 2014;33:90–97. doi: 10.1016/j.clnu.2013.03.001
207. Shuval K, Barlow CE, Finley CE, Gabriel KP, Schmidt MD, DeFina LF. Standing, obesity, and metabolic syndrome: findings from the Cooper Center Longitudinal Study. *Mayo Clin Proc*. 2015;90:1524–1532. doi: 10.1016/j.mayocp.2015.07.022
208. Sabaté J, Wien M. A perspective on vegetarian dietary patterns and risk of metabolic syndrome. *Br J Nutr*. 2015;113(suppl 2):S136–S143. doi: 10.1017/S0007114514004139
209. Benseñor IM, Goulart AC, Molina Mdel C, de Miranda ÉJ, Santos IS, Lotufo PA. Thyrotropin levels, insulin resistance, and metabolic syndrome: a cross-sectional analysis in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Metab Syndr Relat Disord*. 2015;13:362–369. doi: 10.1089/met.2015.0045
210. Vidot DC, Prado G, Hlaing WM, Florez HJ, Arheart KL, Messiah SE. Metabolic syndrome among marijuana users in the United States: an analysis of National Health and Nutrition Examination Survey data. *Am J Med*. 2016;129:173–179. doi: 10.1016/j.amjmed.2015.10.019
211. Kim S, Song Y, Lee JE, Jun S, Shin S, Wie GA, Cho YH, Joung H. Total antioxidant capacity from dietary supplement decreases the likelihood of having metabolic syndrome in Korean adults. *Nutrients*. 2017;9:E1055. doi: 10.3390/nu9101055
212. Baudry J, Lelong H, Adriouch S, Julia C, Allès B, Hercberg S, Touvier M, Lairon D, Galan P, Kesse-Guyot E. Association between organic food consumption and metabolic syndrome: cross-sectional results from the NutriNet-Santé study. *Eur J Nutr*. 2018;57:2477–2488. doi: 10.1007/s00394-107-1520-1
213. Cheriyath P, Duan Y, Qian Z, Nambiar L, Liao D. Obesity, physical activity and the development of metabolic syndrome: the Atherosclerosis Risk in Communities study. *Eur J Cardiovasc Prev Rehabil*. 2010;17:309–313. doi: 10.1097/HJR.0b013e32833189b8
214. Zhang D, Liu X, Liu Y, Sun X, Wang B, Ren Y, Zhao Y, Zhou J, Han C, Yin L, Zhao J, Shi Y, Zhang M, Hu D. Leisure-time physical activity and incident metabolic syndrome: a systematic review and dose-response meta-analysis of cohort studies. *Metabolism*. 2017;75:36–44. doi: 10.1016/j.metabol.2017.08.001
215. Leiter LA, Fitchett DH, Gilbert RE, Gupta M, Mancini GB, McFarlane PA, Ross R, Teoh H, Verma S, Anand S, Camelon K, Chow CM, Cox JL, Després JP, Genest J, Harris SB, Lau DC, Lewanczuk R, Liu PP, Lonn EM, McPherson R, Poirier P, Qaadri S, Rabasa-Lhoret R, Rabkin SW, Sharma AM, Steele AW, Stone JA, Tardif JC, Tobe S, Ur E; Cardiometabolic Risk Working Group: Executive Committee. Cardiometabolic risk in Canada: a detailed analysis and position paper by the Cardiometabolic Risk Working Group. *Can J Cardiol*. 2011;27:e1–e33. doi: 10.1016/j.cjca.2010.12.054
216. López-Jaramillo P, Sánchez RA, Diaz M, Cobos L, Bryce A, Parra Carrillo JZ, Lizcano F, Lanas F, Sinay I, Sierra ID, Peñaherrera E, Bendersky M, Schmid H, Botero R, Urina M, Lara J, Foss MC, Márquez G, Harrap S, Ramírez AJ, Zanchetti A; Latin America Expert Group. Latin American consensus on hypertension in patients with diabetes type 2 and metabolic syndrome. *J Hypertens*. 2013;31:223–238. doi: 10.1097/HJH.0b013e32835c5444
217. Sawant A, Mankeshwar R, Shah S, Raghavan R, Dhongde G, Raje H, D'souza S, Subramanium A, Dhairyawan P, Todur S, Ashavaid TF. Prevalence of metabolic syndrome in urban India. *Cholesterol*. 2011;2011:920983. doi: 10.1155/2011/920983
218. Yadav D, Mahajan S, Subramanian SK, Bisen PS, Chung CH, Prasad GB. Prevalence of metabolic syndrome in type 2 diabetes mellitus using NCEP-ATPIII, IDF and WHO definition and its agreement in Gwalior Chambal region of Central India. *Glob J Health Sci*. 2013;5:142–155. doi: 10.5539/gjhs.v5n6p142
219. Barik A, Das K, Chowdhury A, Rai RK. Metabolic syndrome among rural Indian adults. *Clin Nutr ESPEN*. 2018;23:129–135. doi: 10.1016/j.clnesp.2017.11.002
220. Khanam MA, Qiu C, Lindeboom W, Streatfield PK, Kabir ZN, Wahlin Å. The metabolic syndrome: prevalence, associated factors, and impact on survival among older persons in rural Bangladesh. *PLoS One*. 2011;6:e20259. doi: 10.1371/journal.pone.0020259
221. Amirkalali B, Fakhrzadeh H, Sharifi F, Kelishadi R, Zamani F, Asayesh H, Safiri S, Samavat T, Qorbani M. Prevalence of metabolic syndrome and its components in the Iranian adult population: a systematic review and meta-analysis. *Iran Red Crescent Med J*. 2015;17:e24723. doi: 10.5812/ircmj.24723
222. Oguoma VM, Nwose EU, Richards RS. Prevalence of cardio-metabolic syndrome in Nigeria: a systematic review. *Public Health*. 2015;129:413–423. doi: 10.1016/j.puhe.2015.01.017
223. Peer N, Lombard C, Steyn K, Levitt N. High prevalence of metabolic syndrome in the Black population of Cape Town: the Cardiovascular Risk in Black South Africans (CRIBSA) study. *Eur J Prev Cardiol*. 2015;22:1036–1042. doi: 10.1177/2047487314549744
224. Orces CH, Gavilanez EL. The prevalence of metabolic syndrome among older adults in Ecuador: results of the SABE survey. *Diabetes Metab Syndr*. 2017;11 Suppl 2:S555–S560. doi: 10.1016/j.dsx.2017.04.004
225. Raimi TH, Odusan O, Fasanmade OA, Odewabi AO, Ohwovoriole AE. Metabolic syndrome among apparently healthy Nigerians with the harmonized criteria: prevalence and concordance with the International Diabetes Federation (IDF) and Third Report of the National Cholesterol Education Programme-Adult Treatment Panel III (NCEP-ATP III) criteria." *J Cardiovasc Disease Res*. 2017;8:145–150.
226. Binh TQ, Phuong PT, Nhung BT, Tung do D. Metabolic syndrome among a middle-aged population in the Red River Delta region of Vietnam. *BMC Endocr Disord*. 2014;14:77. doi: 10.1186/1472-6823-14-77
227. Zhao Y, Yan H, Yang R, Li Q, Dang S, Wang Y. Prevalence and determinants of metabolic syndrome among adults in a rural area of Northwest China. *PLoS One*. 2014;9:e91578. doi: 10.1371/journal.pone.0091578
228. van Vliet-Ostaptchouk JV, Nuotio ML, Slagter SN, Doiron D, Fischer K, Foco L, Gaye A, Gögele M, Heier M, Hiekkalinna T, Joensuu A, Newby C, Pang C, Partinen E, Reischl E, Schwienbacher C, Tammesoo ML, Swertz MA, Burton P, Ferretti V, Fortier I, Giepmans L, Harris JR, Hillege HL, Holmen J, Jula A, Kootstra-Ros JE, Kvaløy K, Holmen TL, Männistö S, Metspalu A, Midthjell K, Murtagh MJ, Peters A, Pramstaller PP, Saaristo T, Salomaa V, Stolk RP, Uusitupa M, van der Harst P, van der Klauw MM, Waldenberger M, Perola M, Wolffenbuttel BH. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. *BMC Endocr Disord*. 2014;14:9. doi: 10.1186/1472-6823-14-9
229. Vernay M, Salanave B, de Peretti C, Druet C, Malon A, Deschamps V, Hercberg S, Castetbon K. Metabolic syndrome and socioeconomic status in France: the French Nutrition and Health Survey (ENNS, 2006-2007). *Int J Public Health*. 2013;58:855–864. doi: 10.1007/s00038-013-0501-2
230. de Carvalho Vidigal F, Bressan J, Babio N, Salas-Salvadó J. Prevalence of metabolic syndrome in Brazilian adults: a systematic review. *BMC Public Health*. 2013;13:1198. doi: 10.1186/1471-2458-13-1198
231. Salas R, Bibiloni Mdel M, Ramos E, Villarreal JZ, Pons A, Tur JA, Sureda A. Metabolic syndrome prevalence among Northern Mexican adult population. *PLoS One*. 2014;9:e105581. doi: 10.1371/journal.pone.0105581
232. Li M, McCulloch B, McDermott R. Metabolic syndrome and incident coronary heart disease in Australian indigenous populations. *Obesity (Silver Spring)*. 2012;20:1308–1312. doi: 10.1038/oby.2011.156

11. KIDNEY DISEASE

ICD-10 N18.0. See Charts 11-1 through 11-15

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Definition

CKD, defined as reduced GFR (<60 $mL\cdot min^{-1}\cdot 1.73\ m^{-2}$), excess urinary albumin excretion (≥30 mg/d or mg/gCr), or both, is a serious health condition and a worldwide public health problem that is associated with poor outcomes and a high cost to the US health-care system.[1]

Abbreviations Used in Chapter 11

ACC	American College of Cardiology
ACR	albumin-to-creatinine ratio
AF	atrial fibrillation
AHA	American Heart Association
AI	American Indian
AMI	acute myocardial infarction
AN	Alaska Native
ARIC	Atherosclerosis Risk in Communities Study
ASCVD	atherosclerotic cardiovascular disease
ASHD	atherosclerotic heart disease
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass graft surgery
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CHD	coronary heart disease
CHF	congestive heart failure
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVA	cerebrovascular accident
CVD	cardiovascular disease
DBP	diastolic blood pressure
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
GBD	Global Burden of Disease
GFR	glomerular filtration rate
GWAS	Genome-Wide Association Study
HANDLS	Health Aging in Neighborhoods of Diversity Across the Life Span
HBP	high blood pressure
HF	heart failure
HR	hazard ratio
HTN	hypertension
ICD-10	*International Classification of Diseases, 10th Revision*
IHD	ischemic heart disease
JHS	Jackson Heart Study
KDIGO	Kidney Disease: Improving Global Outcomes
MACE	major adverse cardiovascular events
MDRD	Modification of Diet in Renal Disease
MESA	Multi-Ethnic Study of Atherosclerosis
MR	mitral regurgitation
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey

(Continued)

Abbreviations Used in Chapter 11 Continued

NIS	National (Nationwide) Inpatient Sample
OR	odds ratio
OSA	obstructive sleep apnea
PAD	peripheral artery disease
PCI	percutaneous coronary intervention
PE	pulmonary embolism
PI	Pacific Islander
RR	relative risk
SBP	systolic blood pressure
SCA	sudden cardiac arrest
SCD	sudden cardiac death
SES	socioeconomic status
SHARP	Study of Heart and Renal Protection
SNP	single-nucleotide polymorphism
SPRINT	Systolic Blood Pressure Intervention Trial
SR	self-report
STS	Society of Thoracic Surgeons
TAVR	transcatheter aortic valve replacement
TIA	transient ischemic attack
TVT	Transcatheter Valve Therapy
USRDS	United States Renal Data System
VA	ventricular arrhythmia
VHD	valvular heart disease
VTE	venous thromboembolism

- GFR is usually estimated from the serum creatinine level using equations that account for age, sex, and race. The CKD-EPI equation more accurately estimates GFR from serum creatinine than the previously established MDRD Study equation.[2]
- The spot urine ACR ratio is recommended as a measure of urine albumin excretion.

The KDIGO CKD 2012 guideline recommends characterizing CKD according to eGFR category (G1–G5) and albuminuria category (A1–A3), as well as cause of CKD (Chart 11-1).[3]

ESRD is defined as severe CKD requiring chronic renal replacement treatment such as hemodialysis, peritoneal dialysis, or kidney transplantation.[1] ESRD is an extremely high-risk population for cardiovascular morbidity and mortality.

Prevalence (See Charts 11-1 through 11-4)

- According to the United States Renal Data System, the overall prevalence of CKD in the United States among NHANES participants aged ≥20 years was 14.8% (95% CI, 13.6%–16.0%) in 2011 to 2014.[1] The prevalence of CKD by eGFR and albuminuria categories is shown in Chart 11-1.
- The prevalence of CKD increases substantially with age, as follows[1]:
  - — 6.6% for those 20 to 39 years of age
  - — 10.6% for those 40 to 59 years of age
  - — 32.6% for those ≥60 years of age

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- From 1999 to 2014, the prevalence of ACR ≥30 mg/g was higher but prevalence of eGFR <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ was lower among NH blacks than NH whites.[1]
- At the end of 2015, the unadjusted prevalence of ESRD estimated from cases reported to the Centers for Medicare & Medicaid Services in the United States was 2128 per million (0.21%; Chart 11-2). Of the 703 243 total patients receiving treatment for ESRD in the United States, 63% were on hemodialysis, 7% were on peritoneal dialysis, and 30% had received a kidney transplant.[1]
- The prevalence of ESRD varies regionally across the United States (Chart 11-3), mirroring the prevalence of traditional risk factors such as DM or hypertension.[1]
- ESRD prevalence is highest in Native Hawaiians/Pacific Islanders than in other races, and prevalence is higher among Hispanics than NH individuals (Chart 11-4).[1]

Incidence (See Chart 11-5)

- For US adults aged 30 to 49, 50 to 64, and ≥65 years without CKD, the residual lifetime incidences of CKD are projected to be 54%, 52%, and 42%, respectively, in the CKD Health Policy Model simulation based on 1999 to 2010 NHANES data.[4]
- The incidence of ESRD is higher among blacks than whites, a disparity that persists even after controlling for major ESRD risk factors and that might be explained in part by the higher prevalence of albuminuria and *APOL1* in this population.[5–7]

Secular Trends (See Charts 11-2 and 11-5)

- According to NHANES data, the prevalence of CKD (eGFR 15–59 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) in the United States increased slowly over time until 2003 to 2004 because of an aging population and higher prevalence of risk factors, but the prevalence plateaued from 2004 to 2012.[8]
- The prevalence of ESRD is now increasing more rapidly primarily because of improved survival, because the incidence rate appears to be stabilizing or decreasing slightly (Chart 11-2).[1]
- The prevalence of CKD in adults ≥30 years of age is projected to increase to 14.4% in 2020 and 16.7% in 2030.[4]
- The incidence of ESRD adjusted for age, sex, race, and ethnicity has been stable for >15 years (Chart 11-2). Despite improvements in incidence rate among blacks and Native Americans, substantial disparities persist (Chart 11-5).
- Among the very old (>80 years), the prevalence of an eGFR <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ increased from 40.5% in 1988 to 1994 to 49.9% and 51.2% in 1999 to 2004 and 2005 to 2010, respectively. The prevalence of albuminuria (ACR ≥30 mg/g) was 30.9%, 33.0%, and 30.6% in 1988 to 1994, 1999 to 2004, and 2005 to 2010, respectively.[1]

Costs

- In 2015, Medicare spent over $64 billion caring for people with CKD. More than 70% of CKD spending was attributable to patients who had comorbid DM or CHF.[1]
- The total annual cost of treating ESRD in the United States was $33.9 billion in 2015, which represents >7% of total Medicare claims paid.[1] In 2015, total spending per patient was $88 750 for patients on hemodialysis, $75 140 for those receiving peritoneal dialysis, and $34 084 for transplant patients.[1]

Risk Factors (See Charts 11-6 and 11-7)

- Many traditional CVD risk factors are also risk factors for CKD, including older age, male sex, hypertension, DM, smoking, and family history of CVD (Chart 11-6). In NHANES 2011 to 2014, the prevalence of CKD was 32% in adults aged ≥20 years with HBP and 39% in adults with DM. Among adults with obesity (BMI >30 kg/m^2), nearly 18% had CKD.[1]
- Among those aged ≥60 years with CKD in NHANES 2013 to 2014, 59% had HBP and 35% had DM.[9]
- Even early stages of elevated BP and stage 1 hypertension as defined by the 2017 ACC/AHA guidelines (SBP of 120–139 mm Hg or DBP of 80–89 mm Hg) were associated with incident decreased eGFR (<60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) in a meta-analysis of observational cohorts (RR, 1.19 [95% CI, 1.07–1.33] over a mean follow-up of 6.5 years).[10]
- OSA is associated with CKD and CKD progression independent of BMI and other traditional risk factors.[11]
- Zip code–level poverty is associated with ≈25% higher ESRD incidence after accounting for age, sex, and race/ethnicity, and this association appears to be getting stronger over time (2005–2010 versus 1995–2004).[12]

- Importantly, cardiovascular fitness and healthy lifestyles are associated with decreased risk of CKD.[13–16] For example, having more of the AHA's Life's Simple 7 ideal health factors was associated with progressively lower risk of incident CKD in the ARIC study (Chart 11-7).[15]

Awareness

- Awareness of CKD status in NHANES was particularly low, ranging from 3% to 5% for early-stage CKD to 53% for more advanced CKD (eGFR 15–29 $mL{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$).[17]
- The prevalence of recognized CKD, meaning that a provider or billing coder recognized the prevalence of CKD, was also low in the Medicare 5% sample, but it has increased over time, from 5.9% in 2006 to 11.7% in 2015.[1]

Global Burden of Kidney Disease (See Charts 11-8 through 11-11)

- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories.[17]
  - According to the GBD Study, the prevalence of CKD is rising in almost every country of the world, primarily because of aging populations (Chart 11-8).[17]
- In 2016, the total estimated prevalence is 276 million people (95% CI, 252–300 million), a 31% increase since 2006.[17] Notably, there have been downward revisions of estimated CKD prevalence in recent years compared with prior GBD estimates because of a refinement of modeling methods. The age-standardized prevalence of CKD is highest in the Middle East/North Africa region, sub-Saharan Africa, and central Latin America (Chart 11-9).[17]
- Globally, the burden of years lived with disability attributable to CKD is generally heaviest in high-income countries (Chart 11-10). Total years lived with disability attributable to CKD were 8.8 million (95% CI, 6.6–11.1 million) in 2016.[17]
- The Pacific Island countries had the highest mortality rates attributable to CKD in 2016 (Chart 11-11).[17]
- GBD 2015 has also estimated the global prevalence of CKD by cause and the percentage change from 2005 to 2015[18]:
  - The prevalence of CKD attributable to DM rose 27% during this time period to 101 million (95% CI, 87–116 million), but age-standardized prevalence only increased 2.1%.
  - CKD attributable to HBP rose 26% to 79 million (95% CI, 68–91 million), but age-standardized prevalence only increased 0.2%.
  - CKD attributable to glomerulonephritis rose 29% to 67 million (95% CI, 58–77 million), but age standardized prevalence only increased 1.1%.
  - CKD attributable to other causes rose 26% to 95 million (95% CI, 81–109 million), but age-standardized prevalence only increased by 0.1%.
- CKD rose from the 25th leading cause of death in 1990 to the 17th leading cause of death in 2015.[19]

Family History and Genetics

- There is evidence of moderate heritability for creatinine and GFR, which supports a genetic component of CKD.[20]
- GWASs have revealed several candidate loci for CKD phenotypes, including GFR, albuminuria, kidney injury, and diabetic kidney disease, although the clinical implications and utility of these genetic variants are not yet clear.[20–28]
- Race differences in CKD prevalence might be attributable to differences in genetic risk. The *APOL1* gene has been well studied as a kidney disease locus in individuals of African ancestry.[7] SNPs in *APOL1* that are present in individuals of African ancestry but absent in other racial groups might have been subject to positive selection, conferring protection against trypanosome infection but leading to increased risk of renal disease, potentially through disruption of mitochondrial function.[21]
- Although certain variants of *APOL1* increase risk, it only explains a portion of the disparity in ESRD risk between blacks and nonblacks.[22,23] For example, eGFR decline was faster even for black subjects with low-risk *APOL1* status (0–1 allele) than for whites in CARDIA; this difference was attenuated by adjustment for SES and traditional risk factors.[24]
- *APOL1* does not appear to be associated with overall risk for CVD among blacks with hypertension-attributed CKD.[25]

Social Determinants of CKD

- A recent meta-analysis of 43 studies examining associations between socioeconomic indicators (income, education and occupation) found that lower SES, particularly income, was associated with a higher prevalence of CKD and faster progression to ESRD.[26] This association was observed in higher- versus lower- or middle-income countries and was more pronounced in the United States relative to Europe.

- In a cross-sectional analysis of 9126 lower-income participants from NHANES 2003 to 2008, food insecurity (ie, the inability to acquire nutritional foods) was associated with a 67% higher odds of age-adjusted prevalent CKD in those with DM and a 37% higher odds of age-adjusted prevalent CKD in those with hypertension. A similar analysis in 1239 participants in the HANDLS study revealed a marginally significant higher odds of CKD in the full cohort, with no evidence of stronger associations in individuals with DM or hypertension.[27]
- In a study of 1620 participants from HANDLS with preserved baseline kidney function, self-reported experiences of discrimination were associated with lower kidney function assessed via GFR, and associations were particularly pronounced for African-American females relative to white females, African-American males, and NH white males.[28]

Kidney and CVD

Impact of CKD on CVD Outcomes

- CKD is a risk factor for incident and recurrent CHD events, stroke, HF, VTE, and AF and is considered to be a CHD risk equivalent for the purposes of recommending primary prevention therapies such as statins or aggressive BP control.[29–35]
- The association of reduced eGFR with cardiovascular risk is generally similar across age, race, and sex subgroups,[36] although, albuminuria tends to be a stronger risk factor for females than for males and for older (>65 years) versus younger people.[34]
- The addition of eGFR or albuminuria improves CVD prediction beyond traditional risk factors used in risk equations.[34]

Prevalence of CVD Among People With CKD (See Charts 11-12 and 11-13)

- People with CKD, as well as those with ESRD, have an extremely high prevalence of comorbid CVDs ranging from IHD and HF to arrhythmias and VTE (Charts 11-12 and 11-13).[1]
- Nearly two-thirds (65.8%) of CKD patients aged 66 years or older have CVD, compared with approximately one-third (31.9%) of patients without CKD in this age group.[1]
- The prevalence of CVD in ESRD patients differs by treatment modality. Approximately 70% of ESRD patients on hemodialysis have any CVD, whereas 57% of peritoneal dialysis patients and 42% of transplant patients have any CVD (Chart 11-13).

Incidence of CVD Events Among People With CKD

- In 3 community-based cohort studies (JHS, CHS, and MESA), absolute incidence rates for HF, CHD, and stroke for participants with versus without CKD were 22 versus 6.2 (per 1000 person-years) for HF, 24.5 versus 8.4 for CHD, and 13.4 versus 4.8 for stroke.[37]
- Both eGFR and albuminuria appear to more strongly predict HF events than CHD or stroke events.[34]
- GFR predicts stroke risk but is not as strongly associated as albuminuria. In 4 community-based cohorts, lower eGFR (45 versus 95 mL·min^{-1}·1.73 m^{-2}) was associated with an increased risk for ischemic stroke (HR, 1.30 [95% CI, 1.01–1.68]) but not hemorrhagic stroke (HR, 0.92 [95% CI, 0.47–1.81]). Albuminuria (ACR of 300 versus 5 mg/g) was associated with both ischemic and hemorrhagic stroke (HR, 1.62 [95% CI, 1.27–2.07] and 2.57 [95% CI, 1.37–4.83], respectively).[38] In a meta-analysis of 83 studies of >30 000 strokes, there were linear relationships of both eGFR and albuminuria with stroke regardless of stroke subtype.[33] Among people with CKD, proteinuria but not eGFR independently predicted stroke risk.[39]
- In one study of people with CKD aged 50 to 79 years, the ACC/AHA pooled cohort risk equations appeared to be well calibrated (Hosmer-Lemeshow χ^2=2.7, P=0.45), with moderately good discrimination (C index, 0.71 [95% CI, 0.65–0.77]) for ASCVD events.[40]
- Females with CKD appear to have higher risk of incident PAD than males, particularly at younger ages.[41]
- A patient-level pooled analysis of randomized trials explored the effect of CKD on prognosis for females who undergo PCI.[42] Creatinine clearance <45 mL/min was an independent risk factor for 3-year MACE (adjusted HR, 1.56) and all-cause mortality (adjusted HR, 2.67).
- Despite higher overall event rates than NH whites, NH blacks with CKD have similar (or possibly lower) rates of ASCVD events, HF events, and death after adjustment for demographic factors, baseline kidney function, and cardiovascular risk factors.[43] However, the risk of HF associated with CKD might be greater for blacks and Hispanics than for whites.[37]
- Clinically significant bradyarrhythmias appear to be more common than ventricular arrhythmias among hemodialysis patients and are highest in the immediate hours before dialysis sessions.[44]

Mortality Attributable to CVD Among People With CKD (See Charts 11-14 and 11-15)

- CVD is the leading cause of death among those with kidney disease. For those with ESRD, CVD accounts for more than half of deaths with known causes, with arrhythmias and SCD accounting for nearly 40% (Chart 11-14).[1]
- For people with CKD, death attributable to CVD is more common than progression to ESRD.[1]
- Mortality risk depends not only on eGFR but also on category of albuminuria (Chart 11-15). The adjusted RR of all-cause mortality and cardiovascular mortality is highest in those with eGFR 15 to 30 mL·min^{-1}·1.73 m^{-2} and those with ACR >300 mg/g.
- For patients with severe valvular heart disease, CKD is a particularly strong risk factor for mortality. In the Duke University Echocardiography Database (1999–2013), 5-year survival was substantially lower for CKD than for non-CKD patients (42% versus 67% for severe aortic stenosis and 37% versus 65% for severe MR, CKD versus non-CKD, respectively).[45]
- Elevated levels of the alternative glomerular filtration marker cystatin C have been associated with increased risk for CVD and all-cause mortality in studies from a broad range of cohorts.
  - The addition of cystatin C to the combination of creatinine and ACR significantly improves the prediction of all-cause mortality, cardiovascular death, and development of ESRD.[46]
  - Cystatin C–based eGFR was a stronger predictor of HF than creatinine-based eGFR among patients with CKD in the Chronic Renal Insufficiency Cohort.[47]
  - These strengthened associations with outcomes might be explained in part by non-GFR determinants of cystatin C such as chronic inflammation.[48]

Costs of CVD in People With CKD

- In 2015, admissions for CVD accounted for 26% of all inpatient spending for ESRD patients.[1]
- In the SHARP study of patients in Europe, North America, and Australasia, nonfatal major cardiovascular events were associated with £6133 (95% CI, £5608–£6658) higher costs for ESRD patients on dialysis and £4350 (95% CI, £3819–£4880) for other CKD patients in the year of the event (compared with years before the event).[49]
- Worse preoperative creatinine clearance was associated with higher total costs of CABG from 2000 to 2012 in the STS database ($1250 per 10 mL/min lower clearance).[50]

Prevention and Treatment of CVD in People With CKD

- One potential explanation for the higher CVD event rate in people with CKD is the low uptake of standard therapies. Furthermore, people with advanced CKD and ESRD are often excluded from clinical trials of cardiovascular drugs and devices,[51,52] although recent observational data from large registries can provide insight into the risks and benefits in this population.
- In a nationwide US cohort that included 4726 participants with CKD, only 2366 (50%) were taking statins, whereas an additional 1984 participants (42%) met recommendations for statin treatment according to the ACC/AHA guidelines but were not using statins.[40]
- As shown in SPRINT in patients with hypertension but without DM, intensive SBP lowering (target <120 mm Hg versus <140 mm Hg) reduced rates of major cardiovascular events and all-cause death to a similar extent among participants with and without CKD and had no effect on the primary kidney end point of >50% decrease in eGFR or ESRD (HR, 0.90 [95% CI, 0.44–1.83]).[53]
- For CKD and ESRD patients with multivessel CAD, CABG may be associated with improved outcomes compared with PCI.[54] Similar findings were seen in a Northern California Kaiser Permanente cohort.[55]
- People with CKD are at higher risk of complications after PCI, and accurate estimation of kidney function is required to dose antiplatelet and antithrombotic medications. Compared with older equations (Cockcroft-Gault), the CKD-EPI eGFR equation more accurately predicted kidney outcomes and appropriate drug dosing in a large sample of nearly 130 000 patients undergoing PCI in Michigan.[56]
- In a study of >12 000 people undergoing hemodialysis in the United States Renal Data System who had AF, only 15% initiated warfarin therapy within 30 days, and 70% discontinued use within 1 year.[57] Warfarin was marginally associated with reductions in ischemic stroke and mortality. In a large meta-analysis of observational studies of people with AF, warfarin use was associated with reductions in thromboembolic events (HR, 0.70) and mortality (HR, 0.65) among those with less severe CKD but was not associated with benefit (HR, 0.96 for mortality) in ESRD.[58]
- Low eGFR is an indication for reduced dosing of non–vitamin K antagonist oral anticoagulant drugs. Among nearly 15 000 US Air Force patients prescribed non–vitamin K antagonist oral anticoagulant drugs in an administrative database, 1473 had a renal indication for

reduced dosing, and 43% of these were potentially overdosed. Potential overdosing was associated with increased risk of major bleeding (HR, 2.9 [95% CI, 1.07–4.46]).[59]

- Patients with eGFR <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ and left bundle-branch block (but not other morphologies) appear to derive greater absolute reductions in death and HF from cardiac resynchronization with a defibrillator than patients with higher eGFR.[60]
- For patients undergoing TAVR in the United Kingdom, eGFR <45 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ was associated with higher odds of in-hospital (adjusted OR, 1.45 [95% CI, 1.03–2.05]) and longer-term (median, 543 days; adjusted OR, 1.36 [95% CI, 1.17–1.58]) mortality compared with higher eGFR.[61] Somewhat higher odds of in-hospital mortality after TAVR were seen for those with ESRD compared with all others in the NIS 2011 to 2014 (adjusted OR, 2.21 [95% CI, 1.81–2.69]).[62]
- For patients with eGFR <60 but >15 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ undergoing TAVR in the TVT registry, approximately one-third will die and 1 in 6 will require dialysis within a year.[63]
- In a large, nationally representative sample of hemodialysis patients hospitalized for PAD, the number of endovascular procedures increased nearly 3-fold and the number of surgical procedures dropped by more than two-thirds from 2000 to 2012.[64]

Global Burden of CVD Among People With CKD

- In low- and middle-income countries, the burden of CKD is high (see Global Burden of Kidney Disease), but data on the magnitude of the association between CKD and various cardiovascular outcomes are lacking. These data are necessary to properly model the public health and economic burden of CKD in these countries.

FOOTNOTE

Disclosure: A portion of the data reported has been supplied by the United States Renal Data System.[1] The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government.

				Albuminuria categories		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m²)	G1	Normal to high	≥ 90	54.7	4.3	0.4
	G2	Mildly decreased	60-89	30.4	2.6	0.3
	G3a	Mildly to moderately decreased	45-59	3.9	0.9	0.2
	G3b	Moderately to severely decreased	30-44	1.0	0.5	0.2
	G4	Severely decreased	15-29	0.1	0.1	0.2
	G5	Kidney failure	< 15	<0.001	0.001	0.01

Chart 11-1. Percentage of NHANES participants within the KDIGO 2012 prognosis of chronic kidney disease by GFR and albuminuria categories, 2011 to 2014 (2017 USRDS Annual Report, volume 1, Table 1.1).[1]

GFR indicates glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; NHANES, National Health and Nutrition Examination Survey; and USRDS, United States Renal Data System.

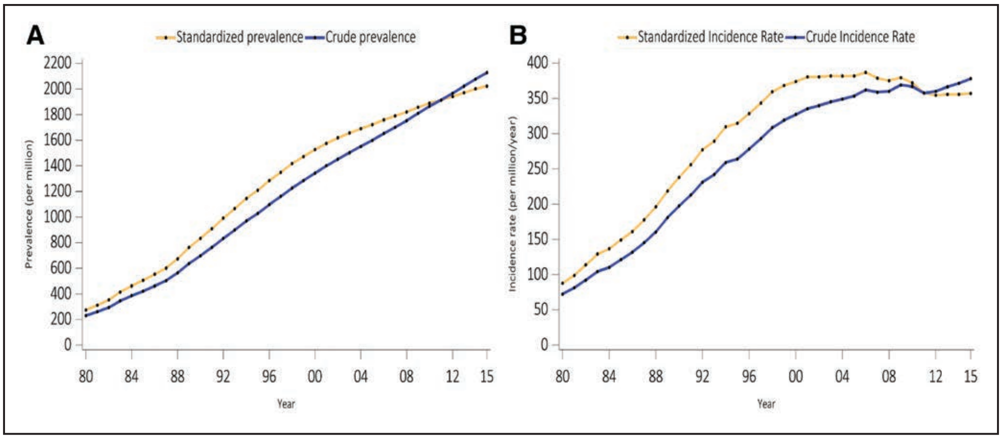

Chart 11-2. Trends in unadjusted and standardized* end-stage renal disease (ESRD) prevalence (A) and incidence rates (B) from 1980 to 2015 in the United States (2017 USRDS Annual Data Report, volume 2, Figures 1.7a and 1.1).[1]
USRDS indicates United States Renal Data System.
*Standardized for age, sex, and race. The standard population was the US population in 2011.
Source: Reference Tables A.2(2), B.2(2), and special analyses, USRDS ESRD database.

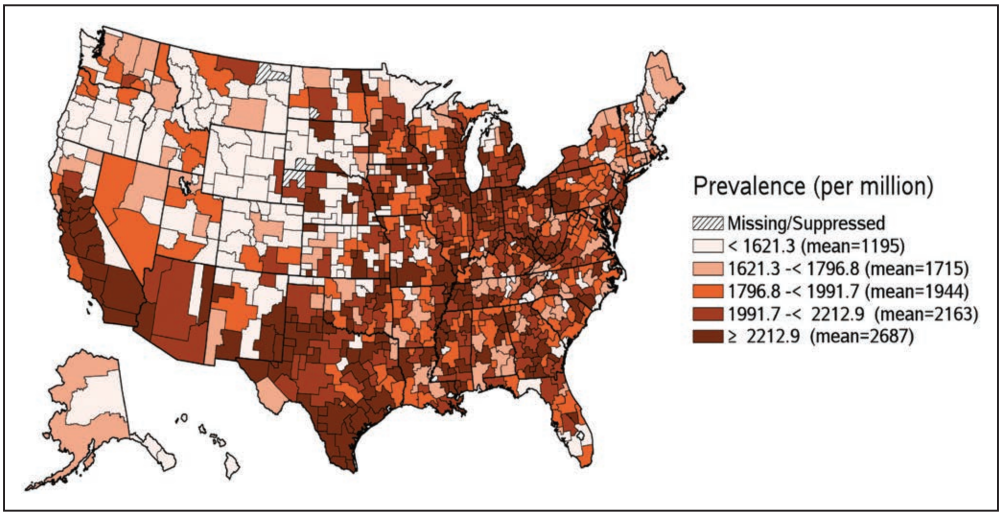

Chart 11-3. Map of the standardized prevalence (per million/year) of end-stage renal disease (ESRD) by health service area in the US population, 2011 to 2015* (2017 USRDS Annual Data Report, volume 2, Figure 1.9).[1]
USRDS indicates United States Renal Data System.
*Standardized for age, sex, and race. The standard population was the US population in 2011. Three health service areas were suppressed because the ratio of unadjusted rate to adjusted rate or adjusted rate to unadjusted rate was >3. Values for cells with ≤10 patients are suppressed.
Source: Special analyses, USRDS ESRD database.

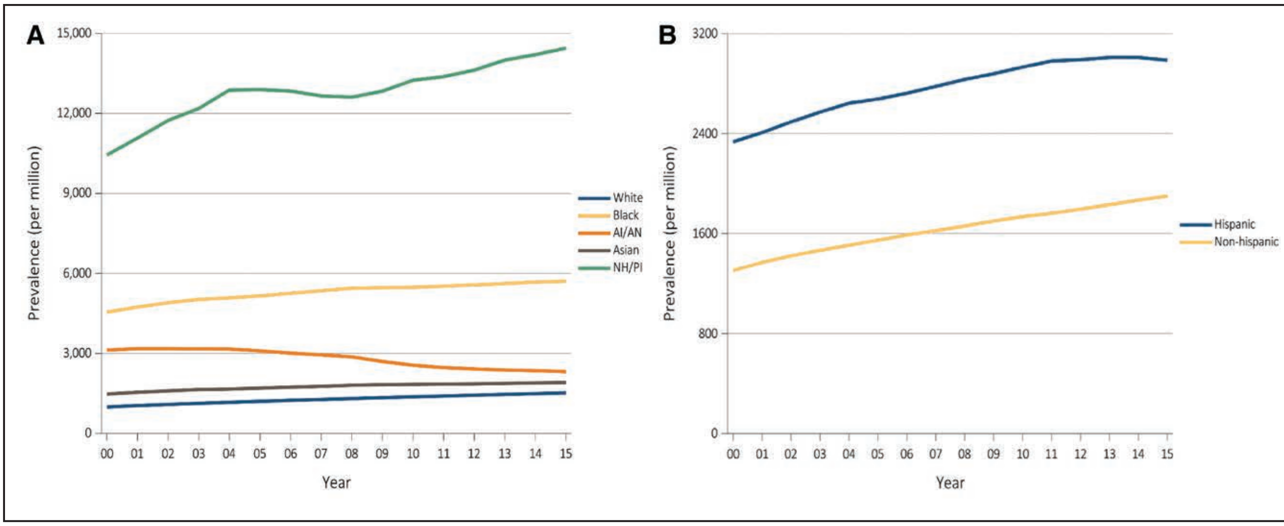

Chart 11-4. Trends in adjusted* prevalence (per million) of end-stage renal disease (ESRD), by race (A) and Hispanic ethnicity (B) in the US population, 2000 to 2015 (2017 USRDS Annual Data Report, volume 2, Figure 1.11 and 1.12).[1]

AI indicates American Indian; AN, Alaska Native; NH, non-Hispanic; PI, Pacific Islander; and USRDS, United States Renal Data System.

*Year-end point prevalence standardized for age and sex; the ethnicity analysis (**B**) is further adjusted for race. The standard population was the US population in 2011.

Source: Tables B.1, B.2(2), and special analyses, USRDS ESRD database.

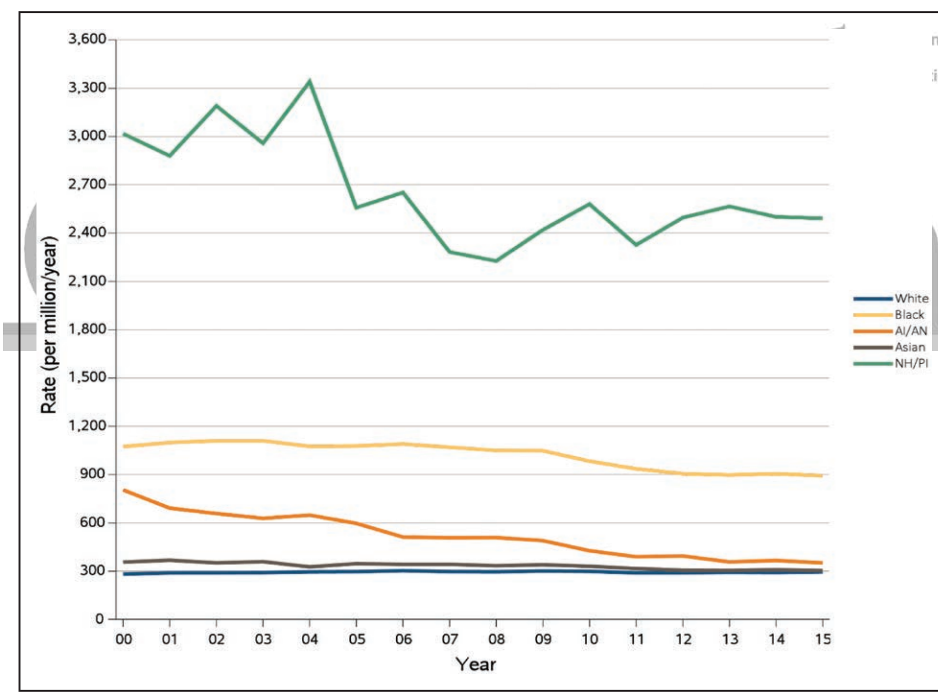

Chart 11-5. Trends in standardized* end-stage renal disease (ESRD) incidence rate (per million/year), by race, in the US population, 2000 to 2015 (2017 USRDS Annual Data Report, volume 2, Figure 1.5).[1]

AI indicates American Indian; AN, Alaska Native; NH, non-Hispanic; PI, Pacific Islander; and USRDS, United States Renal Data System.

*Standardized for age and sex. The standard population was the US population in 2011.

Source: Tables A.2(2) and special analyses, USRDS ESRD database.

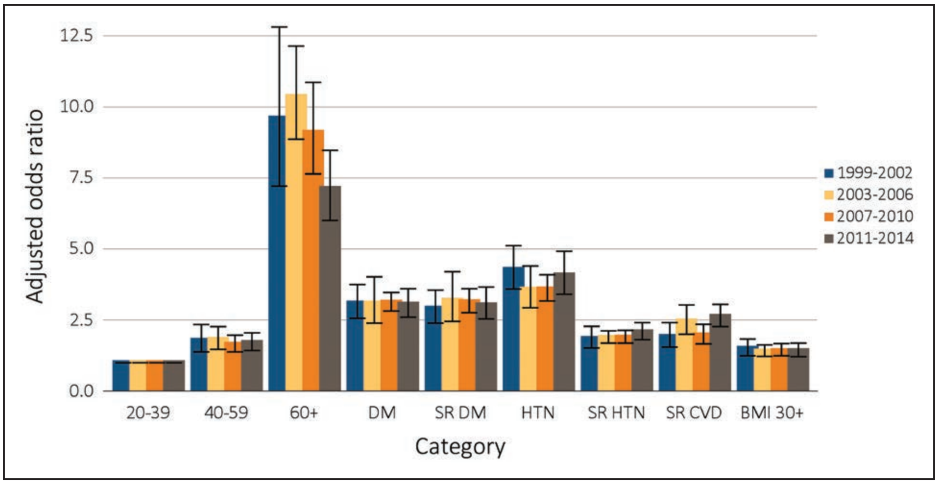

Chart 11-6. Adjusted odds ratios of chronic kidney disease in NHANES participants by risk factor, 1999 to 2014 (2017 USRDS Annual Data Report, volume 1, Figure 1.7b).[1]

Chronic kidney disease was defined as presence of estimated glomerular filtration rate (eGFR) <60 mL·min^{-1}·1.73 m^{-2}, urine albumin-to-creatinine ratio (ACR) ≥30 mg/g, and either eGFR <60 mL·min^{-1}·1.73 m^{-2} or ACR ≥30 mg/g for each of the comorbid conditions. Adjusted for age, sex, and race; single-sample estimates of eGFR and ACR; eGFR calculated with the Chronic Kidney Disease Epidemiology Collaboration equation. Whisker lines indicate 95% CIs.

BMI indicates body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; NHANES, National Health and Nutrition Examination Survey; SR, self-report; and USRDS, US Renal Data System.

Source: NHANES, 1999 to 2002, 2003 to 2006, 2007 to 2010, and 2011 to 2014 participants aged ≥20 years.

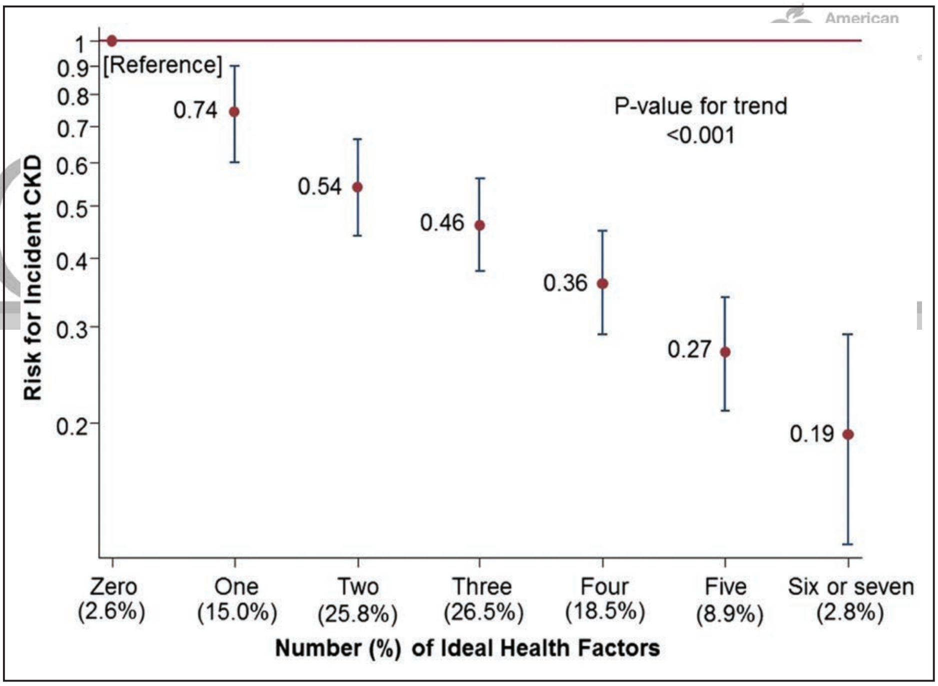

Chart 11-7. Relationship of the AHA's Life's Simple 7 health factors and risk of incident CKD.

Hazard ratio adjusted for age, sex, race, and baseline estimated glomerular filtration rate. Error bars represent the 95% CI.[15]

AHA indicates American Heart Association, and CKD, chronic kidney disease.

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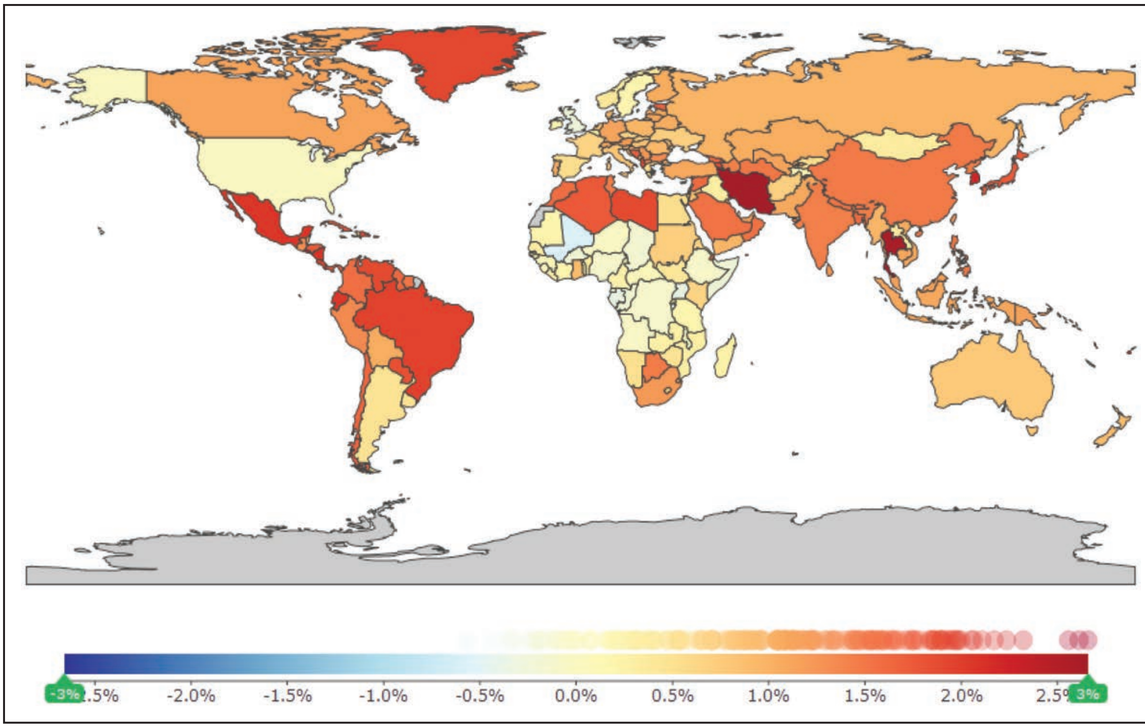

Chart 11-8. Annual percentage change in the prevalence of chronic kidney disease per 100 000 population, all ages, both sexes, 1990 to 2016.
Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[17] Printed with permission. Copyright © 2017, University of Washington.

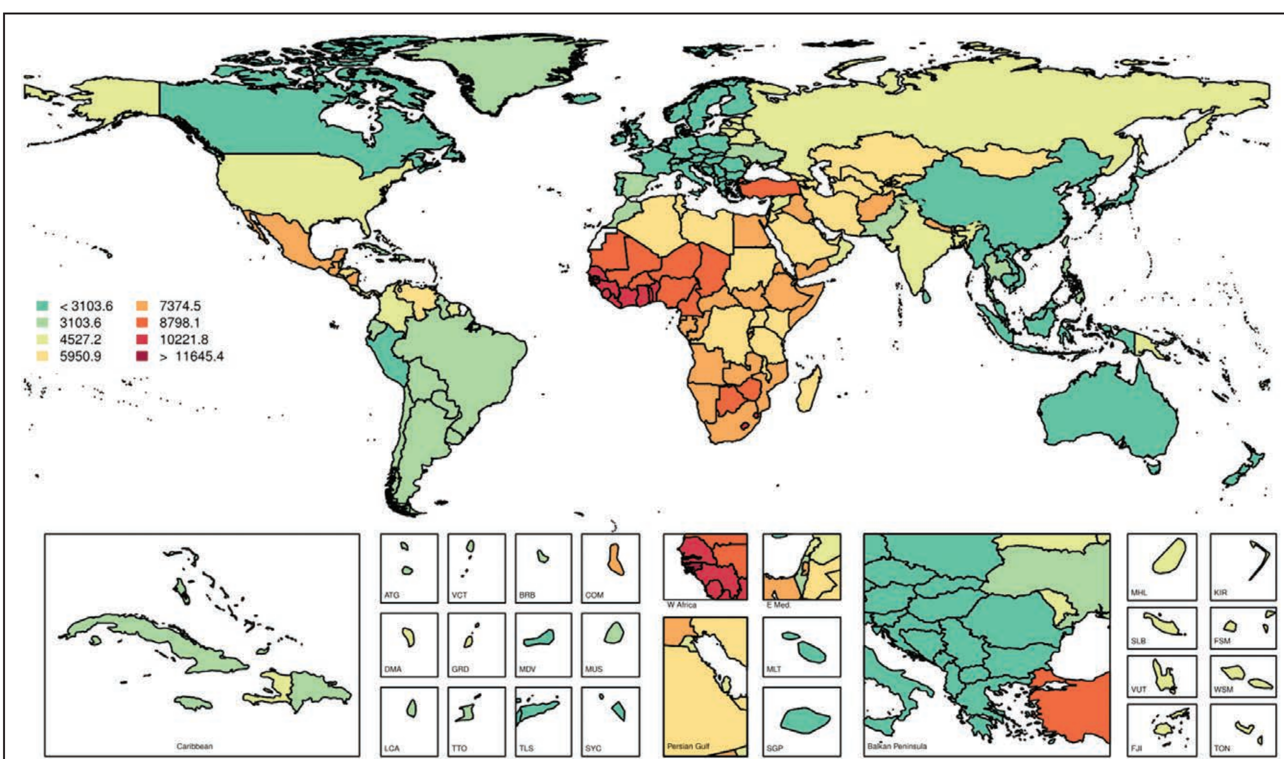

Chart 11-9. Age-standardized global prevalence rates for chronic kidney disease per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[17] Printed with permission. Copyright © 2017, University of Washington.

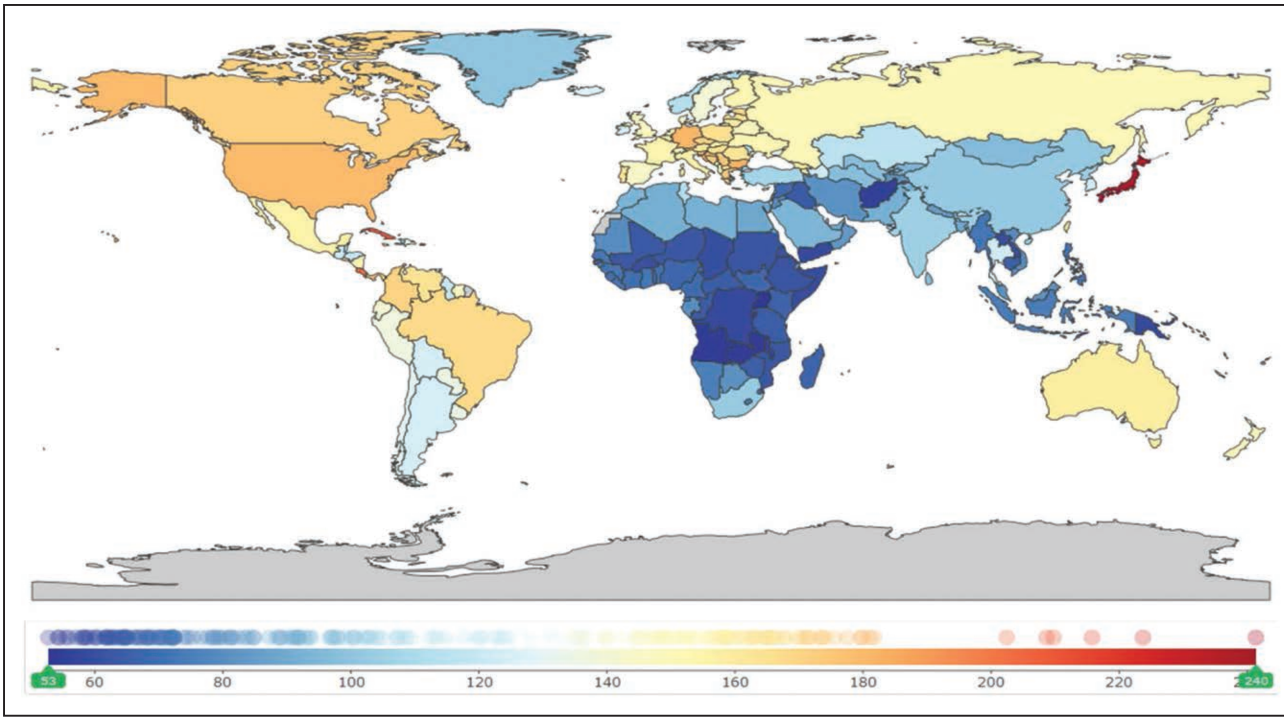

Chart 11-10. Years of life lived with disability attributable to chronic kidney disease, both sexes, all ages, 2016.
Years of life lived with disability per 100 000.
Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[17] Printed with permission. Copyright © 2017, University of Washington.

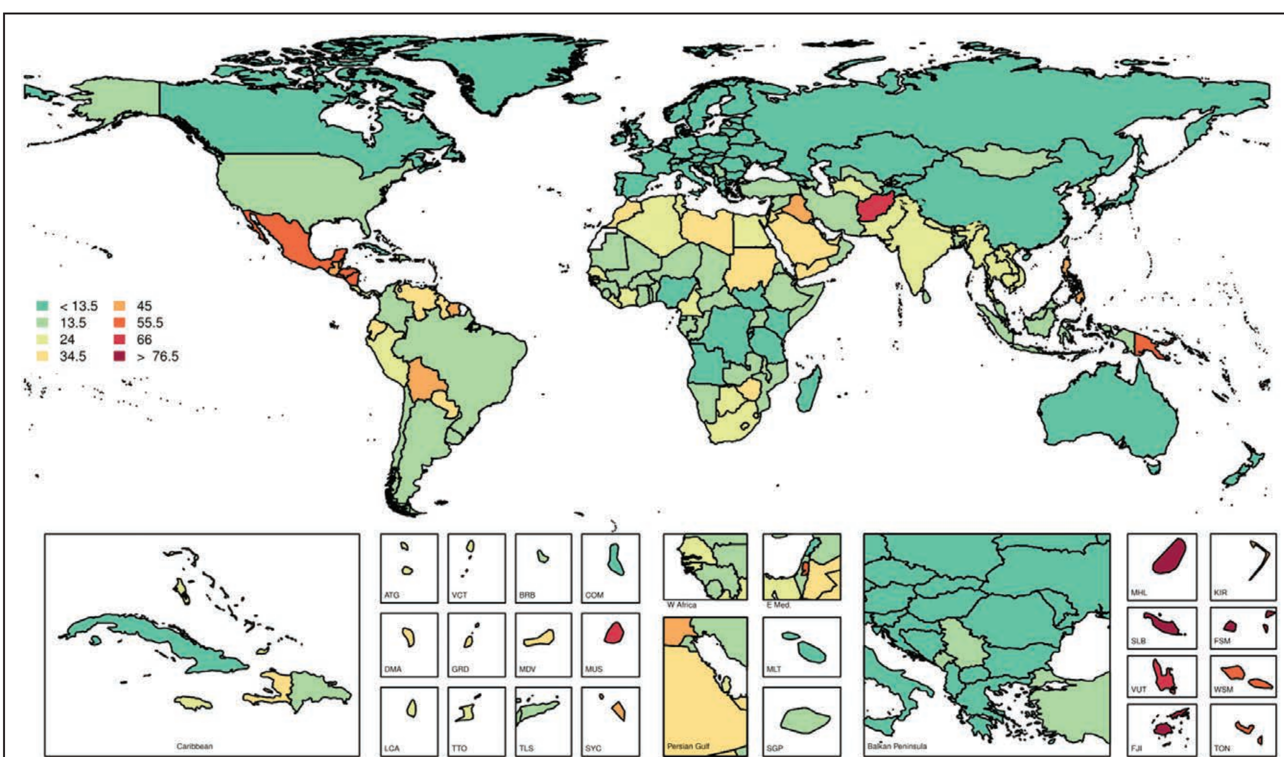

Chart 11-11. Age-standardized global mortality rates for chronic kidney disease per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[17] Printed with permission. Copyright © 2017, University of Washington.

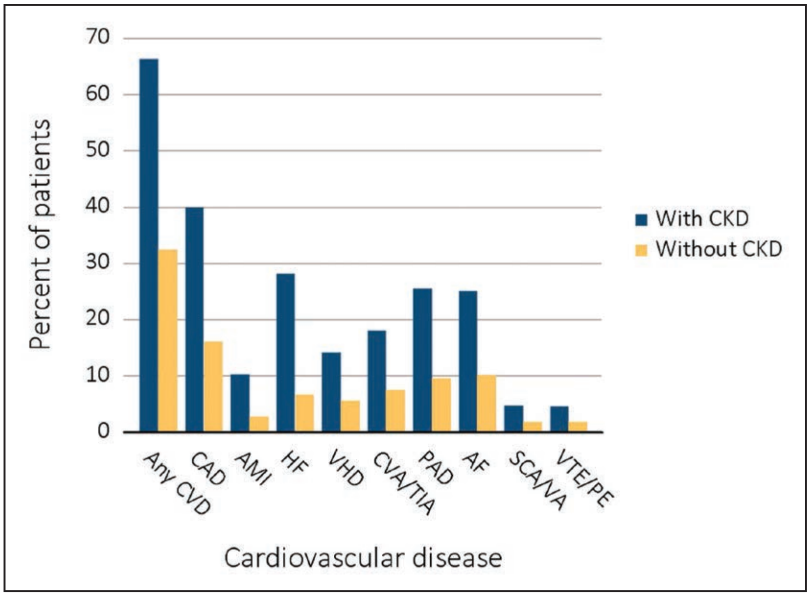

Chart 11-12. Prevalence of CVD in patients with or without CKD, 2015 (2017 USRDS Annual Data Report, volume 1, Figure 4.1).[1]
AF indicates atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CKD, chronic kidney disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; HF, heart failure; PAD, peripheral arterial disease; PE, pulmonary embolism; SCA, sudden cardiac arrest; TIA, transient ischemic attack; USRDS, United States Renal Data System; VA, ventricular arrhythmia; VHD, valvular heart disease; and VTE, venous thromboembolism.
Source: Special analyses, Medicare 5% sample.

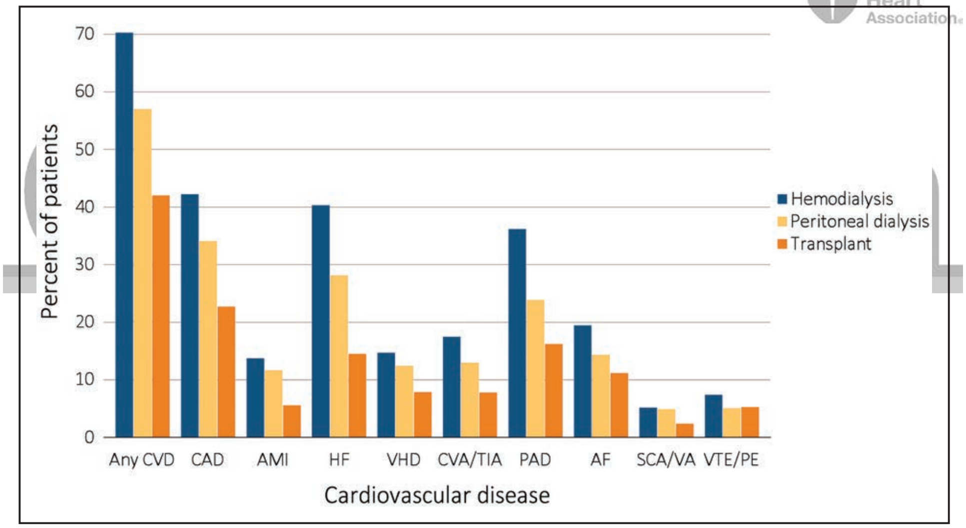

Chart 11-13. Prevalence of CVD in patients with end-stage renal disease (ESRD) by treatment modality, 2015 (2017 USRDS Annual Data Report, volume 2, Figure 9.2).[1]
Point prevalent hemodialysis, peritoneal dialysis, and transplant patients aged ≥22 years, who are continuously enrolled in Medicare Parts A and B, and with Medicare as primary payer from January 1, 2015, to December 31, 2015, and ESRD service date is at least 90 days before January 1, 2015.
AF indicates atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; HF, heart failure; PAD, peripheral arterial disease; PE, pulmonary embolism; SCA, sudden cardiac arrest; TIA, transient ischemic attack; USRDS, United States Renal Data System; VA, ventricular arrhythmia; VHD, valvular heart disease; and VTE, venous thromboembolism.
Source: Special analyses, USRDS ESRD database.

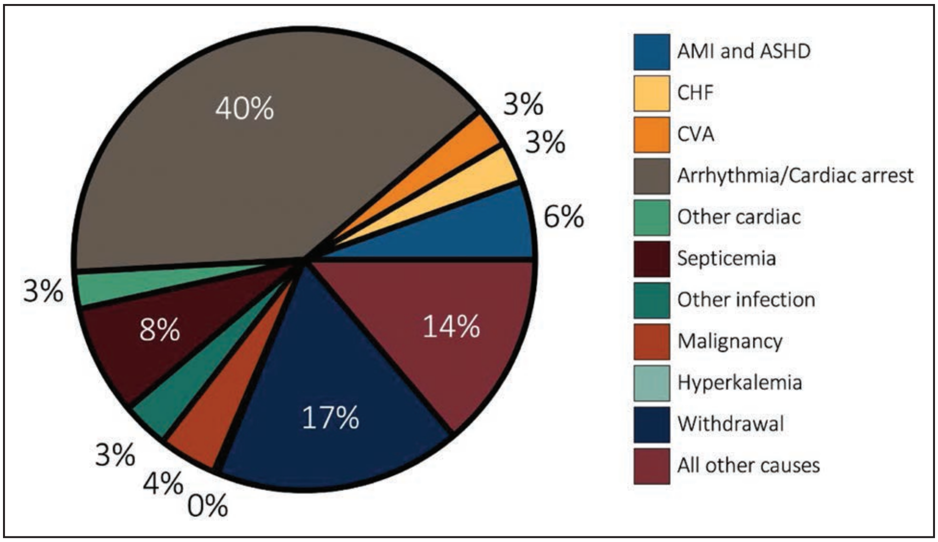

Chart 11-14. Causes of death in patients with end-stage renal disease (ESRD) among those with a known cause of death, 2014 (2017 USRDS Annual Data Report, volume 2, Figure 5.4.a).[1]

Mortality among 2014 prevalent dialysis patients. Denominator excludes missing or unknown causes of death.

AMI indicates acute myocardial infarction; ASHD, atherosclerotic heart disease; CHF, congestive heart failure; CVA, cerebrovascular accident; and USRDS, US Renal Data System.

Source: Special analysis using Reference Table H.12, USRDS ESRD database.

A

	ACR <10	ACR 10-29	ACR 30-299	ACR >300
eGFR >105	0.9	1.3	2.3	2.1
eGFR 90-105	Ref	1.5	1.7	3.7
eGFR 75-90	1.0	1.3	1.6	3.7
eGFR 60-75	1.1	1.4	2.0	4.1
eGFR 45-60	1.5	2.2	2.8	4.3
eGFR 30-45	2.2	2.7	3.4	5.2
eGFR 15-30	14	7.9	4.8	8.1

B

	ACR <10	ACR 10-29	ACR 30-299	ACR >300
eGFR >105	1.1	1.5	2.2	5.0
eGFR 90-105	Ref	1.4	1.5	3.1
eGFR 75-90	1.0	1.3	1.7	2.3
eGFR 60-75	1.0	1.4	1.8	2.7
eGFR 45-60	1.3	1.7	2.2	3.6
eGFR 30-45	1.9	2.3	3.3	4.9
eGFR 15-30	5.3	3.6	4.7	6.6

Chart 11-15. Adjusted relative risk of (A) all-cause mortality and (B) cardiovascular mortality in the general population categorized by KDIGO 2012 categories of chronic kidney disease.

Data are derived from categorical meta-analysis of population cohorts. Pooled relative risks are expressed relative to the reference (Ref) cell. Colors represent the ranking of the adjusted relative risks (green=low risk; yellow=moderate risk; orange=high risk; red=very high risk).

ACR indicates urine albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; and Ref, reference.

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REFERENCES

1. United States Renal Data System. 2017 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2017.
2. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification [published correction appears in *Ann Intern Med*. 2003;139:605]. *Ann Intern Med*. 2003;139:137–147.
3. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report [published correction appears in *Kidney Int*. 2011;80:1000]. *Kidney Int*. 2011;80:17–28. doi: 10.1038/ki.2010.483
4. Hoerger TJ, Simpson SA, Yarnoff BO, Pavkov ME, Ríos Burrows N, Saydah SH, Williams DE, Zhuo X. The future burden of CKD in the United States: a simulation model for the CDC CKD Initiative. *Am J Kidney Dis*. 2015;65:403–411. doi: 10.1053/j.ajkd.2014.09.023
5. Lewis EF, Claggett B, Parfrey PS, Burdmann EA, McMurray JJ, Solomon SD, Levey AS, Ivanovich P, Eckardt KU, Kewalramani R, Toto R, Pfeffer MA. Race and ethnicity influences on cardiovascular and renal events in patients with diabetes mellitus. *Am Heart J*. 2015;170:322–329. doi: 10.1016/j.ahj.2015.05.008
6. McClellan WM, Warnock DG, Judd S, Muntner P, Kewalramani R, Cushman M, McClure LA, Newsome BB, Howard G. Albuminuria and racial disparities in the risk for ESRD. *J Am Soc Nephrol*. 2011;22:1721–1728. doi: 10.1681/ASN.2010101085
7. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, Bowden DW, Langefeld CD, Oleksyk TK, Uscinski Knob AL, Bernhardy AJ, Hicks PJ, Nelson GW, Vanhollebeke B, Winkler CA, Kopp JB, Pays E, Pollak MR. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science*. 2010;329:841–845. doi: 10.1126/science.1193032
8. Murphy D, McCulloch CE, Lin F, Banerjee T, Bragg-Gresham JL, Eberhardt MS, Morgenstern H, Pavkov ME, Saran R, Powe NR, Hsu CY; Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. Trends in prevalence of chronic kidney disease in the United States. *Ann Intern Med*. 2016;165:473–481. doi: 10.7326/M16-0273
9. Centers for Disease Control and Prevention. Chronic Kidney Disease Surveillance System—United States. http://nccd.cdc.gov/CKD. Accessed August 15, 2018.
10. Garofalo C, Borrelli S, Pacilio M, Minutolo R, Chiodini P, De Nicola L, Conte G. Hypertension and prehypertension and prediction of development of decreased estimated GFR in the general population: a meta-analysis of cohort studies. *Am J Kidney Dis*. 2016;67:89–97. doi: 10.1053/j.ajkd.2015.08.027
11. Molnar MZ, Mucsi I, Novak M, Szabo Z, Freire AX, Huch KM, Arah OA, Ma JZ, Lu JL, Sim JJ, Streja E, Kalantar-Zadeh K, Kovesdy CP. Association of incident obstructive sleep apnoea with outcomes in a large cohort of US veterans. *Thorax*. 2015;70:888–895. doi: 10.1136/thoraxjnl-2015-206970
12. Garrity BH, Kramer H, Vellanki K, Leehey D, Brown J, Shoham DA. Time trends in the association of ESRD incidence with area-level poverty in the US population. *Hemodial Int*. 2016;20:78–83. doi: 10.1111/hdi.12325
13. Kokkinos P, Faselis C, Myers J, Sui X, Zhang J, Tsimploulis A, Chawla L, Palant C. Exercise capacity and risk of chronic kidney disease in US veterans: a cohort study. *Mayo Clin Proc*. 2015;90:461–468. doi: 10.1016/j.mayocp.2015.01.013
14. Ricardo AC, Anderson CA, Yang W, Zhang X, Fischer MJ, Dember LM, Fink JC, Frydrych A, Jensvold NG, Lustigova E, Nessel LC, Porter AC, Rahman M, Wright Nunes JA, Daviglus ML, Lash JP; CRIC Study Investigators. Healthy lifestyle and risk of kidney disease progression, atherosclerotic events, and death in CKD: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis*. 2015;65:412–424. doi: 10.1053/j.ajkd.2014.09.016
15. Rebholz CM, Anderson CA, Grams ME, Bazzano LA, Crews DC, Chang AR, Coresh J, Appel LJ. Relationship of the American Heart Association's impact goals (Life's Simple 7) with risk of chronic kidney disease: results from the Atherosclerosis Risk in Communities (ARIC) cohort study. *J Am Heart Assoc*. 2016;5:e003192. doi: 10.1161/JAHA.116.003192
16. Chang A, Van Horn L, Jacobs DR Jr, Liu K, Muntner P, Newsome B, Shoham DA, Durazo-Arvizu R, Bibbins-Domingo K, Reis J, Kramer H. Lifestyle-related factors, obesity, and incident microalbuminuria: the CARDIA (Coronary Artery Risk Development in Young Adults) study. *Am J Kidney Dis*. 2013;62:267–275. doi: 10.1053/j.ajkd.2013.02.363
17. Global Burden of Disease Study 2016. Global Burden of Disease Study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed May 1, 2018.
18. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015 [published correction appears in *Lancet*. 2017;389:e1]. *Lancet*. 2016;388:1545–1602.
19. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015 [published correction appears in *Lancet*. 2017;389:e1]. *Lancet*. 2016;388:1459–1544.
20. Fox CS, Yang Q, Cupples LA, Guo CY, Larson MG, Leip EP, Wilson PW, Levy D. Genomewide linkage analysis to serum creatinine, GFR, and creatinine clearance in a community-based population: the Framingham Heart Study. *J Am Soc Nephrol*. 2004;15:2457–2461. doi: 10.1097/01.ASN.0000135972.13396.6F
21. Ma L, Chou JW, Snipes JA, Bharadwaj MS, Craddock AL, Cheng D, Weckerle A, Petrovic S, Hicks PJ, Hemal AK, Hawkins GA, Miller LD, Molina AJ, Langefeld CD, Murea M, Parks JS, Freedman BI. APOL1 Renal-risk variants induce mitochondrial dysfunction. *J Am Soc Nephrol*. 2017;28:1093–1105. doi: 10.1681/ASN.2016050567
22. Grams ME, Rebholz CM, Chen Y, Rawlings AM, Estrella MM, Selvin E, Appel LJ, Tin A, Coresh J. Race, APOL1 risk, and eGFR decline in the general population. *J Am Soc Nephrol*. 2016;27:2842–2850. doi: 10.1681/ASN.2015070763
23. Foster MC, Coresh J, Fornage M, Astor BC, Grams M, Franceschini N, Boerwinkle E, Parekh RS, Kao WH. APOL1 variants associate with increased risk of CKD among African Americans. *J Am Soc Nephrol*. 2013;24:1484–1491. doi: 10.1681/ASN.2013010113
24. Peralta CA, Bibbins-Domingo K, Vittinghoff E, Lin F, Fornage M, Kopp JB, Winkler CA. APOL1 genotype and race differences in incident albuminuria and renal function decline. *J Am Soc Nephrol*. 2016;27:887–893. doi: 10.1681/ASN.2015020124
25. Chen TK, Appel LJ, Grams ME, Tin A, Choi MJ, Lipkowitz MS, Winkler CA, Estrella MM. APOL1 risk variants and cardiovascular disease: results from the AASK (African American Study of Kidney Disease and Hypertension). *Arterioscler Thromb Vasc Biol*. 2017;37:1765–1769. doi: 10.1161/ATVBAHA.117.309384
26. Zeng X, Liu J, Tao S, Hong HG, Li Y, Fu P. Associations between socioeconomic status and chronic kidney disease: a meta-analysis. *J Epidemiol Community Health*. 2018;72:270–279. doi: 10.1136/jech-2017-209815
27. Crews DC, Kuczmarski MF, Grubbs V, Hedgeman E, Shahinian VB, Evans MK, Zonderman AB, Burrows NR, Williams DE, Saran R, Powe NR; Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. Effect of food insecurity on chronic kidney disease in lower-income Americans. *Am J Nephrol*. 2014;39:27–35. doi: 10.1159/000357595
28. Beydoun MA, Poggi-Burke A, Zonderman AB, Rostant OS, Evans MK, Crews DC. Perceived discrimination and longitudinal change in kidney function among urban adults. *Psychosom Med*. 2017;79:824–834. doi: 10.1097/PSY.0000000000000478
29. Cheung KL, Zakai NA, Folsom AR, Kurella Tamura M, Peralta CA, Judd SE, Callas PW, Cushman M. Measures of kidney disease and the risk of venous thromboembolism in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study. *Am J Kidney Dis*. 2017;70:182–190. doi: 10.1053/j.ajkd.2016.10.039
30. Wanner C, Tonelli M; Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO clinical practice guideline for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int*. 2014;85:1303–1309. doi: 10.1038/ki.2014.31
31. Baber U, Gutierrez OM, Levitan EB, Warnock DG, Farkouh ME, Tonelli M, Safford MM, Muntner P. Risk for recurrent coronary heart disease and all-cause mortality among individuals with chronic kidney disease compared with diabetes mellitus, metabolic syndrome, and cigarette smokers. *Am Heart J*. 2013;166:373–380.e2. doi: 10.1016/j.ahj.2013.05.008
32. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright

JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in *Hypertension*. 2018;71:e140–e144]. *Hypertension*. 2018;71:e13–e115. DOI: 10.1161/HYP.0000000000000065

33. Masson P, Webster AC, Hong M, Turner R, Lindley RI, Craig JC. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2015;30:1162–1169. doi: 10.1093/ndt/gfv009
34. Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, Jafar T, Jassal SK, Landman GW, Muntner P, Roderick P, Sairenchi T, Schöttker B, Shankar A, Shlipak M, Tonelli M, Townend J, van Zuilen A, Yamagishi K, Yamashita K, Gansevoort R, Sarnak M, Warnock DG, Woodward M, Ärnlöv J; CKD Prognosis Consortium. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol*. 2015;3:514–525. doi: 10.1016/S2213-8587(15)00040-6
35. Alonso A, Lopez FL, Matsushita K, Loehr LR, Agarwal SK, Chen LY, Soliman EZ, Astor BC, Coresh J. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2011;123:2946–2953. doi: 10.1161/CIRCULATIONAHA.111.020982
36. Hui X, Matsushita K, Sang Y, Ballew SH, Fülöp T, Coresh J. CKD and cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study: interactions with age, sex, and race. *Am J Kidney Dis*. 2013;62:691–702. doi: 10.1053/j.ajkd.2013.04.010
37. Bansal N, Katz R, Robinson-Cohen C, Odden MC, Dalrymple L, Shlipak MG, Sarnak MJ, Siscovick DS, Zelnick L, Psaty BM, Kestenbaum B, Correa A, Afkarian M, Young B, de Boer IH. Absolute rates of heart failure, coronary heart disease, and stroke in chronic kidney disease: an analysis of 3 community-based cohort studies. *JAMA Cardiol*. 2017;2:314–318. doi: 10.1001/jamacardio.2016.4652
38. Mahmoodi BK, Yatsuya H, Matsushita K, Sang Y, Gottesman RF, Astor BC, Woodward M, Longstreth WT Jr, Psaty BM, Shlipak MG, Folsom AR, Gansevoort RT, Coresh J. Association of kidney disease measures with ischemic versus hemorrhagic strokes: pooled analyses of 4 prospective community-based cohorts. *Stroke*. 2014;45:1925–1931. doi: 10.1161/STROKEAHA.114.004900
39. Sandsmark DK, Messé SR, Zhang X, Roy J, Nessel L, Lee Hamm L, He J, Horwitz EJ, Jaar BG, Kallem RR, Kusek JW, Mohler ER 3rd, Porter A, Seliger SL, Sozio SM, Townsend RR, Feldman HI, Kasner SE; CRIC Study Investigators. Proteinuria, but not eGFR, predicts stroke risk in chronic kidney disease: Chronic Renal Insufficiency Cohort study. *Stroke*. 2015;46:2075–2080. doi: 10.1161/STROKEAHA.115.009861
40. Colantonio LD, Baber U, Banach M, Tanner RM, Warnock DG, Gutiérrez OM, Safford MM, Wanner C, Howard G, Muntner P. Contrasting cholesterol management guidelines for adults with CKD. *J Am Soc Nephrol*. 2015;26:1173–1180. doi: 10.1681/ASN.2014040400
41. Wang GJ, Shaw PA, Townsend RR, Anderson AH, Xie D, Wang X, Nessel LC, Mohler ER, Sozio SM, Jaar BG, Chen J, Wright J, Taliercio JJ, Ojo A, Ricardo AC, Lustigova E, Fairman RM, Feldman HI, Ky B; for the CRIC Study Investigators. Sex differences in the incidence of peripheral artery disease in the Chronic Renal Insufficiency Cohort. *Circ Cardiovasc Qual Outcomes*. 2016;9(suppl 1):S86–S93. doi: 10.1161/CIRCOUTCOMES.115.002180
42. Baber U, Giustino G, Sartori S, Aquino M, Stefanini GG, Steg PG, Windecker S, Leon MB, Wijns W, Serruys PW, Valgimigli M, Stone GW, Dangas GD, Morice MC, Camenzind E, Weisz G, Smits PC, Kandzari D, Von Birgelen C, Mastoris I, Galatius S, Jeger RV, Kimura T, Mikhail GW, Itchhaporia D, Mehta L, Ortega R, Kim HS, Kastrati A, Chieffo A, Mehran R. Effect of chronic kidney disease in women undergoing percutaneous coronary intervention with drug-eluting stents: a patient-level pooled analysis of randomized controlled trials. *JACC Cardiovasc Interv*. 2016;9:28–38. doi: 10.1016/j.jcin.2015.09.023
43. Lash JP, Ricardo AC, Roy J, Deo R, Fischer M, Flack J, He J, Keane M, Lora C, Ojo A, Rahman M, Steigerwalt S, Tao K, Wolf M, Wright JT Jr, Go AS; CRIC Study Investigators. Race/ethnicity and cardiovascular outcomes in adults with CKD: findings from the CRIC (Chronic Renal Insufficiency Cohort) and Hispanic CRIC studies. *Am J Kidney Dis*. 2016;68:545–553. doi: 10.1053/j.ajkd.2016.03.429
44. Roy-Chaudhury P, Tumlin JA, Koplan BA, Costea AI, Kher V, Williamson D, Pokhariyal S, Charytan DM; MiD investigators and committees. Primary outcomes of the Monitoring in Dialysis Study indicate that clinically significant arrhythmias are common in hemodialysis patients and related to dialytic cycle. *Kidney Int*. 2018;93:941–951. doi: 10.1016/j.kint.2017.11.019
45. Samad Z, Sivak JA, Phelan M, Schulte PJ, Patel U, Velazquez EJ. Prevalence and outcomes of left-sided valvular heart disease associated with chronic kidney disease. *J Am Heart Assoc*. 2017;6. doi: 10.1161/JAHA.117.006044
46. Shlipak MG, Matsushita K, Ärnlöv J, Inker LA, Katz R, Polkinghorne KR, Rothenbacher D, Sarnak MJ, Astor BC, Coresh J, Levey AS, Gansevoort RT; CKD Prognosis Consortium. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med*. 2013;369:932–943. doi: 10.1056/NEJMoa1214234
47. He J, Shlipak M, Anderson A, Roy JA, Feldman HI, Kallem RR, Kanthety R, Kusek JW, Ojo A, Rahman M, Ricardo AC, Soliman EZ, Wolf M, Zhang X, Raj D, Hamm L; for the CRIC (Chronic Renal Insufficiency Cohort) Investigators. Risk factors for heart failure in patients with chronic kidney disease: the CRIC (Chronic Renal Insufficiency Cohort) study. *J Am Heart Assoc*. 2017;6:e005336. doi: 10.1161/JAHA.116.005336
48. Schei J, Stefansson VT, Mathisen UD, Eriksen BO, Solbu MD, Jenssen TG, Melsom T. Residual associations of inflammatory markers with eGFR after accounting for measured GFR in a community-based cohort without CKD. *Clin J Am Soc Nephrol*. 2016;11:280–286. doi: 10.2215/CJN.07360715
49. Kent S, Schlackow I, Lozano-Kühne J, Reith C, Emberson J, Haynes R, Gray A, Cass A, Baigent C, Landray MJ, Herrington W, Mihaylova B; SHARP Collaborative Group. What is the impact of chronic kidney disease stage and cardiovascular disease on the annual cost of hospital care in moderate-to-severe kidney disease? *BMC Nephrol*. 2015;16:65. doi: 10.1186/s12882-015-0054-0
50. LaPar DJ, Rich JB, Isbell JM, Brooks CH, Crosby IK, Yarboro LT, Ghanta RK, Kern JA, Brown M, Quader MA, Speir AM, Ailawadi G. Preoperative renal function predicts hospital costs and length of stay in coronary artery bypass grafting. *Ann Thorac Surg*. 2016;101:606–612. doi: 10.1016/j.athoracsur.2015.07.079
51. Konstantinidis I, Nadkarni GN, Yacoub R, Saha A, Simoes P, Parikh CR, Coca SG. Representation of patients with kidney disease in trials of cardiovascular interventions: an updated systematic review. *JAMA Intern Med*. 2016;176:121–124. doi: 10.1001/jamainternmed.2015.6102
52. Konstantinidis I, Patel S, Camargo M, Patel A, Poojary P, Coca SG, Nadkarni GN. Representation and reporting of kidney disease in cerebrovascular disease: a systematic review of randomized controlled trials. *PLoS One*. 2017;12:e0176145. doi: 10.1371/journal.pone.0176145
53. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, Cushman WC, Hawfield AT, Johnson KC, Lewis CE, Oparil S, Rocco MV, Sink KM, Whelton PK, Wright JT Jr, Basile J, Beddhu S, Bhatt U, Chang TI, Chertow GM, Chonchol M, Freedman BI, Haley W, Ix JH, Katz LA, Killeen AA, Papademetriou V, Ricardo AC, Servilla K, Wall B, Wolfgram D, Yee J; SPRINT Research Group. Effects of intensive BP control in CKD. *J Am Soc Nephrol*. 2017;28:2812–2823. doi: 10.1681/ASN.2017020148
54. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J, Hannan EL. Revascularization in patients with multivessel coronary artery disease and chronic kidney disease: everolimus-eluting stents versus coronary artery bypass graft surgery. *J Am Coll Cardiol*. 2015;66:1209–1220. doi: 10.1016/j.jacc.2015.06.1334
55. Krishnaswami A, McCulloch CE, Tawadrous M, Jang JJ, Lee H, Melikian V, Yee G, Leong TK, Go AS. Coronary artery bypass grafting and percutaneous coronary intervention in patients with end-stage renal disease. *Eur J Cardiothorac Surg*. 2015;47:e193–e198. doi: 10.1093/ejcts/ezv104
56. Parsh J, Seth M, Aronow H, Dixon S, Heung M, Mehran R, Gurm HS. Choice of estimated glomerular filtration rate equation impacts drug-dosing recommendations and risk stratification in patients with chronic kidney disease undergoing percutaneous coronary interventions. *J Am Coll Cardiol*. 2015;65:2714–2723. doi: 10.1016/j.jacc.2015.04.037
57. Shen JI, Montez-Rath ME, Lenihan CR, Turakhia MP, Chang TI, Winkelmayer WC. Outcomes after warfarin initiation in a cohort of hemodialysis patients with newly diagnosed atrial fibrillation. *Am J Kidney Dis*. 2015;66:677–688. doi: 10.1053/j.ajkd.2015.05.019
58. Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. Stroke, major bleeding, and mortality outcomes in warfarin users with atrial fibrillation and chronic kidney disease: a meta-analysis of observational studies. *Chest*. 2016;149:951–959. doi: 10.1378/chest.15-1719
59. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. *J Am Coll Cardiol*. 2017;69:2779–2790. doi: 10.1016/j.jacc.2017.03.600
60. Daimee UA, Moss AJ, Biton Y, Solomon SD, Klein HU, McNitt S, Polonsky B, Zareba W, Goldenberg I, Kutyifa V. Long-term outcomes with cardiac resynchronization therapy in patients with mild heart failure with

moderate renal dysfunction. *Circ Heart Fail*. 2015;8:725–732. doi: 10.1161/CIRCHEARTFAILURE.115.002082
61. Ferro CJ, Chue CD, de Belder MA, Moat N, Wendler O, Trivedi U, Ludman P, Townend JN; UK TAVI Steering Group; National Institute for Cardiovascular Outcomes Research. Impact of renal function on survival after transcatheter aortic valve implantation (TAVI): an analysis of the UK TAVI registry. *Heart*. 2015;101:546–552. doi: 10.1136/heartjnl-2014-307041
62. Bhatia N, Agrawal S, Yang S, Yadav K, Agarwal M, Garg L, Agarwal N, Shirani J, Fredi JL. In-hospital outcomes of transcatheter aortic valve implantation in patients with end-stage renal disease on dialysis from a large national database. *Am J Cardiol*. 2017;120:1355–1358. doi: 10.1016/j.amjcard.2017.07.022
63. Hansen JW, Foy A, Yadav P, Gilchrist IC, Kozak M, Stebbins A, Matsouaka R, Vemulapalli S, Wang A, Wang DD, Eng MH, Greenbaum AB, O'Neill WO. Death and dialysis after transcatheter aortic valve replacement: an analysis of the STS/ACC TVT registry. *JACC Cardiovasc Interv*. 2017;10:2064–2075. doi: 10.1016/j.jcin.2017.09.001
64. Garimella PS, Balakrishnan P, Correa A, Poojary P, Annapureddy N, Chauhan K, Patel A, Patel S, Konstantinidis I, Chan L, Agarwal SK, Jaar BG, Gidwani U, Matsushita K, Nadkarni GN. Nationwide trends in hospital outcomes and utilization after lower limb revascularization in patients on hemodialysis. *JACC Cardiovasc Interv*. 2017;10:2101–2110. doi: 10.1016/j.jcin.2017.05.050

12. SLEEP

See Charts 12-1 through 12-5

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Sleep can be characterized in many different ways, including quantity of sleep (sleep duration), quality of sleep, or the presence of a sleep disorder, such as insomnia or OSA. All of these characteristics of sleep have been associated with CVD and stroke.

Prevalence (See Charts 12-1 through 12-4)

- The American Academy of Sleep Medicine and the Sleep Research Society published a consensus statement recommending that adults obtain ≥7 hours of sleep per night to promote optimal health.[1] The American Academy of Sleep Medicine and Sleep Research Society also published guidelines for pediatric populations: infants 4 to 12 months old should sleep 12 to 16 hours per day; children 1 to 2 years old should sleep 11 to 14 hours per day; children 3 to 5 years old should sleep 10 to 13 hours per day; children 6 to 12 years old should sleep 9 to 12 hours per day; and adolescents 13 to 18 years old should sleep 8 to 10 hours per day.[2]
- The CDC analyzed data from the 2014 BRFSS to determine the age-adjusted prevalence of a healthy sleep duration (≥7 hours) in the United States and found that 11.8% of people reported a sleep duration ≤5 hours, 23.0% reported 6 hours, 29.5% reported 7 hours, 27.7% reported 8 hours, 4.4% reported 9 hours, and 3.6% reported ≥10 hours. Overall, 65.2% met the recommended sleep duration of ≥7 hours.[3]
- Analysis of NHANES data (2005–2008) indicated that the proportion of adults getting inadequate sleep (<7 hours) was 36.8%. Younger people were more likely to report sleeping <7 hours, and males were more likely to report sleeping <7 hours at younger ages (20–59 years) (Chart 12-1).
- The prevalence of inadequate sleep (<7 hours) varied by state or territory: in 2014, the lowest prevalence was seen in South Dakota (28.4%), Colorado (28.5%), and Minnesota (29.2%), and the highest was found in Guam (48.6%), Hawaii (43.6%), and Kentucky (39.4%).[4]
- Analysis of time diaries indicated that the prevalence of short sleepers was 7.6% in 1975 and 9.3% in 2006 and that this increase in prevalence was observed predominantly in full-time workers.[5]
- Prevalence of OSA varies by sex. On the basis of data from the Wisconsin Cohort Study, OSA prevalence estimates among 30- to 70-year-old subjects in the United States in 2007 to 2010 were 33.9% among males and 17.4% among females for AHI ≥5 (mild to severe OSA).[6] Prevalence estimates of moderate to severe OSA (AHI ≥15) were 13.0% for males and 5.6% for females. These estimates are higher than estimates for 1988 to 1994 from the same study, which were 26.4% in males and 8.8% in females for mild to severe OSA.[6]
- The prevalence of insomnia symptoms, that is, difficulty falling or staying asleep or nonrestorative sleep, has been estimated to be 30% to 48% in the general population, whereas the prevalence of a diagnosis of insomnia was 6%.[7]
- The proportion of people who reported (a) trouble falling asleep often or almost always was 17.3%, (b) trouble staying asleep often or almost always was 20.4%, and (c) waking too early often or almost always was 16.8%. (unpublished NHANES 2005–2008). Females were more likely to report these sleep problems than males at all ages (Charts 12-2 to 12-4).
- Females have a greater risk of insomnia than males. For example, a meta-analysis of 31 studies reported an RR of 1.41 (95% CI, 1.28–1.55) comparing females to males.[8] Furthermore, sex differences increased with age and were largest in those ≥65 years of age.[8]

Abbreviations Used in Chapter 12

AF	atrial fibrillation
AHI	apnea-hypopnea index
AMI	acute myocardial infarction
BMI	body mass index
BRFSS	Behavioral Risk Factor Surveillance System
CARDIA	Coronary Artery Risk Development in Young Adults
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CI	confidence interval
CPAP	continuous positive airway pressure
CVD	cardiovascular disease
DM	diabetes mellitus
HF	heart failure
Hisp	Hispanic
HR	hazard ratio
Mex Amer	Mexican American
MI	myocardial infarction
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NSTEMI	non–ST-segment–elevation myocardial infarction
OR	odds ratio
OSA	obstructive sleep apnea
PA	physical activity
RCT	randomized controlled trial
RR	relative risk
STEMI	ST-segment–elevation myocardial infarction
TIA	transient ischemic attack
UA	unstable angina

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Children/Adolescents

- National poll data indicated that 63.3% of children 6 to 11 years old and 56.7% of children 12 to 17 years old obtained sufficient sleep, whereas 47.2% of children 6 to 11 years old and 38.5% of children 12 to 17 years old had excellent sleep quality.[9]
- The estimated prevalence of snoring in pediatric populations (as reported by the parent) is 7.5%, whereas the prevalence of sleep-disordered breathing using diagnostic testing is likely between 1% and 4% (varies depending on definitions and methodologies used).[10]

Adults: Young, Middle-Aged, and Old

- Older adults are more likely to report adequate sleep. Age-specific and age-adjusted percentages of adults who reported adequate sleep (≥7 hours per 24-hour period) were as follows: 67.8% for 18- to 24-year-old adults, 62.1% for 25- to 34-year-old adults, 61.7% for 35- to 44-year-old adults, 62.7% for 45- to 64-year-old adults, and 73.7% for adults aged ≥65 years.[3]
- Prevalence of OSA is higher among older adults. The prevalence of mild to severe OSA (AHI ≥5) was 26.6% for 30- to 49-year-old males and 43.2% for 50- to 70-year-old males, whereas it was 8.7% for 30- to 49-year old females and 27.8% for 50 to 70-year-old females.[6]

Race/Ethnicity and Sleep (See Chart 12-5)

- Data from the CDC indicated that the age-adjusted prevalence of healthy sleep duration was lower among Native Hawaiians/Pacific Islanders (53.7%), NH blacks (54.2%), multiracial NH people (53.6%), and American Indians/Alaska Natives (59.6%) compared with NH whites (66.8%), Hispanics (65.5%), and Asians (62.5%).[3]
- The CARDIA study estimated sleep duration using wrist activity monitoring and found that the average sleep duration was 5.1 hours for black males, 5.9 hours for black females, 5.8 hours for white males, and 6.5 hours for white females, after adjustment for numerous confounders including socioeconomic indicators. This study also observed a similar race/sex pattern of sleep quality measures.[11]
- The Chicago Area Health Study also used wrist activity monitoring, and the adjusted mean sleep duration was 6.7 hours for blacks, 6.8 hours for Asians, 6.9 hours for Hispanic/Latinos, and 7.5 hours for whites.[12] This study also observed lower sleep quality in blacks and Hispanic/Latinos compared with whites.
- In NHANES 2005 to 2008, blacks and individuals of other races were significantly more likely to report sleeping <7 hours than NH whites (unpublished NHANES data; Chart 12-5).
- In NHANES 2005 to 2008, whites were more likely to report trouble falling asleep and trouble staying asleep (unpublished NHANES data; Chart 12-5).

Mortality

- A meta-analysis of 43 studies indicated that both short sleep (<7 hours per night; RR, 1.13 [95% CI, 1.10–1.17]) and long sleep (>8 hours per night; RR, 1.35 [95% CI, 1.29–1.41]) were associated with a greater risk of all-cause mortality.[13]
  — A prospective cohort study found that the association between sleep duration and mortality varied with age.[14] Among adults <65 years old, short sleep duration (≤5 hours per night) and long sleep duration (≥8 hours per night) were both associated with increased mortality risk (HR, 1.37 [95% CI, 1.09–1.71] and HR, 1.27 [95% CI, 1.08–1.48], respectively). Sleep duration was not significantly associated with mortality in adults >65 years of age.
- Data from NHANES indicated that long sleep duration (>8 hours per night) was associated with an increased risk of all-cause mortality in the full sample (HR, 1.90 [95% CI, 1.38–2.60]), among males (HR, 1.48 [95% CI, 1.05–2.09]), among females (HR, 2.32 [95% CI, 1.48–3.61]), and among those >65 years of age (HR, 1.80 [95% CI, 1.30–2.50]) but not among those <65 years of age.[15] No significant associations were observed between short sleep (<7 hours per night) and all-cause mortality in this analysis.
- A meta-analysis of 27 cohort studies found that mild OSA (HR, 1.19 [95% CI, 0.86–1.65]), moderate OSA (HR, 1.28 [95% CI, 0.96–1.69]), and severe OSA (HR, 2.13 [95% CI, 1.68–2.68]) were associated with all-cause mortality in a dose-response fashion. Only severe OSA was associated with cardiovascular mortality (HR, 2.73 [95% CI, 1.94–3.85]).[16]
- A study of US males found that insomnia symptoms were associated with increased risk of all-cause mortality. Specifically, mortality risk was higher for males who reported difficulty initiating sleep (HR, 1.25 [95% CI, 1.04–1.50]) and nonrestorative sleep (HR, 1.24 [95% CI, 1.05–1.46]).[17]
- A study among males and females aged 21 to 75 years found that compared with those who

never reported insomnia symptoms, those who reported persistent insomnia symptoms at 2 time points ≈5 years apart had an increased risk of all-cause mortality (HR, 1.58 [95% CI, 1.02–2.45]), but those who reported insomnia at only 1 time point did not.[18]

Risk Factors

- In addition to age, sex, and race/ethnicity, characteristics associated with short sleep duration include lower education (OR, 0.68 [95% CI, 0.56–0.84] for greater than high school versus less than high school), not being married (OR, 1.43 [95% CI, 1.25–1.67] for not married versus married), poverty (OR, 0.65 [95% CI, 0.54–0.79] for poverty/income ratio ≥2 versus <1), smoking (OR, 0.063 [95% CI, 0.51–0.79] for ex-smokers and OR, 0.68 [95% CI, 0.53–0.85] for smokers versus never-smokers), physical inactivity (OR, 1.48 [95% CI, 1.15–1.86] for no PA versus PA), poor diet (OR, 0.93 [95% CI, 0.91–0.95] per point on nutrient adequacy scale), obesity (OR, 1.39 [95% CI, 1.17–1.65] for BMI ≥30 versus <25 kg/m^2), fair/poor subjective health (OR, 1.93 [95% CI, 1.63–2.32] versus excellent, very good, and good combined), and depressive symptoms (OR, 2.80 [95% CI, 2.01–3.90] for ≥10 versus <10 on the Patient Health Questionnaire).[15]
- In addition to age, sex, and race/ethnicity, characteristics associated with trouble sleeping include not being married (OR, 1.16 [95% CI, 1.01–1.36], not married versus married), smoking (OR, 0.39 [95% CI, 0.36–0.43] for never-smoker versus current smoker), no alcohol consumption (OR, 0.39 [95% CI, 0.36–0.43] for alcohol consumption versus no consumption), obesity (OR, 1.25 [95% CI, 1.02–1.54] for BMI ≥30 versus <25 kg/m^2), fair/poor subjective health (OR, 1.97 [95% CI, 1.60–2.41] versus excellent/very good/good), and depressive symptoms (OR, 4.71 [95% CI, 3.60–6.17] for ≥10 versus <10 on the Patient Health Questionnaire).[15]
- Predictors of OSA (AHI ≥15) include male sex (OR, 1.51 [95% CI, 1.50–1.90]), larger BMI (OR, 1.55 [95% CI, 1.41–1.71] per 5.3 kg/m^2), larger neck circumference (OR, 1.42 [95% CI, 1.25–1.61] per 1.7 inches), habitual snoring (OR, 1.75 [95% CI, 1.18–2.62]), and loud snoring (OR, 2.21 [95% CI, 1.56–3.14]).[19]
- National data indicate that the following characteristics are associated with increased risk of incident diagnosed insomnia: age >45 years (HR, 1.69 [95% CI, 1.40–2.03] for 45–64 years and HR, 2.11 [95% CI, 1.63–2.73] for ≥65 years) versus 18 to 44 years, high school degree (HR, 1.44 [95% CI, 1.18–1.75]) versus college or more, underweight (HR, 1.37 [95% CI, 1.06–1.77]) versus normal weight, greater comorbidities based on Charlson comorbidity index (HR, 1.69 [95% CI, 1.45–1.98] for a score of 1 or 2 and HR, 1.76 [95% CI, 1.32–2.36] for a score ≥3), ever having smoked (HR, 1.45 [95% CI, 1.20–1.76]) versus never having smoked, and physical inactivity (HR, 1.22 [95% CI, 1.06–1.42]) versus PA.[20] The following are associated with reduced risk of incident diagnosed insomnia: male sex (HR, 0.57 [95% CI, 0.48–0.69]) and having never been married (HR, 0.73 [95% CI, 0.59–0.90]) versus being married or cohabitating.[20]

Family History and Genetics

- Genetic factors can influence sleep either directly by controlling sleep disorders or indirectly through modulation of risk factors such as obesity.
- Heritability of sleep behaviors varies but is estimated to be ≈40%.[21] Genetic studies have identified variants associated with OSA.[22] Data suggest genetic control of interindividual variability in circadian rhythms, with variants in clock genes such as *CRY1* and *CRY2* being of particular interest.[23–25]

Aftermath

- Short sleep duration has been associated with several cardiovascular and metabolic health outcomes, including prevalent obesity (OR, 1.55 [95% CI, 1.43–1.68])[26], incident obesity (OR, 1.45 [95% CI, 1.25–1.67]),[27] incident DM (OR, 1.28 [95% CI, 1.03–1.60]),[28] CHD morbidity or mortality (RR, 1.48 [95% CI, 1.22–1.80]),[29] and stroke (RR, 1.15 [95% CI, 1.00–1.31]).[29]
- Long duration of sleep was also associated with a greater risk of CHD morbidity or mortality (RR 1.38 [95% CI, 1.15–1.66]), stroke (RR, 1.65 [95% CI, 1.45–1.87]), and total CVD (RR, 1.41 [95% CI, 1.19–1.68]).[29]
- A meta-analysis examined sleep duration and total CVD (26 articles), CHD (22 articles), and stroke (16 articles).[13] Short sleep (<7 hours per night) was associated with total CVD (RR, 1.14 [95% CI, 1.09–1.20]) and CHD (RR, 1.22 [95% CI, 1.13–1.31]) but not stroke (RR, 1.09 [95% CI, 0.99–1.19]). Long sleep duration was associated with total CVD (RR, 1.36 [95% CI, 1.26–1.48]), CHD (RR, 1.21 [95% CI, 1.12–1.30]), and stroke (RR, 1.45 [95% CI, 1.30–1.62]).
- Insomnia symptoms have also been associated with incident DM, including difficulty falling

asleep (OR, 1.57 [95% CI, 1.25–1.97]) and difficulty staying asleep (OR, 1.84 [95% CI, 1.39–2.43]).[28]

- The deepest stage of non–rapid-eye movement sleep, also called *slow-wave sleep*, is thought to be a restorative stage of sleep. In the Sleep Heart Health Study, which used in-home polysomnography to characterize sleep, it was found that participants with a lower proportion of slow-wave sleep had significantly greater odds of incident hypertension (quartile 1 versus quartile 3: OR, 1.69 [95% CI, 1.21–2.36]).[30]
- Short sleep duration was associated with increased risk of incident hypertension in adults aged <65 years on the basis of a meta-analysis of 4 studies (OR, 1.33 [95% CI, 1.11–1.61]).[31]
- A meta-analysis of 15 prospective studies observed a significant association between the presence of OSA and the risk of cerebrovascular disease (HR, 1.94 [95% CI, 1.31–2.89]).[32]
- Among patients with AMI, the presence of moderate to severe OSA is associated with a greater likelihood of an NSTEMI versus STEMI (OR, 1.59 [95% CI, 1.07–2.37]), and the prevalence of NSTEMI increases with increasing severity of OSA: 18.3% for no OSA, 35.4% for mild OSA, 33.9% for moderate OSA, and 41.6% for severe OSA.[33]
- Central sleep apnea was associated with 2 to 3 times increased odds of incident AF, but OSA was not associated with incident AF.[34]

Awareness, Treatment, and Control

- OSA is often undiagnosed. One study reported that 93% of females and 82% of males with moderate to severe OSA have not been clinically diagnosed.[35]
- A meta-analysis of 8 studies found that all-cause mortality (HR, 0.66 [95% CI, 0.59–0.73]) and cardiovascular mortality (HR, 0.37 [95% CI, 0.16–0.54]) were significantly lower in CPAP-treated than in untreated patients.[16]
- An RCT tested the effect of early nasal CPAP treatment in patients with first-ever ischemic stroke and moderate to severe OSA over a 24-month period.[36] Patients assigned to nasal CPAP but who refused the treatment were excluded. The cardiovascular mortality rate was 0% in the nasal CPAP group (0 of 57 patients) compared with 4.3% in the control group (3 of 69 patients; *P*=0.16). The average time from stroke onset until the appearance of the first cardiovascular event was significantly longer in the nasal CPAP group than in the control group (14.9 versus 7.9 months; *P*=0.044). No differences were observed in CVD events or all-cause mortality.
- Another RCT enrolled people aged 45 to 75 years with moderate-to-severe OSA without excessive daytime sleepiness and who also had coronary or cerebrovascular disease, to compare CPAP plus usual care to usual care alone.[37] A total of 2687 patients were included in this secondary prevention trial and followed up for an average of 3.7 years. No statistically significant difference was observed for a composite of primary end points (HR, 1.10 [95% CI 0.91–1.32]), including death attributable to cardiovascular causes, MI, stroke, or hospitalization for HF, UA, and TIA.

Costs

- Analysis of direct and indirect costs related to sleep disorders and other health consequences of sleep disorders suggested that the approximate cost for a population the size of the United States would have been approximately $109 billion in 2004.[38]

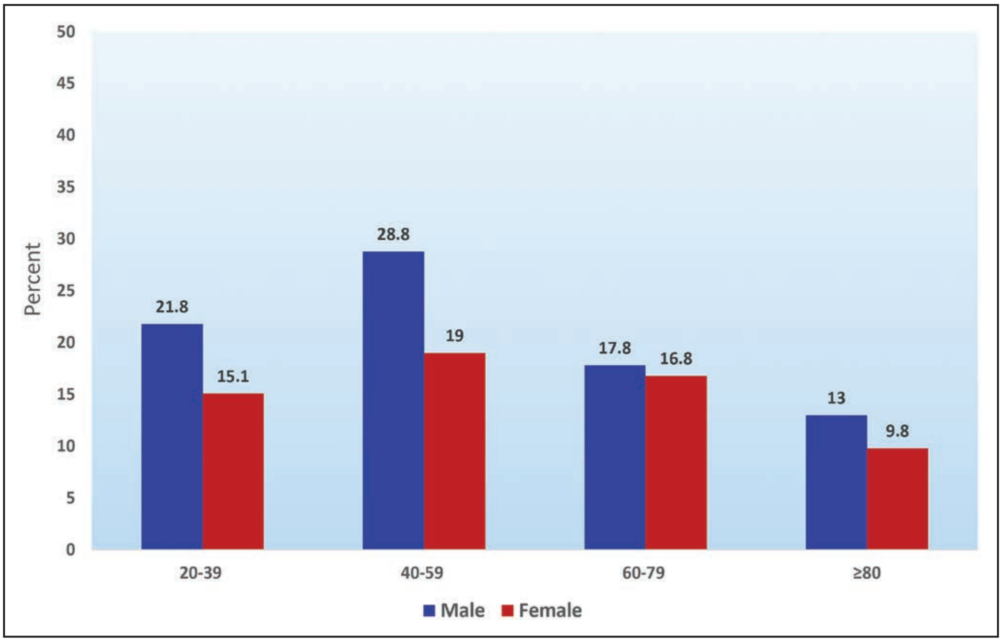

Chart 12-1. Prevalence of inadequate sleep (<7 h) in US adults by age and sex.
Data source: National Health and Nutrition Examination Survey, 2015 to 2016.

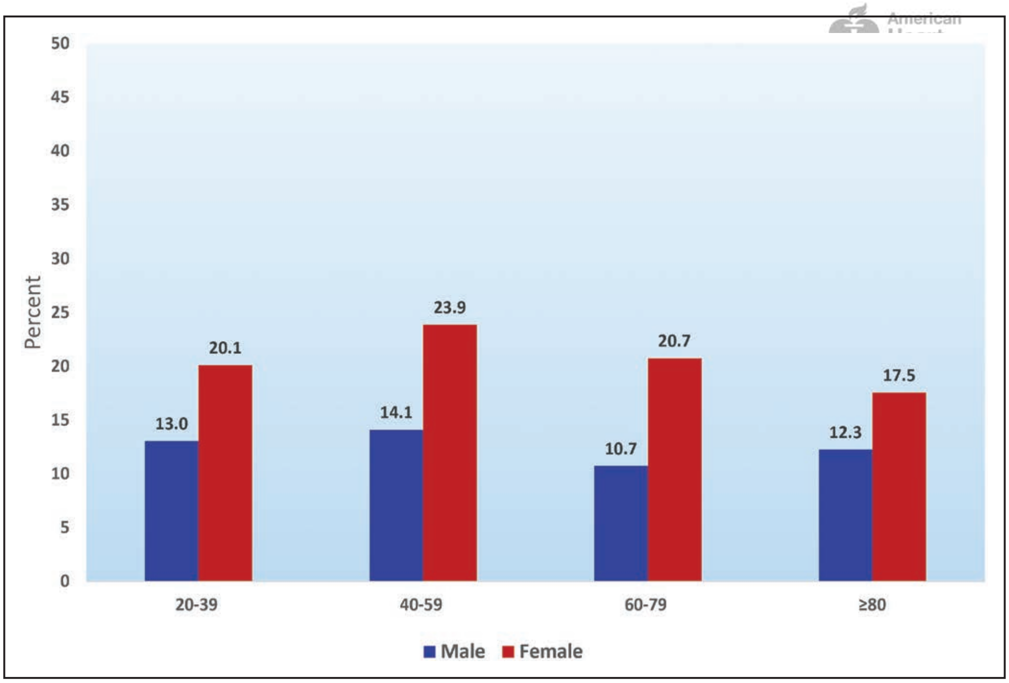

Chart 12-2. Prevalence of trouble falling asleep in US adults by age and sex.
Data source: National Health and Nutrition Examination Survey, 2005 to 2008.

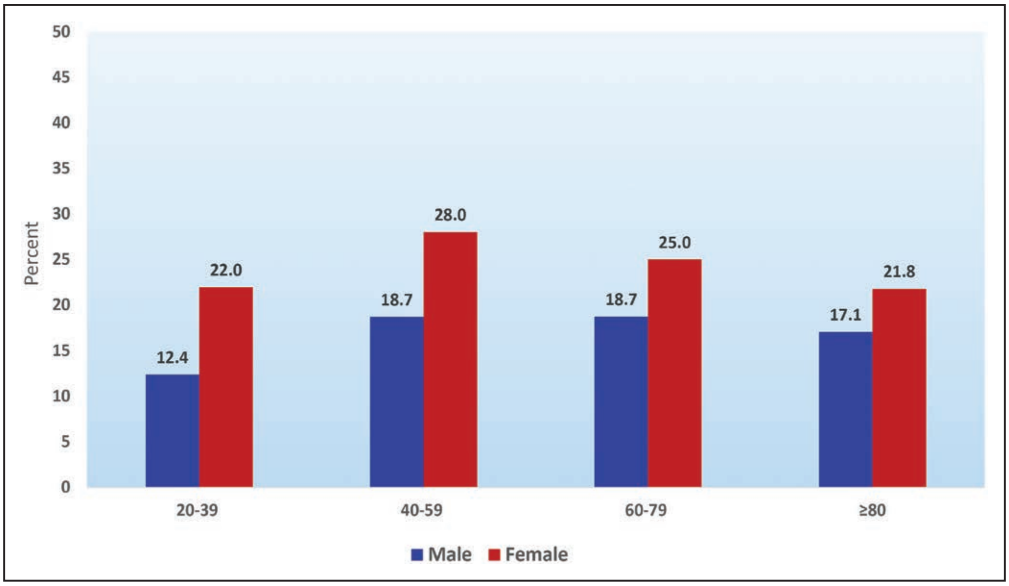

Chart 12-3. Prevalence of trouble staying asleep in US adults by age and sex.
Data source: National Health and Nutrition Examination Survey, 2005 to 2008.

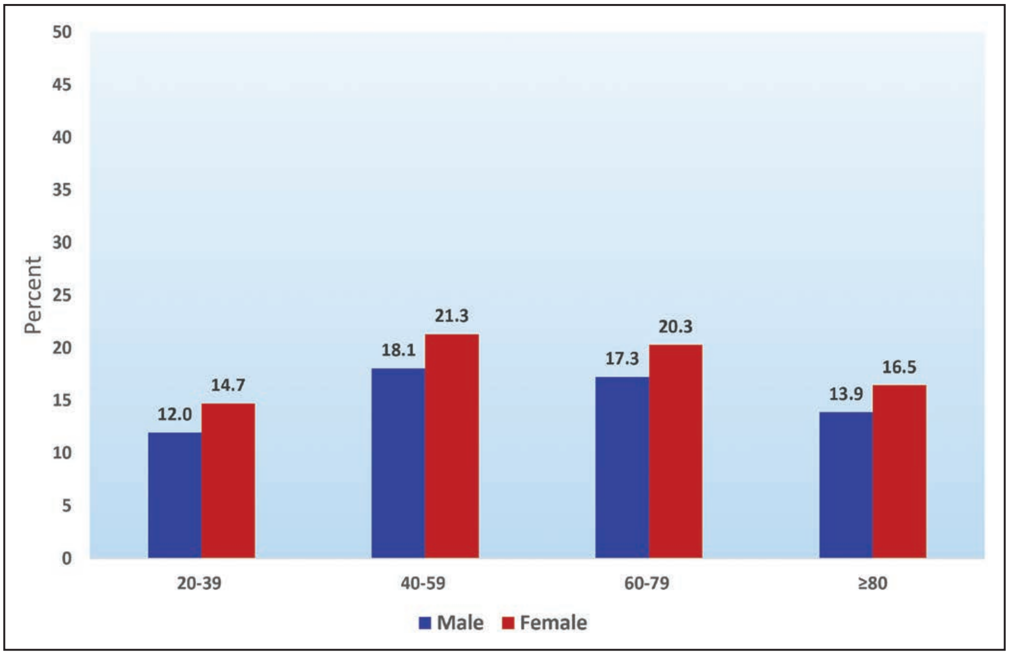

Chart 12-4. Prevalence of waking too early in US adults by age and sex.
Data source: National Health and Nutrition Examination Survey, 2005 to 2008.

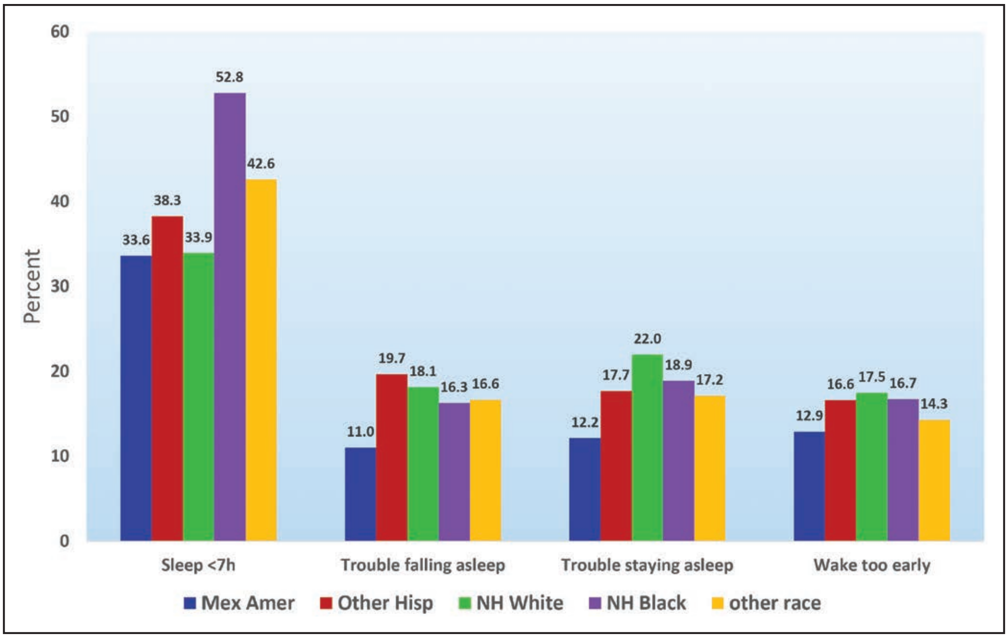

Chart 12-5. Prevalence of inadequate sleep (<7 h) and insomnia symptoms, trouble falling asleep, trouble staying asleep, and waking too early in US adults by race/ethnicity.
Hisp indicates Hispanic; Mex Amer, Mexican American; and NH, non-Hispanic.
Data source: National Health and Nutrition Examination Survey, 2005 to 2008.

REFERENCES

1. Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, Malhotra RK, Martin JL, Patel SR, Quan SF, Tasali E. Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep*. 2015;38:843–844. doi: 10.5665/sleep.4716
2. Paruthi S, Brooks LJ, D'Ambrosio C, Hall WA, Kotagal S, Lloyd RM, Malow BA, Maski K, Nichols C, Quan SF, Rosen CL, Troester MM, Wise MS. Consensus statement of the American Academy of Sleep Medicine on the recommended amount of sleep for healthy children: methodology and discussion. *J Clin Sleep Med*. 2016;12:1549–1561. doi: 10.5664/jcsm.6288
3. Liu Y, Wheaton AG, Chapman DP, Cunningham TJ, Lu H, Croft JB. Prevalence of healthy sleep duration among adults–United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2016;65:137–141. doi: 10.15585/mmwr.mm6506a1
4. Gamble S, Mawokomatanda T, Xu F, Chowdhury PP, Pierannunzi C, Flegel D, Garvin W, Town M. Surveillance for certain health behaviors and conditions among states and selected local areas - Behavioral Risk Factor Surveillance System, United States, 2013 and 2014. *MMWR Surveill Summ*. 2017;66:1–144. doi: 10.15585/mmwr.ss6616a1
5. Knutson KL, Van Cauter E, Rathouz PJ, DeLeire T, Lauderdale DS. Trends in the prevalence of short sleepers in the USA: 1975-2006. *Sleep*. 2010;33:37–45.
6. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol*. 2013;177:1006–1014. doi: 10.1093/aje/kws342
7. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev*. 2002;6:97–111.
8. Zhang B, Wing YK. Sex differences in insomnia: a meta-analysis. *Sleep*. 2006;29:85–93.
9. Buxton OM, Chang AM, Spilsbury JC, Bos T, Emsellem H, Knutson KL. Sleep in the modern family: protective family routines for child and adolescent sleep. *Sleep Health*. 2015;1:15–27.
10. Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. *Proc Am Thorac Soc*. 2008;5:242–252. doi: 10.1513/pats.200708-135MG
11. Lauderdale DS, Knutson KL, Yan LL, Rathouz PJ, Hulley SB, Sidney S, Liu K. Objectively measured sleep characteristics among early-middle-aged adults: the CARDIA study. *Am J Epidemiol*. 2006;164:5–16. doi: 10.1093/aje/kwj199
12. Carnethon MR, De Chavez PJ, Zee PC, Kim KY, Liu K, Goldberger JJ, Ng J, Knutson KL. Disparities in sleep characteristics by race/ethnicity in a population-based sample: Chicago Area Sleep Study. *Sleep Med*. 2016;18:50–55. doi: 10.1016/j.sleep.2015.07.005
13. Yin J, Jin X, Shan Z, Li S, Huang H, Li P, Peng X, Peng Z, Yu K, Bao W, Yang W, Chen X, Liu L. Relationship of sleep duration with all-cause mortality and cardiovascular events: a systematic review and dose-response meta-analysis of prospective cohort studies. *J Am Heart Assoc*. 2017;6:e005947. doi: 10.1161/JAHA.117.005947
14. Åkerstedt T, Ghilotti F, Grotta A, Bellavia A, Lagerros YT, Bellocco R. Sleep duration, mortality and the influence of age. *Eur J Epidemiol*. 2017;32:881–891. doi: 10.1007/s10654-017-0297-0
15. Beydoun HA, Beydoun MA, Chen X, Chang JJ, Gamaldo AA, Eid SM, Zonderman AB. Sex and age differences in the associations between sleep behaviors and all-cause mortality in older adults: results from the National Health and Nutrition Examination Surveys. *Sleep Med*. 2017;36:141–151. doi: 10.1016/j.sleep.2017.05.006
16. Fu Y, Xia Y, Yi H, Xu H, Guan J, Yin S. Meta-analysis of all-cause and cardiovascular mortality in obstructive sleep apnea with or without continuous positive airway pressure treatment. *Sleep Breath*. 2017;21:181–189. doi: 10.1007/s11325-016-1393-1
17. Li Y, Zhang X, Winkelman JW, Redline S, Hu FB, Stampfer M, Ma J, Gao X. Association between insomnia symptoms and mortality: a prospective study of U.S. men. *Circulation*. 2014;129:737–746. doi: 10.1161/CIRCULATIONAHA.113.004500
18. Parthasarathy S, Vasquez MM, Halonen M, Bootzin R, Quan SF, Martinez FD, Guerra S. Persistent insomnia is associated with mortality risk. *Am J Med*. 2015;128:268–75.e2. doi: 10.1016/j.amjmed.2014.10.015
19. Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, Walsleben JA, Finn L, Enright P, Samet JM; Sleep Heart Health Study Research Group. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. *Arch Intern Med*. 2002;162:893–900.
20. Chen LJ, Steptoe A, Chen YH, Ku PW, Lin CH. Physical activity, smoking, and the incidence of clinically diagnosed insomnia. *Sleep Med*. 2017;30:189–194. doi: 10.1016/j.sleep.2016.06.040
21. Mukherjee S, Saxena R, Palmer LJ. The genetics of obstructive sleep apnoea. *Respirology*. 2018;23:18–27. doi: 10.1111/resp.13212
22. van der Spek A, Luik AI, Kocevska D, Liu C, Brouwer RWW, van Rooij JGJ, van den Hout MCGN, Kraaij R, Hofman A, Uitterlinden AG, van IJcken WFJ, Gottlieb DJ, Tiemeier H, van Duijn CM, Amin N. Exome-wide meta-analysis identifies rare 3′-UTR variant in ERCC1/CD3EAP

associated with symptoms of sleep apnea. *Front Genet*. 2017;8:151. doi: 10.3389/fgene.2017.00151
23. Koskenvuo M, Hublin C, Partinen M, Heikkilä K, Kaprio J. Heritability of diurnal type: a nationwide study of 8753 adult twin pairs. *J Sleep Res*. 2007;16:156–162. doi: 10.1111/j.1365-2869.2007.00580.x
24. Patke A, Murphy PJ, Onat OE, Krieger AC, Özçelik T, Campbell SS, Young MW. Mutation of the human circadian clock gene CRY1 in familial delayed sleep phase disorder. *Cell*. 2017;169:203–215.e13. doi: 10.1016/j.cell.2017.03.027
25. Hirano A, Shi G, Jones CR, Lipzen A, Pennacchio LA, Xu Y, Hallows WC, McMahon T, Yamazaki M, Ptacek LJ and Fu YH. A Cryptochrome 2 mutation yields advanced sleep phase in humans. *eLife*. 2016;5:e16695. doi: 10.7554/eLife.16695
26. Cappuccio FP, Taggart FM, Kandala NB, Currie A, Peile E, Stranges S, Miller MA. Meta-analysis of short sleep duration and obesity in children and adults. *Sleep*. 2008;31:619–626.
27. Wu Y, Zhai L, Zhang D. Sleep duration and obesity among adults: a meta-analysis of prospective studies. *Sleep Med*. 2014;15:1456–1462. doi: 10.1016/j.sleep.2014.07.018
28. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care*. 2010;33:414–420. doi: 10.2337/dc09-1124
29. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J*. 2011;32:1484–1492. doi: 10.1093/eurheartj/ehr007
30. Javaheri S, Zhao YY, Punjabi NM, Quan SF, Gottlieb DJ and Redline S. Slow-wave sleep is associated with incident hypertension: the Sleep Heart Health Study. *Sleep*. 2018;41:zsx179. doi: 10.1093/sleep/zsx179
31. Wang Q, Xi B, Liu M, Zhang Y, Fu M. Short sleep duration is associated with hypertension risk among adults: a systematic review and meta-analysis. *Hypertens Res*. 2012;35:1012–1018. doi: 10.1038/hr.2012.91
32. Wu Z, Chen F, Yu F, Wang Y, Guo Z. A meta-analysis of obstructive sleep apnea in patients with cerebrovascular disease. *Sleep Breath*. 2018;22:729–742. doi: 10.1007/s11325-017-1604-4
33. Ludka O, Stepanova R, Sert-Kuniyoshi F, Spinar J, Somers VK, Kara T. Differential likelihood of NSTEMI vs STEMI in patients with sleep apnea. *Int J Cardiol*. 2017;248:64–68. doi: 10.1016/j.ijcard.2017.06.034
34. Tung P, Levitzky YS, Wang R, Weng J, Quan SF, Gottlieb DJ, Rueschman M, Punjabi NM, Mehra R, Bertisch S, Benjamin EJ, Redline S. Obstructive and central sleep apnea and the risk of incident atrial fibrillation in a community cohort of men and women. *J Am Heart Assoc*. 2017;6:e004500. doi: 10.1161/JAHA.116.004500
35. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep*. 1997;20:705–706.
36. Parra O, Sánchez-Armengol A, Bonnin M, Arboix A, Campos-Rodríguez F, Pérez-Ronchel J, Durán-Cantolla J, de la Torre G, González Marcos JR, de la Peña M, Carmen Jiménez M, Masa F, Casado I, Luz Alonso M, Macarrón JL. Early treatment of obstructive apnoea and stroke outcome: a randomised controlled trial. *Eur Respir J*. 2011;37:1128–1136. doi: 10.1183/09031936.00034410
37. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, Mediano O, Chen R, Drager LF, Liu Z, Chen G, Du B, McArdle N, Mukherjee S, Tripathi M, Billot L, Li Q, Lorenzi-Filho G, Barbe F, Redline S, Wang J, Arima H, Neal B, White DP, Grunstein RR, Zhong N, Anderson CS; SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med*. 2016;375:919–931. doi: 10.1056/NEJMoa1606599
38. Hillman DR, Murphy AS, Pezzullo L. The economic cost of sleep disorders. *Sleep*. 2006;29:299–305.

13. TOTAL CARDIOVASCULAR DISEASES

***ICD-9* 390 to 459; *ICD-10* I00 to I99. See Tables 13-1 through 13-4 and Charts 13-1 through 13-22**

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Prevalence (See Table 13-1 and Chart 13-1)

- On the basis of NHANES 2013 to 2016 data, the prevalence of CVD (comprising CHD, HF, stroke, and hypertension) in adults ≥20 years of age is 48.0% overall (121.5 million in 2016) and increases with age in both males and females. CVD prevalence excluding hypertension (CHD, HF, and stroke only) is 9.0% overall (24.3 million in 2016) (Table 13-1 and Chart 13-1).
- The AHA's 2020 Impact Goals are to improve the cardiovascular health of all Americans by 20% while reducing deaths attributable to CVDs and stroke by 20%.[1]

Abbreviations Used in Chapter 13

AF	atrial fibrillation
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities Study
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
BP	blood pressure
CARDIA	Coronary Artery Risk Development in Young Adults
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
CLRD	chronic lower respiratory disease
CVD	cardiovascular disease
DM	diabetes mellitus
ED	emergency department
FHS	Framingham Heart Study
GBD	Global Burden of Disease
HBP	high blood pressure
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HDL	high-density lipoprotein
HF	heart failure
HIV	human immunodeficiency virus
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
IHD	ischemic heart disease
IMPACT	International Model for Policy Analysis of Agricultural Commodities and Trade
LDL-C	low-density lipoprotein cholesterol
MEPS	Medical Expenditure Panel Survey
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
NAMCS	National Ambulatory Medical Care Survey
NCHS	National Center for Health Statistics
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHDS	National Hospital Discharge Survey
NHLBI	National Heart, Lung, and Blood Institute
PA	physical activity
RR	relative risk
SBP	systolic blood pressure
SES	socioeconomic status
SNAP	Supplemental Nutrition Assistance Program
TC	total cholesterol

Mortality (See Tables 13-1 through 13-3 and Charts 13-2 through 13-17)

***ICD-10* I00 to I99 for CVD; C00 to C97 for cancer; C33 to C34 for lung cancer; C50 for breast cancer; J40 to J47 for CLRD; G30 for Alzheimer disease; E10 to E14 for DM; and V01 to X59 and Y85 to Y86 for accidents.**

- Deaths attributable to diseases of the heart and CVD in the United States increased steadily during the 1900s to the 1980s and declined into the 2010s (Charts 13-2 through 13-4).
- CHD (43.2%) is the leading cause of CVD death in the United States, followed by stroke (16.9%), HBP (9.8%), HF (9.3%), diseases of the arteries (3.0%), and other minor CVD causes combined (17.7%) (Chart 13-4).
- The age-adjusted death rate attributable to CVD decreased from 269.6 per 100 000 population in 2006 to 219.4 per 100 000 in 2016, which amounts to an 18.6% decrease.
- On the basis of 2016 mortality data[2]:
  - — CVD currently claims more lives each year than cancer and chronic lung disease combined (Charts 13-5 through 13-15). More than 360 000 people died in 2016 of CHD, the most common type of HD.
  - — In 2016, 2 744 248 resident deaths were registered in the United States. Ten leading causes accounted for 74.1% of all registered deaths. The 10 leading causes of death in 2016 were the same as in 2015; these include HD (No. 1), cancer (No. 2), unintentional injuries (No. 3), CLRDs (No. 4), stroke (No. 5), Alzheimer disease (No. 6), DM (No. 7), influenza and pneumonia (No. 8), kidney disease (No. 9), and suicide (No. 10). Seven of the 10 leading causes of death had a decrease in age-adjusted death rates. The age-adjusted death rates decreased 1.8% for HD, 1.7% for cancer, 2.4% for CLRDs, 0.8% for stroke, 1.4% for DM, 11.2% for influenza and pneumonia, and

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2.2% for kidney disease. The age-adjusted rate increased 9.7% for unintentional injuries, 3.1% for Alzheimer disease, and 1.5% for suicide.[3]

- HD accounted for 635 260 of all 840 678 CVD deaths in 2016. The number of CVD deaths was 428 434 for males and 412 244 for females (Charts 13-2 and 13-3). The number was 332 556 for NH white males, 52 874 for NH black males, 27 801 for Hispanic males, 11 023 for NH Asian and Pacific Islander males, 322 328 for NH white females, 51 767 for NH black females, 24 428 for Hispanic females, and 10 672 for NH Asian and Pacific Islander females. Among other causes of death, cancer accounted for 598 031 deaths; chronic lung disease, 154 592; accidents, 161 346; and Alzheimer disease, 116 103 (Chart 13-6).
- Approximately 161 438 Americans, or 19.2%, who were <65 years of age died of CVD, and 306 638, or 36.5% of deaths attributed to CVD, occurred before the age of 75 years, which is well below the average US life expectancy of 78.6 years in 2016.[3]
- The CVD mortality trends for males and females in the United States declined from 1979 to 2016 (Chart 13-16).
- The age-adjusted death rates per 100 000 population for CVD, CHD, and stroke differ by US state (Chart 13-17; Table 13-2) and globally (Table 13-3).
- CVD death rates also vary among United States counties. In 2014, the ratio between counties at the 90th and 10th percentile was 2.0 for IHD (119.1 versus 235.7 deaths per 100 000 people) and 1.7 for cerebrovascular disease (40.3 versus 68.1 deaths per 100 000 people). For other CVD causes, the ratio ranged from 1.4 (aortic aneurysm: 3.5 versus 5.1 deaths per 100 000 people) to 4.2 (hypertensive HD: 4.3 versus 17.9 deaths per 100 000 people). A region of higher CVD mortality extends from southeastern Oklahoma along the Mississippi River Valley to eastern Kentucky.[4]

Hospital Discharges, Ambulatory Care Visits, Home Healthcare Patients, Nursing Home Residents, and Hospice Care Discharges (See Table 13-1 and Charts 13-18 and 13-19)

- From 2004 to 2014, the number of inpatient discharges from short-stay hospitals with CVD as the principal diagnosis decreased from 5 797 000 to 4 791 000 (HCUP, hospital discharges 2014; NHDS, NCHS, and NHLBI; Table 13-1). The CVD principal diagnosis discharges in 2014 comprised 2 571 000 males and 2 220 000 females (unpublished NHDS, NCHS, and NHLBI tabulation).
- From 1993 to 2014, the number of hospital discharges for CVD in the United States increased in the first decade and then began to decline in the second decade (Chart 13-18).
- In 2014, cardiovascular causes were the leading diagnostic group of hospital discharges in the United States (Chart 13-19).
- In 2015, there were 88 343 000 physician office visits with a primary diagnosis of CVD (NAMCS, NHLBI tabulation).[5] In 2015, there were 4 704 000 ED visits with a primary diagnosis of CVD (NHAMCS, NHLBI tabulation).[6]

Operations and Procedures (See Chapter 25 for detailed information.)

- In 2014, an estimated 7 971 000 inpatient cardiovascular operations and procedures were performed in the United States (unpublished NHLBI tabulation of HCUP data).

Cost (See Chapter 26 for detailed information.)

- In the United States, 22.2% of adults (53 316 677 people) report any disability. In 2006, 26.7% of resident adult healthcare expenditures were associated with disability care and totaled $397.8 billion.[7] For people with disabilities in the United States, HD, stroke, and hypertension were among the 15 leading conditions that caused those disabilities. Disabilities were defined as difficulty with activities of daily living or instrumental activities of daily living, specific functional limitations (except vision, hearing, or speech), and limitation in ability to do housework or work at a job or business.[8,9] The estimated direct and indirect cost of CVD for 2014 to 2015 was $351.2 billion (MEPS, NHLBI tabulation).
- In 2016, the AHA estimated that by 2035, 45.1% of the US population would have some form of CVD. Total costs of CVD are expected to reach $1.1 trillion in 2035, with direct medical cost projected to reach $748.7 billion and indirect costs estimated to reach $368 billion.[10]

Risk Factors

- A recent study using the GBD methodology examined the burden of CVD among US states and found that a large proportion of CVD is attributable to (in decreasing order of contribution) dietary risk, high SBP, high BMI, high TC level, high fasting plasma glucose level, tobacco smoking, and low levels of PA.[11]
- It is estimated that 47% of all Americans have at least 1 of the 3 well-established key risk factors for CVD, which are HBP, high cholesterol, and smoking.[12]
- In 2005, HBP was the single largest risk factor for cardiovascular mortality in the United States and was responsible for an estimated 395 000 (95% CI, 372 000–414 000) cardiovascular deaths (45% of all cardiovascular deaths). Additional risk factors for cardiovascular mortality were overweight/obesity, physical inactivity, high LDL-C, smoking, high dietary salt, high dietary *trans* fatty acids, and low dietary omega-3 fatty acids.[13]
- When added to traditional CVD risk factors, nontraditional CVD risk factors such as CKD, SBP variability, migraine, severe mental illness, systemic lupus erythematosus, use of corticosteroid or antipsychotic medications, or erectile dysfunction improved CVD prediction by the United Kingdom–based QRISK score.[14]
- In Nurses' Health Study participants, compared with a more typical reproductive lifespan and age at first menarche, early age at menopause (age <40 years) was associated with a 32% higher CVD risk; extremely early age at menarche (age ≤10 years) was associated with a 22% higher CVD risk.[15]
- People living with HIV are more likely to experience CVD before age 60 years than uninfected people. Cumulative lifetime CVD risk in people living with HIV (65% for males, 44% for females) is higher than in the general population and similar to that of people living with DM (67% for males, 57% for females).[16]
- Patients living with type 1 DM are at increased risk of early CVD. In Pittsburgh Epidemiology of Diabetes Complications Study participants with type 1 DM and aged 40 to 44 years at baseline, mean absolute 10-year CVD risk was 14.8%. Mean absolute 10-year CVD risk was 6.3% in those aged 30 to 39 years.[17]
- Neighborhood-level socioeconomic deprivation was associated with greater risk of CVD mortality in older males in Britain, independent of individual social class or risk factors.[18] In the United States, there are significant state-level variations in poor cardiovascular health explained in part by individual and state-level factors such as policies, food, and PA environments.[19]

Impact of Healthy Lifestyle and Low Risk Factor Levels (See Chapter 2 for more detailed statistics regarding healthy lifestyle and low risk factor levels.)

- A study of the decrease in US deaths attributable to CHD from 1980 to 2000 suggested that ≈47% of the decrease was attributable to increased use of evidence-based medical therapies for secondary prevention and 44% to changes in risk factors in the population attributable to lifestyle and environmental changes.[8]
- Approximately 80% of CVDs can be prevented through not smoking, eating a healthy diet, engaging in PA, maintaining a healthy weight, and controlling HBP, DM, and elevated lipid levels. The presence of a greater number of optimal cardiovascular health metrics is associated with a graded and significantly lower risk of total and CVD mortality.[20]
- During more than 5 million person-years of follow-up combined in the Nurses' Health Studies and Health Professionals Follow-Up Study, regular consumption of peanuts and tree nuts (≥2 times weekly) or walnuts (≥1 time weekly) was associated with a 13% to 19% lower risk of total CVD.[21]
- Seventeen-year mortality data from the NHANES II Mortality Follow-up Study indicated that the RR for fatal CHD was 51% lower for males and 71% lower for females with none of the 3 major risk factors (hypertension, current smoking, and elevated TC [≥240 mg/dL]) than for those with ≥1 risk factor. If all 3 major risk factors had not occurred, it is hypothesized that 64% of all CHD deaths among females and 45% of CHD deaths in males could have been avoided.[22]
- Data from the Cardiovascular Lifetime Risk Pooling Project, which involved 18 cohort studies and combined data on 257 384 people (both black and white males and females), indicate that at 45 years of age, participants with optimal risk factor profiles had a substantially lower lifetime risk of CVD events than those with 1 major risk factor (1.4% versus 39.6% among males; 4.1% versus 20.2% among females). Having ≥2 major risk factors further increased lifetime risk to 49.5% in males and 30.7% in females.[23]

- In another study, FHS investigators conducted follow-up of 2531 males and females who were examined between the ages of 40 and 50 years and observed their overall rates of survival and survival free of CVD to 85 years of age and beyond. Low levels of the major risk factors in middle age were associated with overall survival and morbidity-free survival to ≥85 years of age.[24]
- In young adults aged 18 to 30 years in the CARDIA study and without clinical risk factors, a Healthy Heart Score combining self-reported information on modifiable lifestyle factors including smoking status, alcohol intake, and healthful dietary pattern predicted risk for early ASCVD (before age 55 years).[25]
- Data from NHANES 2005 to 2010 showed that only 8.8% of adults complied with ≥6 heart-healthy behaviors. Of the 7 factors studied, healthy diet was the least likely to be achieved (only 22% of adults with a healthy diet).[20]
- In the United States, higher whole grain consumption was associated with lower CVD mortality, independent of other dietary and lifestyle factors. Every serving (28 g/d) of whole grain consumption was associated with a 9% (95% CI, 4%–13%) lower CVD mortality.[26]

Disparities in CVD Risk Factors (See Chart 13-20)

- Although traditional cardiovascular risk factors are generally similar for males and females, there are several female-specific risk factors, such as disorders of pregnancy, adverse pregnancy outcomes, and menopause.[27]
- CVD risk factor levels vary among counties and states within the continental United States. Within-state differences in the county prevalence of uncontrolled hypertension were as high as 7.8 percentage points in 2009.[28]
- Analysis of >14 000 middle-aged participants in the ARIC study sponsored by the NHLBI showed that ≈90% of CVD events in black participants, compared with ≈65% in white participants, appeared to be explained by elevated or borderline risk factors. Furthermore, the prevalence of participants with elevated risk factors was higher in black participants; after accounting for education and known CVD risk factors, the incidence of CVD was identical in black and white participants. Although organizational and social barriers to primary prevention do exist, the primary prevention of elevated risk factors might substantially impact the future incidence of CVD, and these beneficial effects would likely be applicable not only for white but also for black participants.[29]
- Mortality data from the National Vital Statistics System from 2001 to 2010 show that the avoidable death rate among blacks was nearly twice that of whites.[30]
- Data from the CDC's Vital and Health Statistics 2008 to 2010 showed that smokers with family incomes below the poverty level were more than twice as likely as adults in the highest family income group to be current smokers (29.2% versus 13.9%, respectively; NCHS/CDC, 2013).[31]
- The US IMPACT Food Policy Model, a computer simulation model, projected that a national policy combining a 30% fruit and vegetable subsidy targeted to low-income SNAP recipients and a population-wide 10% price reduction in fruits and vegetables in the remaining population could prevent ≈230 000 deaths by 2030 and reduce the socioeconomic disparity in CVD mortality by 6%.[32]
- A study of nearly 1500 participants in MESA found that Hispanics with hypertension, hypercholesterolemia, or DM who spoke Spanish at home (as a proxy of lower levels of acculturation) or had spent less than half a year in the United States had higher SBP, LDL-C, and fasting blood glucose, respectively, than Hispanics who were preferential English speakers and who had lived a longer period of time in the United States.[33]
- Findings from >15 000 Hispanics of diverse backgrounds demonstrated that a sizeable proportion of both males and females had major CVD risk factors, with higher prevalence among Puerto Rican subgroups and those with lower SES and a higher level of acculturation.[34]

Family History and Genetics (See Table 13-4)

- A family history of CVD increases risk of CVD, with the largest increase in risk if the family member's CVD was premature (Table 13-4).[35]
- A reported family history of premature parental CHD is associated with incident MI or CHD in offspring. In FHS, the occurrence of a validated premature atherosclerotic CVD event in either a parent[36] or a sibling[37] was associated with an ≈2-fold elevated risk for CVD, independent of other traditional risk factors. Addition of a family history of premature CVD to a model that contained traditional risk factors provided improved prognostic value in FHS.[36]

- The association of a family history of CVD with increased risk of CVD appears to be present across ethnic subgroups.[38,39]
- Family history is also associated with subtypes of CVD, including HF,[40] stroke, AF,[41] and thoracic aortic disease.[42]
- Estimates of familial clustering of CVD are likely underestimated by self-report; in the multigenerational FHS, only 75% of participants with a documented parental history of a heart attack before age 55 years reported that history when asked.[43]
- A comprehensive scientific statement on the role of genetics and genomics for the prevention and treatment of CVD is available elsewhere.[44]

Awareness of Warning Signs and Risk Factors for CVD

- Surveys conducted every 3 years since 1997 by the AHA to evaluate trends in females' awareness, knowledge, and perceptions related to CVD found most recently (in 2012) that awareness of HD as the leading cause of death among females was 56%, compared with 30% in 1997 (*P*<0.05). Awareness among black and Hispanic females in 2012 was similar to that of white females in 1997; however, awareness rates in 2012 among black and Hispanic females remained below that of white females. Awareness of heart attack signs remained low for all racial/ethnic and age groups surveyed during the same time.[45]

Global Burden of CVD (See Table 13-3 and Charts 13-21 and 13-22)

- The death rates for all causes and CVD in 31 selected countries in 2016 are presented in Table 13-3.
- In 2016, ≈17.6 million (95% CI, 17.3–18.1 million) deaths were attributed to CVD globally, which amounted to an increase of 14.5% (95% CI, 12.1%–17.1%) from 2006. The age-adjusted death rate per 100 000 population was 277.9 (95% CI, 272.1–284.6), which represents a decrease of 14.5% (95% CI, −16.2% to −12.5%) from 2006. Overall, the crude prevalence of CVD was 470.8 million (95% CI, 453.4–488.7 million) in 2016, an increase of 26.7% (95% CI, 25.6%–27.8%) compared with 2006; however, the age-adjusted prevalence was 6877.9 (95% CI, 6623.3–7141.3), a decrease of 0.8% (95% CI, −1.6% to −0.0%) from 2006.[11]
- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories. CVD mortality and prevalence vary widely among world regions[46]:
  - — The highest mortality rates attributable to CVD were in Eastern Europe and Central Asia (Chart 13-21).
  - — CVD prevalence is highest in sub-Saharan Africa, the North Africa/Middle East region, Eastern and Central Europe, and Central Asia (Chart 13-22).
- CVD is the leading global cause of death and is expected to account for >23.6 million deaths by 2030.[47] Deaths attributable to IHD increased by an estimated 41.7% from 1990 to 2013.[48]
- In 2011, data from the World Economic Forum found that CVD represented 50% of noncommunicable disease deaths.[48] CVD represents 37% of deaths of individuals <70 years of age that are attributable to noncommunicable diseases.[49]
- In 2013, ≈70% of CVD deaths occurred in low- to middle-income countries.[50] CVD is a major cause of death in both males and females worldwide.[42]
- In May 2012, during the World Health Assembly, ministers of health agreed to adopt a global target to reduce premature (age 30–70 years) noncommunicable disease mortality by 25% by 2025.[51] Targets for 6 risk factors (tobacco and alcohol use, salt intake, obesity, and raised BP and glucose) were also agreed on to address this goal. It was projected that if the targets are met, premature deaths attributable to CVDs in 2025 will be reduced by 34%, with 11.4 million and 15.9 million deaths delayed or prevented in those aged 30 to 69 years and ≥70 years, respectively.[52]

Table 13-1. Cardiovascular Diseases

Population Group	Prevalence, 2013–2016: Age ≥20 y	Prevalence, 2013–2016: Age ≥20 y*	Mortality, 2016: All Ages†	Hospital Discharge, 2014: All Ages	Cost, 2014–2015
Both sexes	121 500 000 (48.0%)	24 300 000 (9.0%)	840 678	4 791 000	$351.2 Billion
Males	61 500 000 (51.2%)	12 300 000 (9.6%)	428 434 (51.0%)‡	2 571 000	$224.7 Billion
Females	60 000 000 (44.7%)	12 000 000 (8.4%)	412 244 (49.0%)‡	2 220 000	$126.5 Billion
NH white males	50.6%	9.7%	332 556	…	…
NH white females	43.4%	8.1%	322 328	…	…
NH black males	60.1%	10.7%	52 874	…	…
NH black females	57.1%	10.5%	51 767	…	…
Hispanic males	49.0%	7.8%	27 801	…	…
Hispanic females	42.6%	8.0%	24 428	…	…
NH Asian males	47.4%	6.5%	11 023§	…	…
NH Asian females	37.2%	4.6%	10 672§	…	…
NH American Indian/ Alaska Native	…	…	4313	…	…

Ellipses (…) indicate data not available; and NH, non-Hispanic.

*Prevalence excluding hypertension.

†Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

‡These percentages represent the portion of total cardiovascular disease mortality that is attributable to males vs females.

§Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander.

Sources: Prevalence: National Health and Nutrition Examination Survey 2013 to 2016, National Center for Health Statistics (NCHS) and National Heart, Lung, and Blood Institute. Percentages for racial/ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2014 US population estimates. Mortality: Centers for Disease Control and Prevention/NCHS, 2016 Mortality Multiple Cause-of-Death–United States. These data represent underlying cause of death only for *International Classification of Diseases, 10th Revision* codes I00 to I99 (diseases of the circulatory system). Mortality for NH Asians includes Pacific Islanders. Hospital discharges: Healthcare Cost and Utilization Project, National (Nationwide) Inpatient Sample, 2014. Agency for Healthcare Research and Quality. Cost: Medical Expenditure Panel Survey, average annual 2014 to 2015 (direct costs) and mortality data from NCHS and present value of lifetime earnings from the Institute for Health and Aging, University of California, San Francisco (indirect costs).

Table 13-2. Age-Adjusted Death Rates per 100 000 Population for CVD, CHD, and Stroke by State, 2014 to 2016

State	CVD			CHD			Stroke		
	Rank	Death Rate	% Change, 2004–2006 to 2014–2016	Rank	Death Rate	% Change, 2004–2006 to 2014–2016	Rank	Death Rate	% Change, 2004–2006 to 2014–2016
Alabama	51	295.4	−17.4	21	89.2	−31.1	52	50.7	−18.4
Alaska	13	197.2	−15.5	12	80.4	−14.1	26	36.2	−30.3
Arizona	6	186.2	−24.2	22	89.7	−34.9	7	29.6	−27.8
Arkansas	49	284.7	−14.2	51	133.7	−22.1	50	46.0	−26.5
California	14	198.0	−27.9	23	90.1	−39.5	23	35.7	−28.5
Colorado	3	178.5	−22.1	5	69.5	−33.7	19	34.5	−18.2
Connecticut	7	186.8	−21.3	9	77.1	−34.3	3	27.0	−27.0
Delaware	30	218.9	−23.4	34	101.9	−35.5	37	40.0	−7.1
District of Columbia	46	259.5	−23.9	46	117.9	−39.4	28	36.8	−8.2
Florida	17	199.8	−22.6	28	94.8	−35.9	24	35.9	−11.0
Georgia	39	242.9	−23.0	10	77.5	−36.2	46	44.1	−21.9
Hawaii	5	180.0	−20.7	2	67.2	−24.8	21	35.5	−25.5
Idaho	26	207.6	−17.9	17	84.6	−27.9	27	36.8	−31.8
Illinois	34	223.1	−22.3	26	90.7	−37.6	32	37.9	−22.5
Indiana	38	240.1	−20.8	35	102.6	−29.9	38	40.1	−23.3
Iowa	28	210.8	−19.6	38	105.0	−28.9	11	33.2	−30.5
Kansas	33	222.2	−17.1	19	87.7	−27.7	36	38.8	−22.4

(*Continued*)

Table 13-2. Continued

State	CVD			CHD			Stroke		
	Rank	Death Rate	% Change, 2004–2006 to 2014–2016	Rank	Death Rate	% Change, 2004–2006 to 2014–2016	Rank	Death Rate	% Change, 2004–2006 to 2014–2016
Kentucky	45	258.5	−21.0	41	107.4	−32.8	41	41.0	−24.2
Louisiana	48	275.2	−17.3	37	103.6	−31.9	48	45.9	−19.9
Maine	15	198.1	−19.9	14	82.7	−31.2	13	33.4	−26.7
Maryland	32	221.9	−21.2	30	96.6	−35.9	35	38.5	−19.6
Massachusetts	4	179.0	−24.7	7	74.5	−33.8	6	28.4	−30.2
Michigan	43	255.8	−17.0	47	121.6	−26.6	33	38.2	−21.4
Minnesota	2	164.3	−20.2	1	59.6	−31.3	12	33.3	−23.2
Mississippi	52	306.7	−19.1	42	107.7	−33.5	51	50.7	−12.5
Missouri	41	251.1	−19.5	45	111.7	−31.6	40	40.7	−23.3
Montana	19	201.2	−14.2	16	84.3	−16.4	16	34.2	−24.8
Nebraska	18	200.2	−19.0	8	76.0	−24.7	14	33.8	−28.4
Nevada	42	252.8	−18.7	44	110.9	−12.4	22	35.6	−25.5
New Hampshire	10	190.8	−24.0	15	84.1	−36.9	4	27.9	−29.7
New Jersey	27	210.7	−22.4	32	97.2	−36.6	8	30.9	−19.6
New Mexico	11	193.7	−19.5	29	95.4	−22.5	17	34.3	−14.6
New York	31	221.8	−25.3	49	123.2	−36.7	1	25.9	−18.9
North Carolina	29	218.8	−24.1	24	90.5	−33.9	45	43.6	−24.6
North Dakota	12	196.7	−20.8	18	86.4	−35.9	15	33.8	−31.4
Ohio	40	246.6	−18.4	43	107.8	−33.2	39	40.4	−18.3
Oklahoma	50	291.5	−17.5	52	139.7	−28.9	43	42.6	−27.7
Oregon	9	190.0	−22.6	3	67.6	−35.5	30	37.6	−31.5
Pennsylvania	36	228.6	−21.4	33	100.0	−32.8	29	37.5	−20.6
Puerto Rico	1	157.8	−29.2	6	70.4	−36.5	5	28.0	−33.6
Rhode Island	16	198.4	−27.0	40	105.7	−41.0	2	26.5	−28.3
South Carolina	37	239.8	−20.2	27	91.0	−30.8	47	45.5	−24.3
South Dakota	22	205.4	−19.0	39	105.2	−27.6	25	35.9	−25.8
Tennessee	47	267.5	−20.0	50	129.3	−28.6	49	45.9	−24.9
Texas	35	226.9	−21.8	31	96.6	−34.8	42	42.1	−20.8
Utah	20	202.4	−12.7	4	68.3	−21.0	34	38.3	−13.7
Vermont	21	203.8	−15.7	36	102.7	−20.0	10	32.4	−19.7
Virginia	25	206.1	−25.3	13	82.2	−34.0	31	37.7	−29.4
Washington	8	187.6	−23.8	11	80.4	−35.4	20	34.8	−28.8
West Virginia	44	258.3	−22.1	48	122.1	−28.6	44	43.6	−16.4
Wisconsin	24	205.7	−19.5	20	88.5	−27.3	18	34.5	−27.2
Wyoming	23	205.6	−19..2	25	90.5	−23.5	9	31.2	−31.2
Total United States		220.7	−22.1		96.8	-33.9		37.2	−22.5

Rates are most current data available as of April 2018. Rates are per 100 000 people. *International Classification of Diseases, 10th Revision* codes used were I00 to I99 for CVD, I20 to I25 for CHD, and I60 to I69 for stroke. CHD indicates coronary heart disease; and CVD, cardiovascular disease.

Sources: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

Table 13-3. Death Rates for CVDs and All Causes in Selected Countries, 2016

Sorted Alphabetically by Country	CVD	CHD	Stroke	Total	Sorted by Descending CVD Death Rate	CVD	CHD	Stroke	Total
Males aged 35–74 y									
Australia (15)	112.5	66.0	16.3	515.6	Belarus (14)	979.5	710.6	175.9	1884.6
Austria (16)	161.6	94.1	19.2	647.8	Ukraine (15)	972.1	661.3	187.7	1853.4
Belarus (14)	979.5	710.6	175.9	1884.6	Russia (13)	956.8	536.2	234.4	2060.5
Belgium (15)	138.2	58.3	23.6	669.8	Romania (16)	535.0	213.5	135.2	1366.5
Croatia (16)	329.7	171.2	79.6	1003.3	Hungary (16)	500.2	257.4	82.7	1361.1
Czech Republic (16)	301.3	156.4	45.1	914.3	Serbia (15)	466.0	131.9	101.4	1241.6
Denmark (15)	128.9	49.6	28.3	655.0	Slovakia (14)	400.6	222.5	89.0	1173.6
Finland (14)	217.6	124.7	35.4	698.1	Croatia (16)	329.7	171.2	79.6	1003.3
France (14)	106.5	40.9	19.5	656.2	Czech Republic (16)	301.3	156.4	45.1	914.3
Germany (15)	193.0	92.5	25.9	727.4	United States (16)	236.6	123.5	27.6	824.4
Hungary (16)	500.2	257.4	82.7	1361.1	Finland (14)	217.6	124.7	35.4	698.1
Ireland (13)	175.3	109.4	23.1	599.1	Germany (15)	193.0	92.5	25.9	727.4
Israel (15)	100.3	45.8	20.4	541.2	Ireland (13)	175.3	109.4	23.1	599.1
Italy (15)	134.7	59.5	23.9	541.0	Taiwan (16)	174.6	51.9	50.1	833.0
Japan (15)	125.0	40.9	40.6	531.7	Austria (16)	161.6	94.1	19.2	647.8
Korea, South (15)	104.1	32.4	42.0	611.6	United Kingdom (15)	161.4	97.7	23.1	613.9
Netherlands (16)	111.9	38.9	21.0	546.1	Portugal (14)	160.9	68.3	46.6	733.6
New Zealand (13)	153.1	93.8	22.1	548.0	New Zealand (13)	153.1	93.8	22.1	548.0
Norway (15)	112.0	59.7	18.2	503.1	Sweden (15)	147.2	82.4	20.8	514.1
Portugal (14)	160.9	68.3	46.6	733.6	Belgium (15)	138.2	58.3	23.6	669.8
Romania (16)	535.0	213.5	135.2	1366.5	Italy (15)	134.7	59.5	23.9	541.0
Russia (!3)	956.8	536.2	234.4	2060.5	Spain (15)	131.3	59.5	23.2	598.7
Serbia (15)	466.0	131.9	101.4	1241.6	Denmark (15)	128.9	49.6	28.3	655.0
Slovakia (14)	400.6	222.5	89.0	1173.6	Japan (15)	125.0	40.9	40.6	531.7
Spain (15)	131.3	59.5	23.2	598.6	Australia (15)	112.5	66.0	16.3	515.6
Sweden (15)	147.2	82.4	20.8	514.1	Switzerland (13)	112.1	54.3	13.8	506.0
Switzerland (13)	112.1	54.3	13.8	506.0	Norway (15)	112.0	59.7	18.2	503.1
Taiwan (16)	174.6	51.9	50.1	833.0	Netherlands (16)	111.9	38.9	21.0	546.1
Ukraine (15)	972.1	661.3	187.7	1853.4	France (14)	106.5	40.9	19.5	656.2
United Kingdom (15)	161.4	97.7	23.1	613.9	Korea, South (15)	104.1	32.4	42.0	611.6
United States (16)	236.6	123.5	27.6	824.4	Israel (15)	100.3	45.8	20.4	541.2
Females aged 35–74 y									
Australia (15)	46.7	18.2	11.6	310.7	Ukraine (15)	393.3	261.5	94.1	723.2
Austria (16)	67.6	28.6	14.5	350.5	Russia (13)	374.1	183.9	117.2	793.5
Belarus (14)	348.3	228.0	88.6	662.2	Belarus (14)	348.3	228.0	88.6	662.2
Belgium (15)	62.4	17.6	15.3	391.5	Serbia (15)	234.1	49.9	63.4	663.6
Croatia (16)	122.0	51.0	39.0	442.4	Romania (16)	232.4	77.4	71.9	605.0
Czech Republic (16)	116.1	45.3	21.2	438.0	Hungary (16)	193.4	86.8	37.4	624.6
Denmark (15)	58.1	17.0	17.3	422.5	Slovakia (14)	154.6	77.9	40.0	505.1
Finland (14)	68.5	26.8	20.0	336.6	Croatia (16)	122.0	51.0	39.0	442.4
France (13)	38.3	9.0	11.0	311.2	United States (16)	117.5	47.5	20.4	518.4
Germany (15)	77.8	26.2	15.4	391.8	Czech Republic (16)	116.1	45.3	21.2	438.0
Hungary (16)	193.4	86.8	37.4	624.6	Germany (15)	77.8	26.2	15.4	391.8
Ireland (13)	65.7	29.2	15.1	372.1	United Kingdom (15)	71.4	30.1	18.1	404.3

(*Continued*)

Table 13-3. Continued

Sorted Alphabetically by Country	CVD	CHD	Stroke	Total	Sorted by Descending CVD Death Rate	CVD	CHD	Stroke	Total
Israel (15)	42.0	12.6	11.4	311.9	Finland (1)	68.5	26.8	20.0	336.6
Italy (15)	55.0	15.9	14.4	300.6	Austria (16)	67.6	28.6	14.5	350.5
Japan (15)	44.9	10.0	17.1	244.7	New Zealand (13)	67.5	30.3	16.1	367.5
Korea, South (15)	42.1	8.6	20.4	245.1	Ireland (13)	65.7	29.2	19.7	372.1
Netherlands (16)	54.9	13.1	15.5	388.4	Portugal (14)	63.7	17.0	23.9	315.9
New Zealand (13)	67.5	30.3	16.1	367.5	Taiwan (16)	63.5	16.0	19.7	372.6
Norway (15)	45.0	15.2	12.6	326.4	Belgium (15)	62.4	17.6	15.3	391.5
Portugal (14)	63.7	17.0	23.9	315.9	Sweden (15)	61.2	24.5	14.1	336.1
Romania (16)	232.4	77.4	71.9	605.0	Denmark (15)	58.1	17.0	17.3	422.5
Russia (13)	374.1	183.9	117.2	793.5	Italy (15)	55.0	15.9	14.4	300.6
Serbia (15)	234.1	49.9	63.4	663.6	Netherlands (16)	54.9	13.1	15.5	388.4
Slovakia (14)	154.6	77.9	40.0	505.1	Australia (15)	46.7	18.2	11.6	310.7
Spain (15)	46.7	13.6	12.7	269.9	Spain (15)	46.7	13.6	12.7	269.9
Sweden (15)	61.2	24.5	14.1	336.1	Norway (15)	45.0	15.2	12.6	326.4
Switzerland (13)	44.7	14.2	10.7	295.0	Japan (15)	44.9	10.0	17.1	244.7
Taiwan (16)	63.5	16.0	19.7	372.6	Switzerland (13)	44.7	14.2	10.7	295.0
Ukraine (15)	393.3	261.5	94.1	723.2	Korea, South (15)	42.1	8.6	20.4	245.1
United Kingdom (15)	71.4	30.1	18.1	404.3	Israel (15)	42.0	12.6	11.4	311.9
United States (16)	117.5	47.5	20.4	518.4	France (14)	38.3	9.0	11.0	311.2

Rates are for the most recent year available (shown in parentheses as last 2 digits of year); most current data available as of April 2018. Rates are per 100 000 people, adjusted to the European Standard population. *International Classification of Diseases, 10th Revision* codes used were I00 to I99 for cardiovascular disease, I20 to I25 for coronary heart disease, and I60 to I69 for stroke. CHD indicates coronary heart disease; and CVD, cardiovascular disease.

Sources: The World Health Organization; National Center for Health Statistics; and National Heart, Lung, and Blood Institute.

Table 13-4. OR for Combinations of Parental Heart Attack History

	OR (95% CI)
No family history	1.00
One parent with heart attack ≥50 y of age	1.67 (1.55–1.81)
One parent with heart attack <50 y of age	2.36 (1.89–2.95)
Both parents with heart attack ≥50 y of age	2.90 (2.30–3.66)
Both parents with heart attack, one <50 y of age	3.26 (1.72–6.18)
Both parents with heart attack, both <50 y of age	6.56 (1.39–30.95)

OR indicates odds ratio.

Data derived from Chow et al.[35]

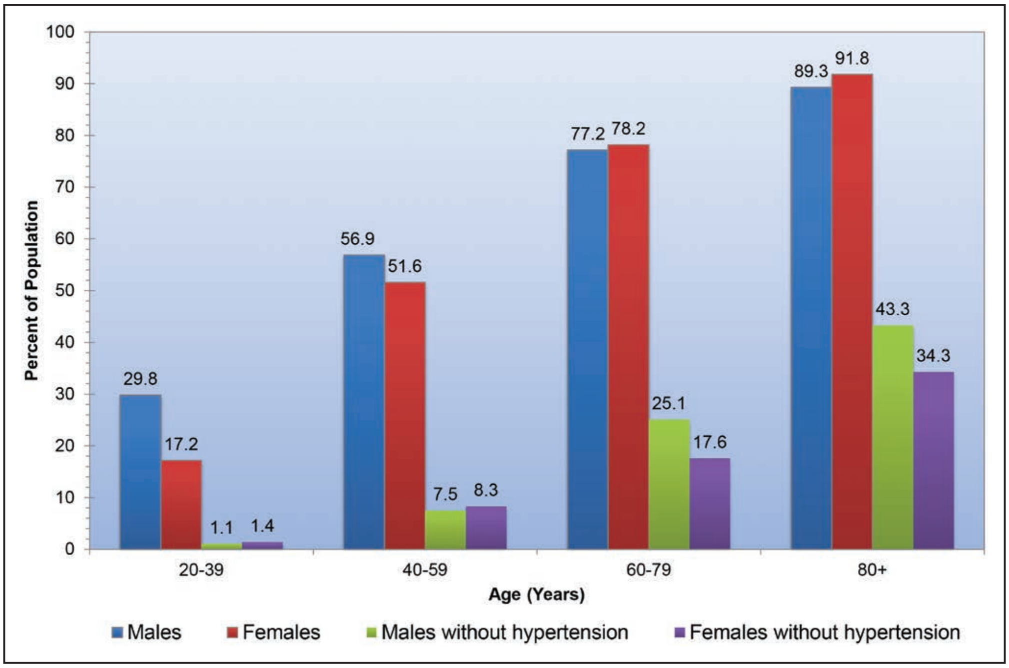


Chart 13-1. Prevalence of cardiovascular disease in adults ≥20 years of age, by age and sex (NHANES, 2013–2016), with and without hypertension.
These data include coronary heart disease, heart failure, stroke, and with and without hypertension.
NHANES indicates National Health and Nutrition Examination Survey.
Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

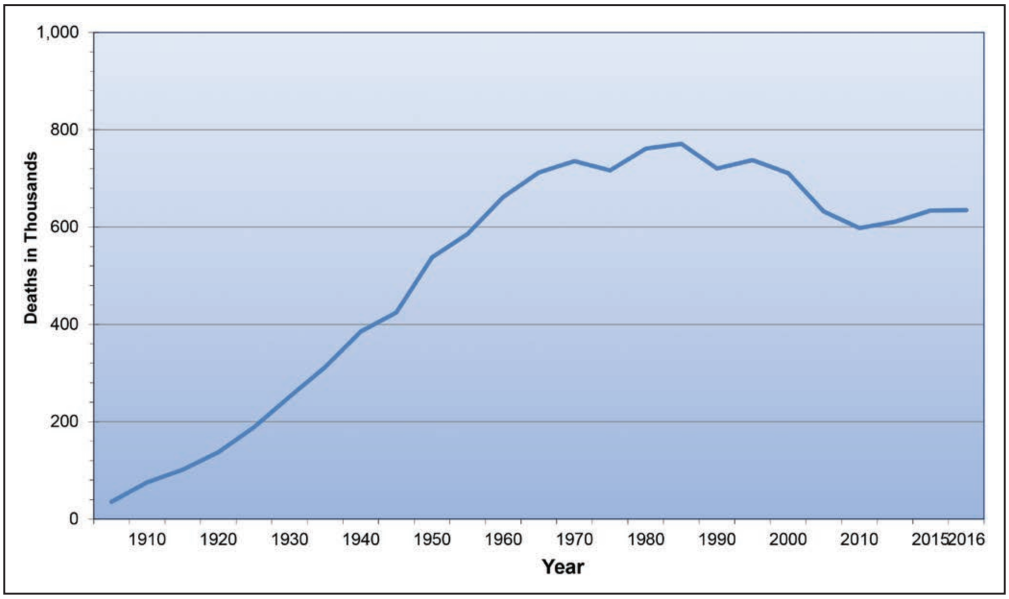


Chart 13-2. Deaths attributable to diseases of the heart (United States, 1900–2016).
See Glossary (Chapter 28) for an explanation of "diseases of the heart." In the years 1900 to 1920, the *International Classification of Diseases* codes were 77 to 80; for 1925, 87 to 90; for 1930 to 1945, 90 to 95; for 1950 to 1960, 402 to 404 and 410 to 443; for 1965, 402 to 404 and 410 to 443; for 1970 to 1975, 390 to 398 and 404 to 429; for 1980 to 1995, 390 to 398, 402, and 404 to 429; and for 2000 to 2014, I00 to I09, I11, I13, and I20 to I51. Before 1933, data are for a death registration area and not the entire United States. In 1900, only 10 states were included in the death registration area, and this increased over the years, so part of the increase in numbers of deaths is attributable to an increase in the number of states.
Source: National Heart, Lung, and Blood Institute.

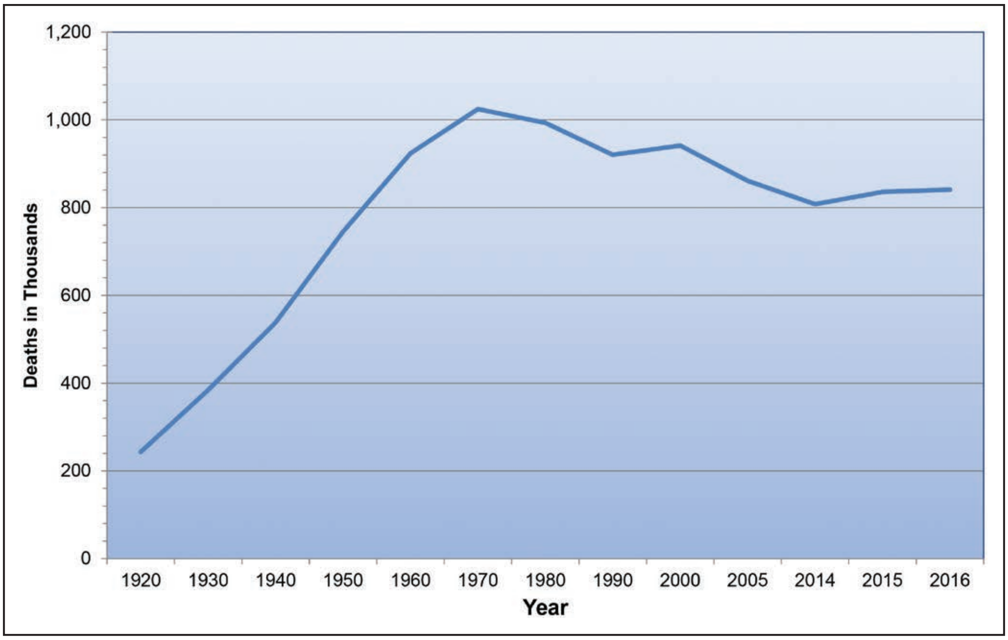


Chart 13-3. Deaths attributable to cardiovascular disease (United States, 1910–2016).
Cardiovascular disease (*International Classification of Diseases, 10th Revision* codes I00–I99) does not include congenital heart disease. Before 1933, data are for a death registration area and not the entire United States.
Source: National Heart, Lung, and Blood Institute.

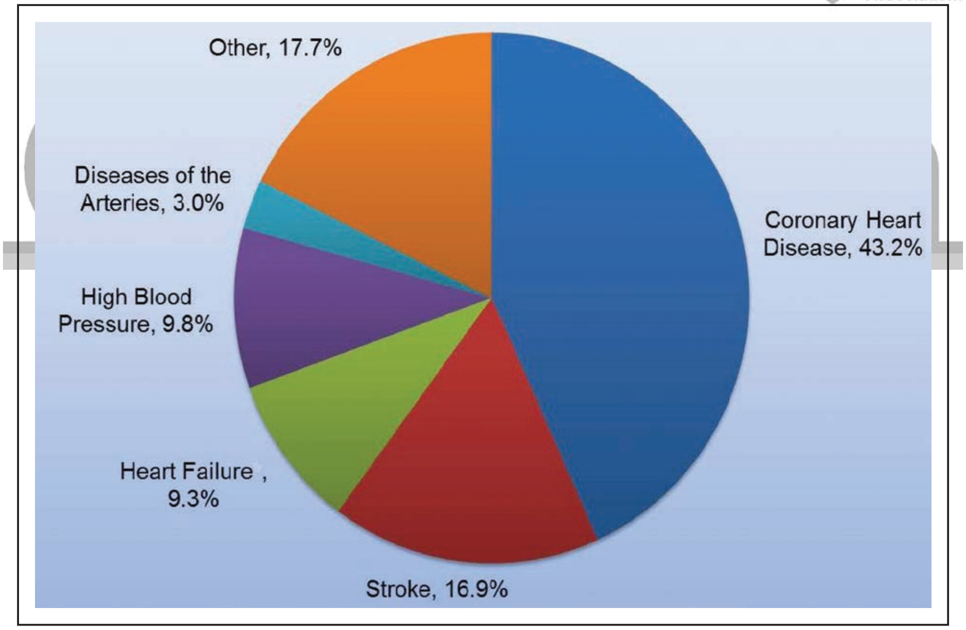
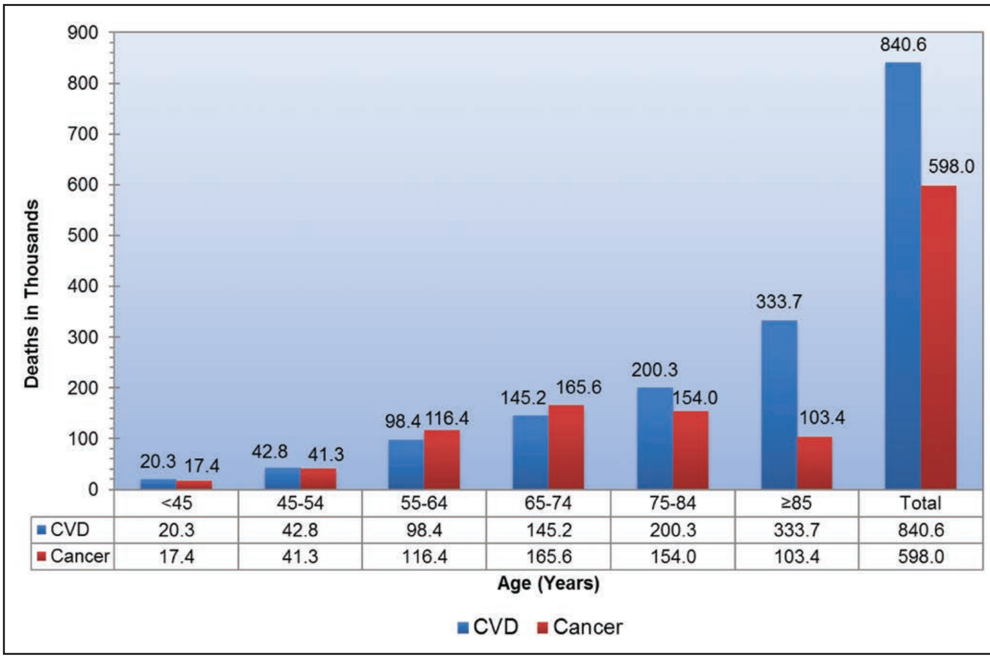


Chart 13-4. Percentage breakdown of deaths attributable to cardiovascular disease (United States, 2016).
Total may not add to 100 because of rounding. Coronary heart disease includes *International Classification of Diseases, 10th Revision* (*ICD-10*) codes I20 to I25; stroke, I60 to I69; heart failure, I50; high blood pressure, I10 to I15; diseases of the arteries, I70 to I78; and other, all remaining *ICD-I0* I categories.
Source: National Heart, Lung, and Blood Institute from National Center for Health Statistics reports and data sets.



	<45	45-54	55-64	65-74	75-84	≥85	Total
CVD	20.3	42.8	98.4	145.2	200.3	333.7	840.6
Cancer	17.4	41.3	116.4	165.6	154.0	103.4	598.0

Chart 13-5. CVD deaths vs cancer deaths by age (United States, 2016).
CVD includes *International Classification of Diseases, 10th Revision* codes I00 to I99; cancer, C00 to C97.
CVD indicates cardiovascular disease.
Source: National Center for Health Statistics.

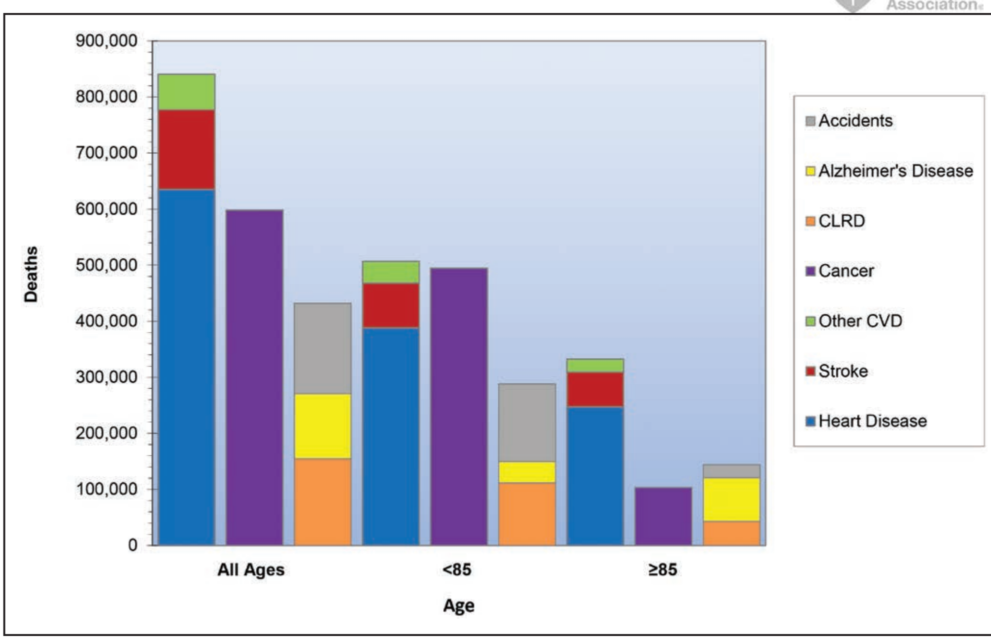


Chart 13-6. CVD and other major causes of death: all ages, <85 years of age, and ≥85 years of age.
Deaths among both sexes, United States, 2016. Heart disease includes *International Classification of Diseases, 10th Revision* codes I00 to I09, I11, I13, and I20 to I51; stroke, I60 to I69; all other CVD, I10, I12, I15, and I70 to I99; cancer, C00 to C97; CLRD, J40 to J47; Alzheimer disease, G30; and accidents, V01 to X59 and Y85 and Y86.
CLRD indicates chronic lower respiratory disease; and CVD, cardiovascular disease.
Source: National Heart, Lung, and Blood Institute.

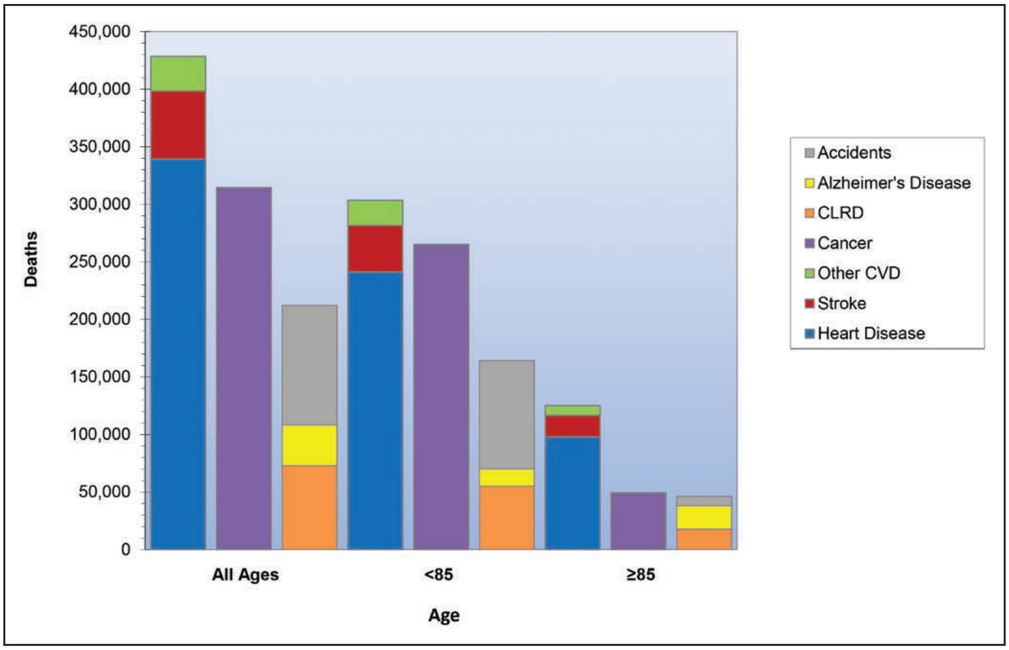


Chart 13-7. CVD and other major causes of death in males: all ages, <85 years of age, and ≥85 years of age.
Deaths among males, United States, 2016. Heart disease includes *International Classification of Diseases, 10th Revision* codes I00 to I09, I11, I13, and I20 to I51; stroke, I60 to I69; all other CVD, I10, I12, I15, and I70 to I99; cancer, C00 to C97; CLRD, J40 to J47; and accidents, V01 to X59 and Y85 and Y86.
CLRD indicates chronic lower respiratory disease; and CVD, cardiovascular disease.
Source: National Heart, Lung, and Blood Institute.

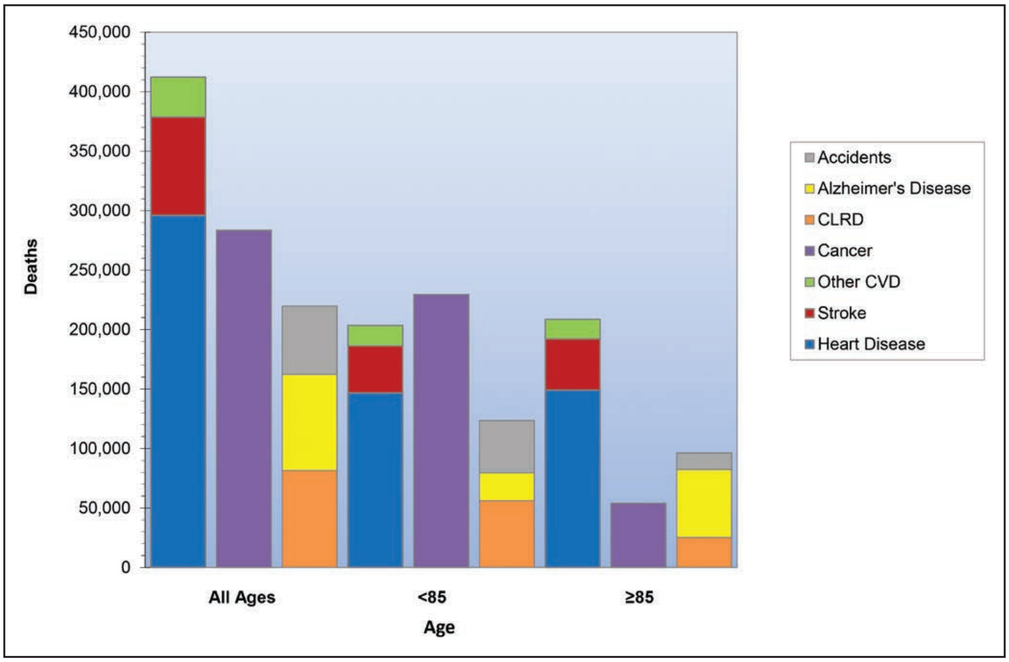


Chart 13-8. CVD and other major causes of death in females: all ages, <85 years of age, and ≥85 years of age.
Deaths among females, United States, 2016. Heart disease includes *International Classification of Diseases, 10th Revision* codes I00 to I09, I11, I13, and I20 to I51; stroke, I60 to I69; all other CVD, I10, I12, I15, and I70 to I99; cancer, C00 to C97; CLRD, J40 to J47; and Alzheimer disease, G30.
CLRD indicates chronic lower respiratory disease; and CVD, cardiovascular disease.
Source: National Heart, Lung, and Blood Institute.

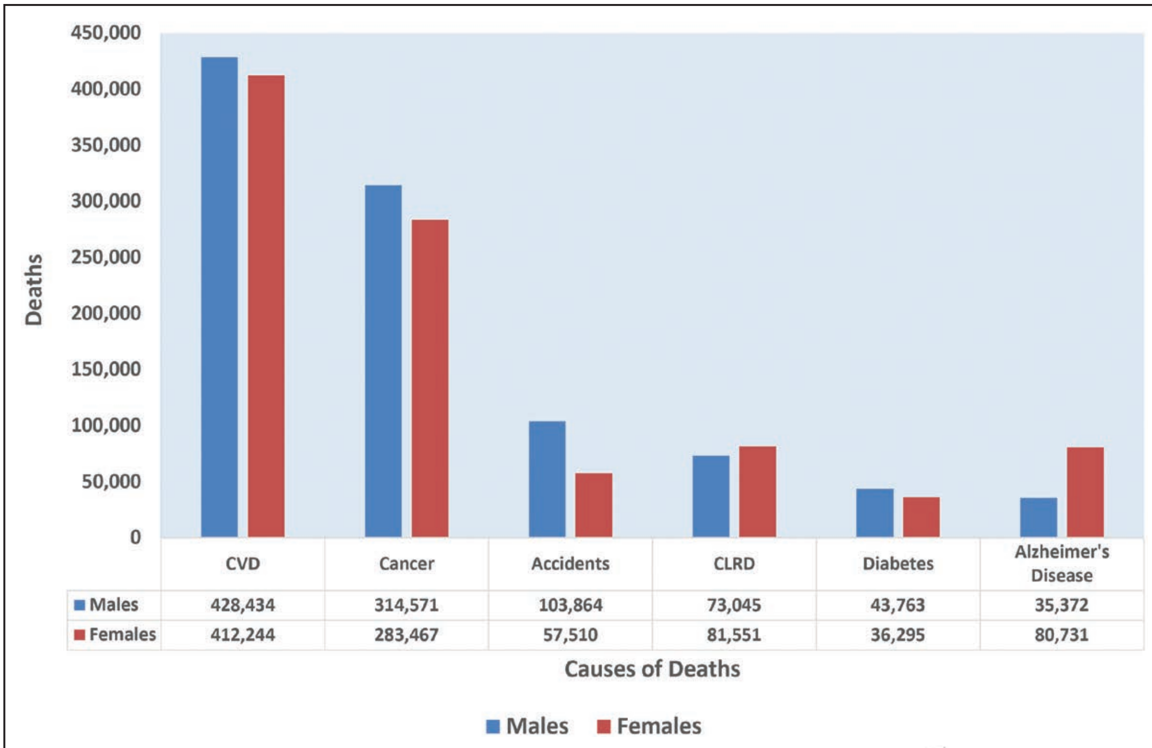


Chart 13-9. **CVD and other major causes of death for all males and females (United States, 2016).**
Diseases included: CVD (*International Classification of Diseases, 10th Revision* codes I00–I99); cancer (C00–C97); accidents (V01–X59 andY85–Y86); CLRD (J40–J47); diabetes mellitus (E10–E14); and Alzheimer disease (G30).
CLRD indicates chronic lower respiratory disease; and CVD, cardiovascular disease.
Source: National Heart, Lung, and Blood Institute.

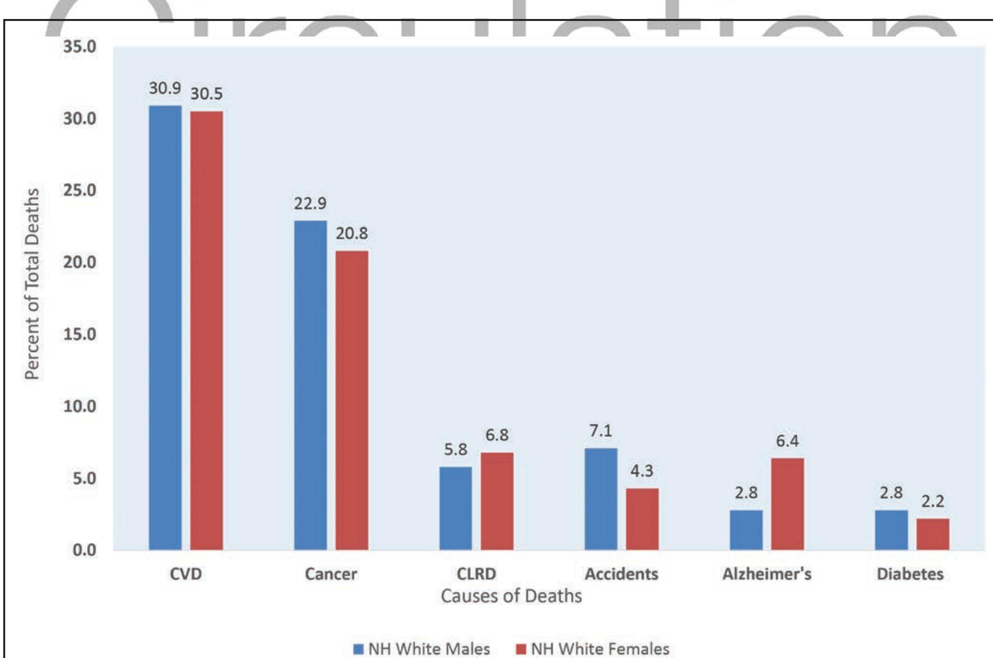


Chart 13-10. **CVD and other major causes of death for NH white males and females (United States, 2016).**
Diseases included: CVD (*International Classification of Diseases, 10th Revision* codes I00–I99); cancer (C00–C97); CLRD (J40–J47); accidents (V01–X59 andY85–Y86); Alzheimer disease (G30); and diabetes mellitus (E10–E14).
CLRD indicates chronic lower respiratory disease; CVD, cardiovascular disease; and NH, non-Hispanic.
Source: National Heart, Lung, and Blood Institute.

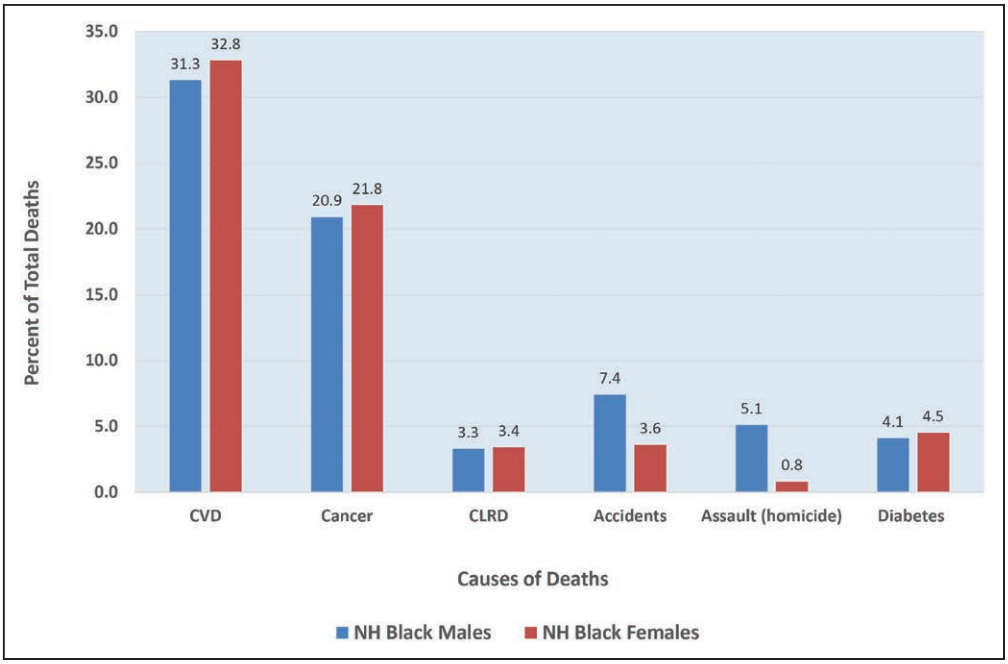


Chart 13-11. CVD and other major causes of death for NH black males and females (United States, 2016).
Diseases included: CVD (*International Classification of Diseases, 10th Revision* codes I00–I99); cancer (C00–C97); CLRD (J40–J47); accidents (V01–X59 and Y85–Y86); assault (X92-Y09); and diabetes mellitus (E10–E14).
CLRD indicates chronic lower respiratory disease; CVD, cardiovascular disease; and NH, non-Hispanic.
Source: National Heart, Lung, and Blood Institute.

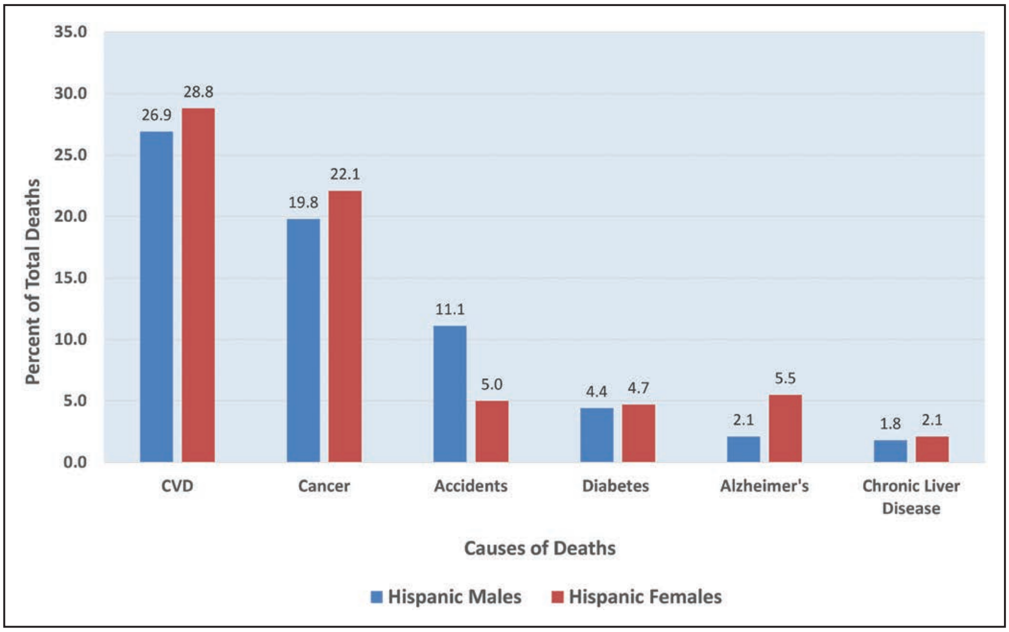


Chart 13-12. CVD and other major causes of death for Hispanic or Latino males and females (United States, 2016).
Number of deaths shown may be lower than actual because of underreporting in this population. Diseases included: CVD (*International Classification of Diseases, 10th Revision* codes I00–I99); cancer (C00–C97); accidents (V01–X59 andY85–Y86); diabetes mellitus (E10–E14); Alzheimer disease (G30); and chronic liver disease (K70, K73, and K74).
CVD indicates cardiovascular disease.
Source: National Heart, Lung, and Blood Institute.

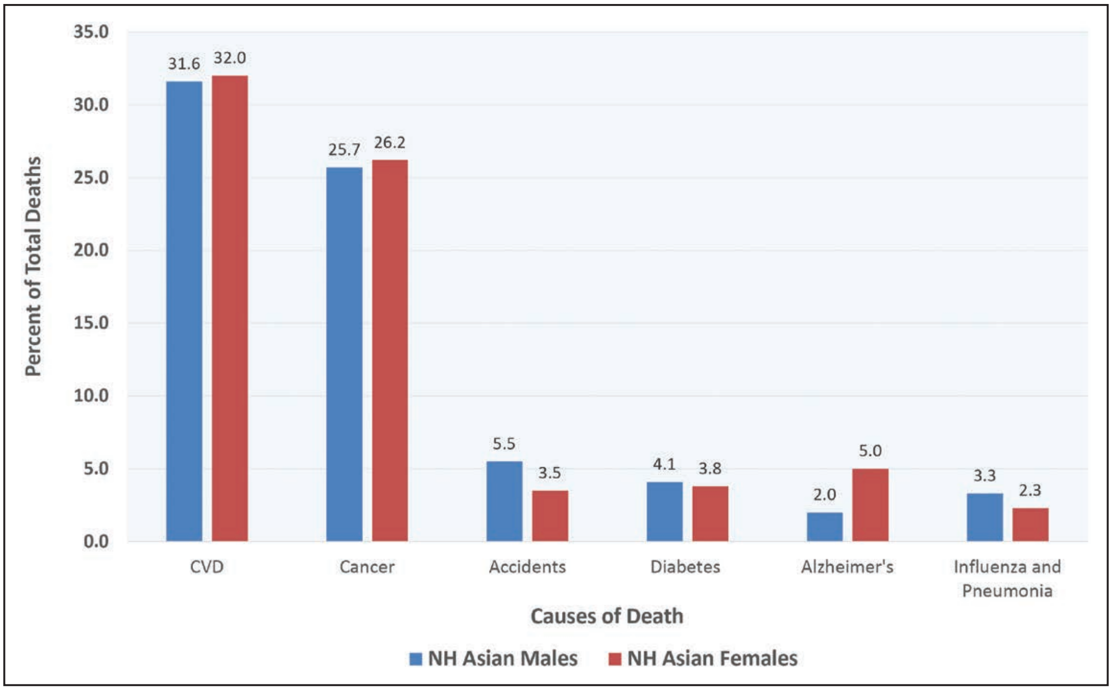


Chart 13-13. CVD and other major causes of death for NH Asian or Pacific Islander males and females (United States, 2016).
"Asian or Pacific Islander" is a heterogeneous category that includes people at high CVD risk (eg, South Asian) and people at low CVD risk (eg, Japanese). More specific data on these groups are not available. Number of deaths shown may be lower than actual because of underreporting in this population. Diseases included: CVD (*International Classification of Diseases, 10th Revision* codes I00–I99); cancer (C00–C97); accidents (V01–X59 andY85–Y86); diabetes mellitus (E10–E14); Alzheimer disease (G30); and influenza and pneumonia (J09-J18).
CVD indicates cardiovascular disease; and NH, non-Hispanic.
Source: National Heart, Lung, and Blood Institute.

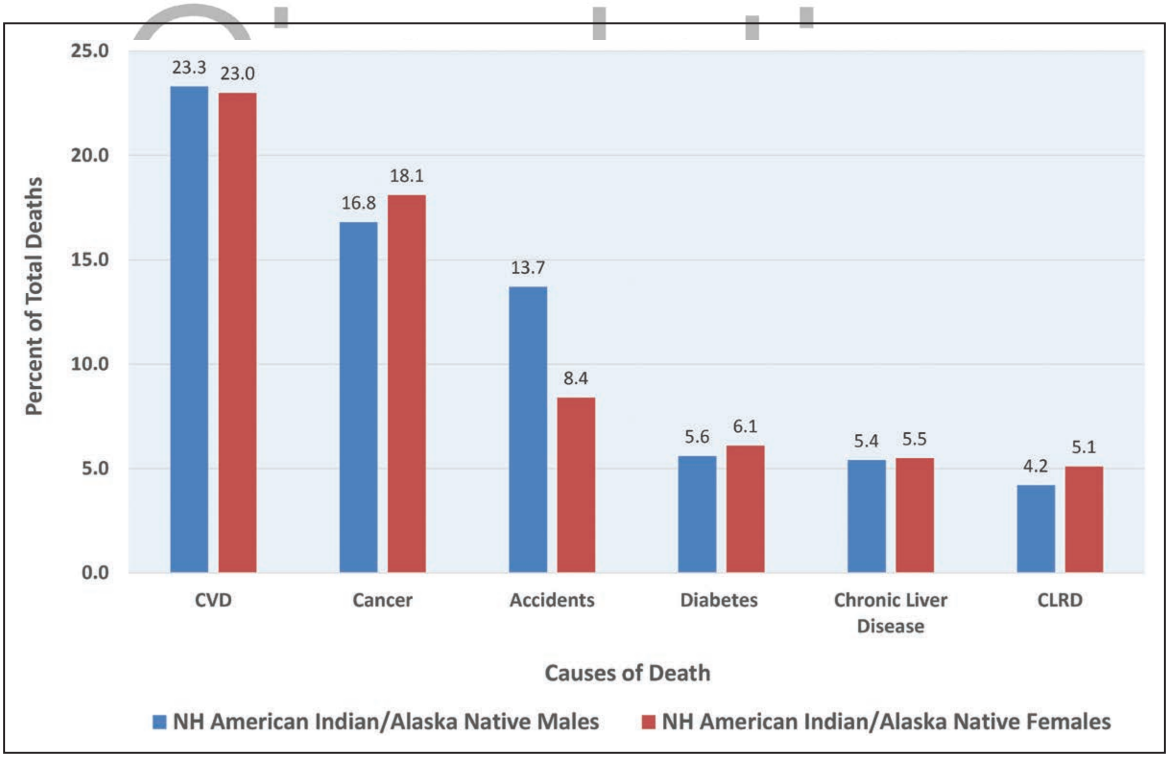


Chart 13-14. CVD and other major causes of death for NH American Indian or Alaska Native males and females (United States, 2016).
Number of deaths shown may be lower than actual because of underreporting in this population. Diseases included: CVD (*International Classification of Diseases, 10th Revision* codes I00–I99); cancer (C00–C97); accidents (V01–X59 andY85–Y86); diabetes mellitus (E10–E14); chronic liver disease (K70, K73, and K74); and CLRD (J40–J47).
CLRD indicates chronic lower respiratory disease; CVD, cardiovascular disease; and NH, non-Hispanic.
Source: National Heart, Lung, and Blood Institute.

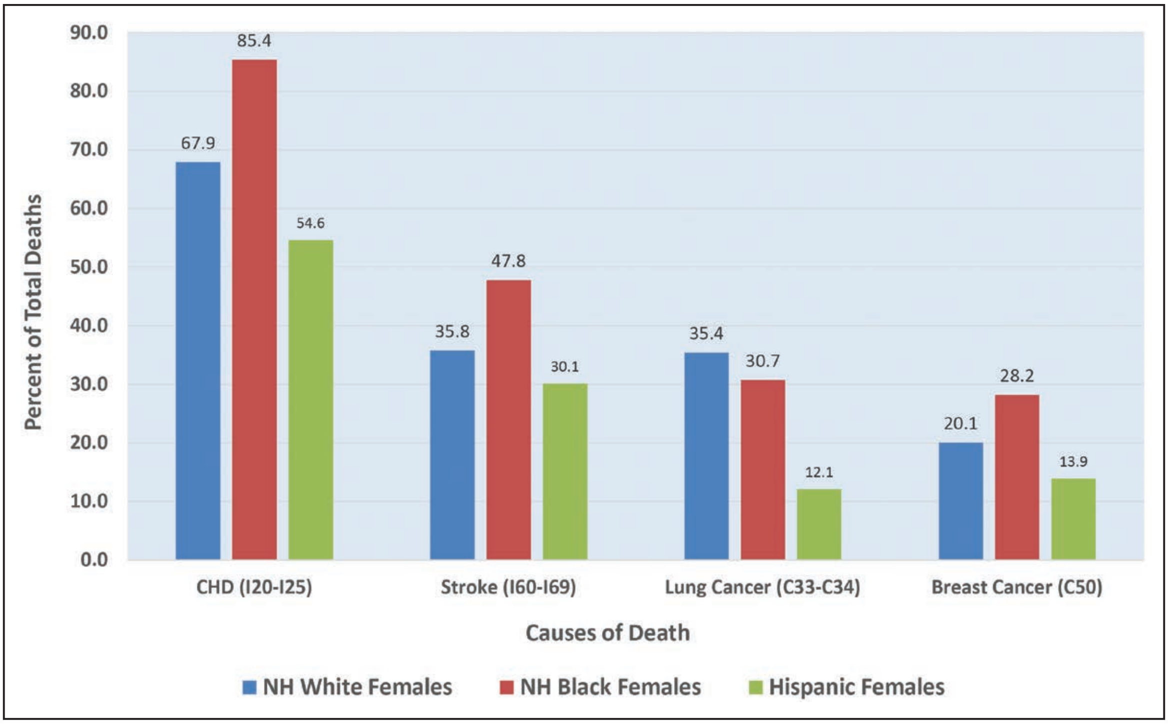


Chart 13-15. Age-adjusted death rates for CHD, stroke, and lung and breast cancer for NH white and black females (United States, 2016).
CHD includes *International Classification of Diseases, 10th Revision* codes I20 to I25; stroke, I60 to I69; lung cancer, C33 to C34; and breast cancer, C50.
CHD indicates coronary heart disease; and NH, non-Hispanic.
Source: National Heart, Lung, and Blood Institute.

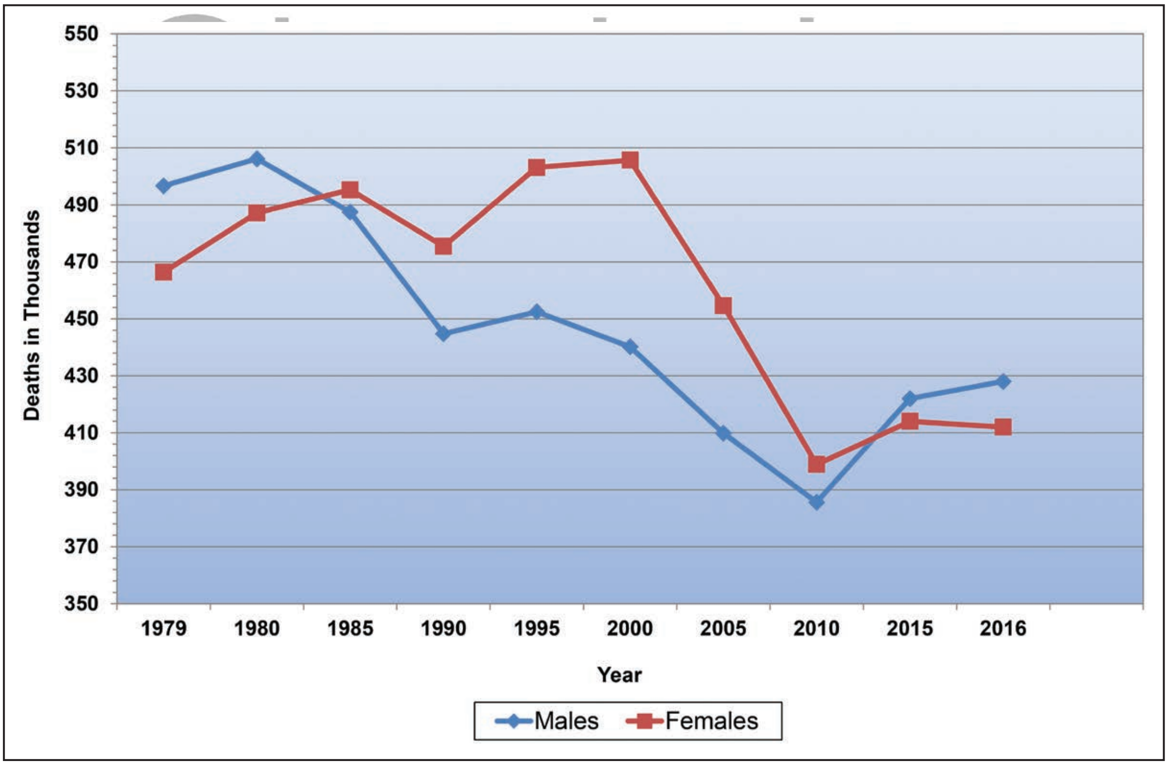


Chart 13-16. Cardiovascular disease (CVD) mortality trends for males and females (United States, 1979–2016).
CVD excludes congenital cardiovascular defects (*International Classification of Diseases, 10th Revision* [*ICD-10*] codes I00–I99). The overall comparability for cardiovascular disease between the *International Classification of Diseases, 9th Revision* (1979–1998) and *ICD-10* (1999–2015) is 0.9962. No comparability ratios were applied.
Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

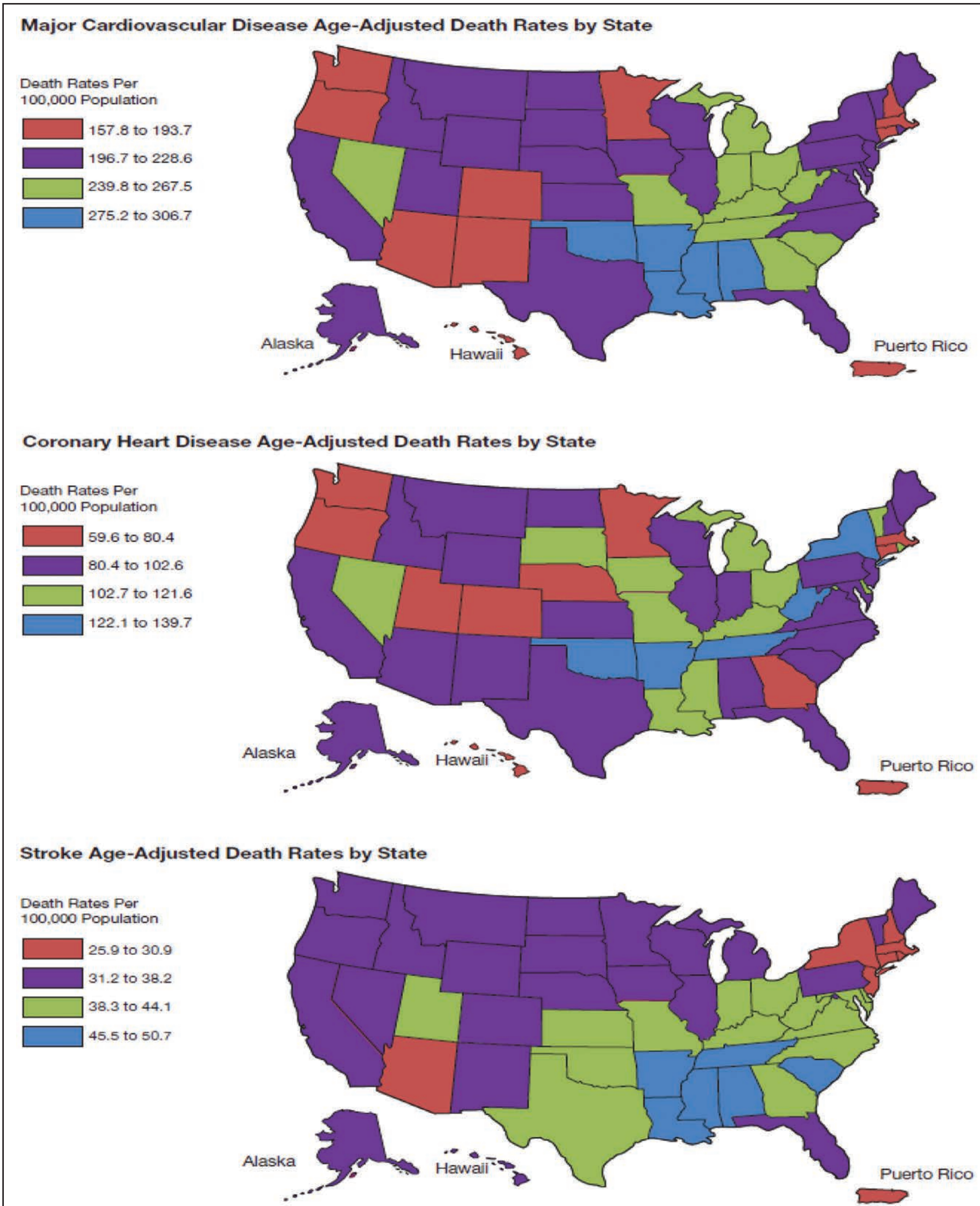


Chart 13-17. US maps corresponding to the state age-adjusted death rates per 100 000 population for cardiovascular disease, coronary heart disease, and stroke (including the District of Columbia), 2016.

Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.[2]

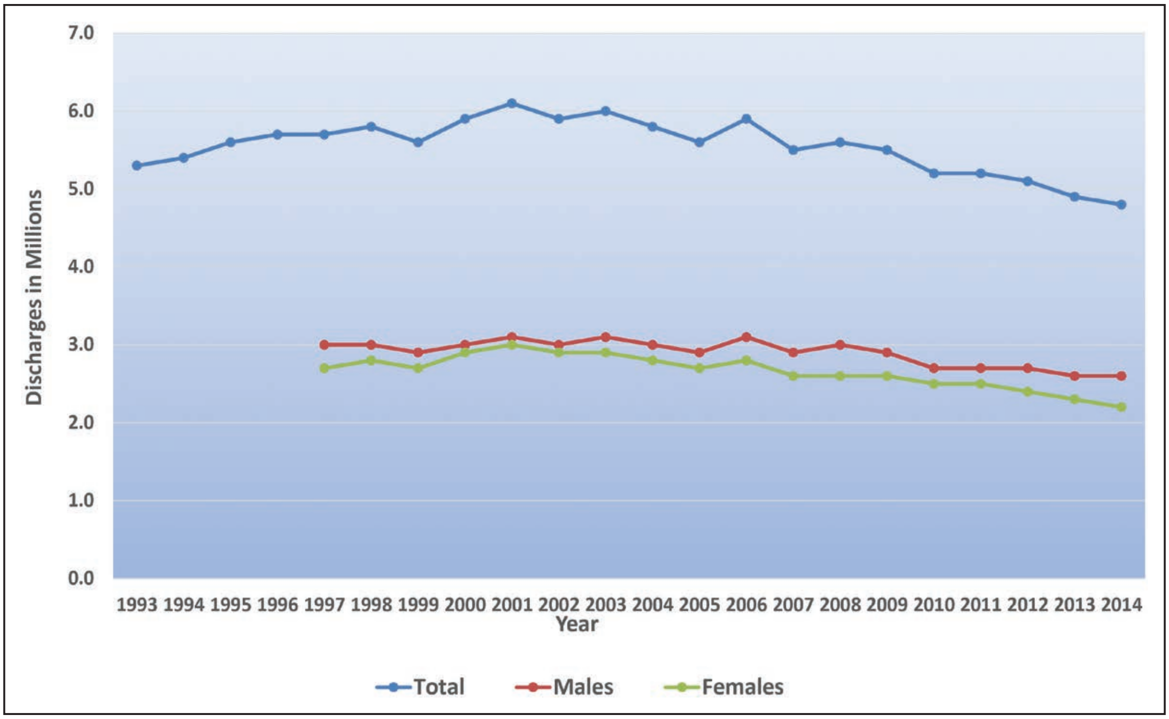


Chart 13-18. Hospital discharges for cardiovascular disease (United States, 1993–2014).
Hospital discharges include people discharged alive, dead, and "status unknown."
Source: Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality, and National Heart, Lung, and Blood Institute.

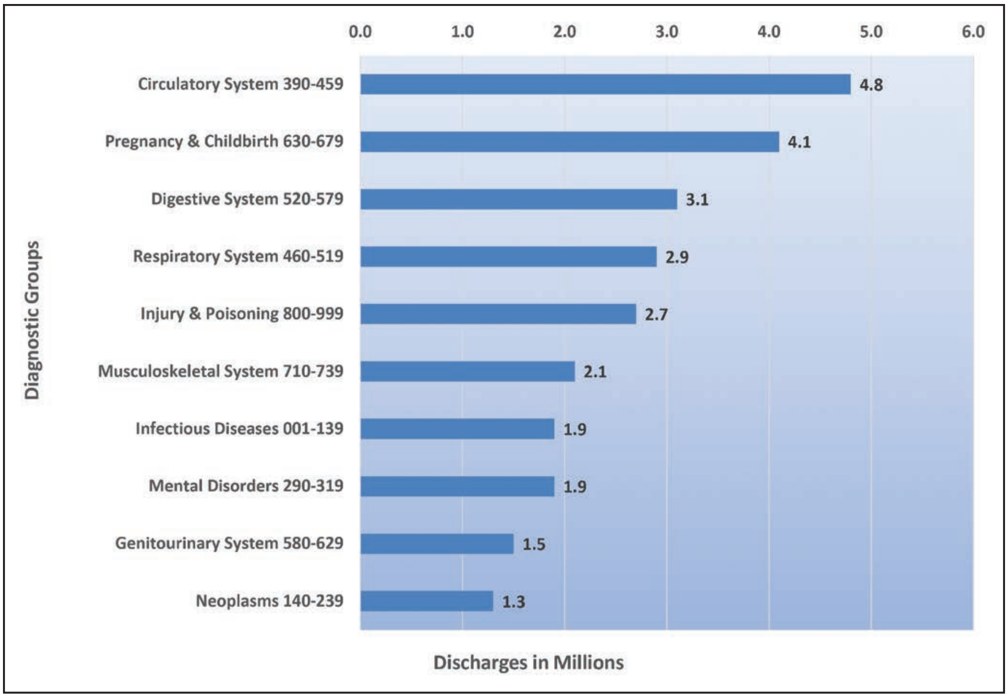
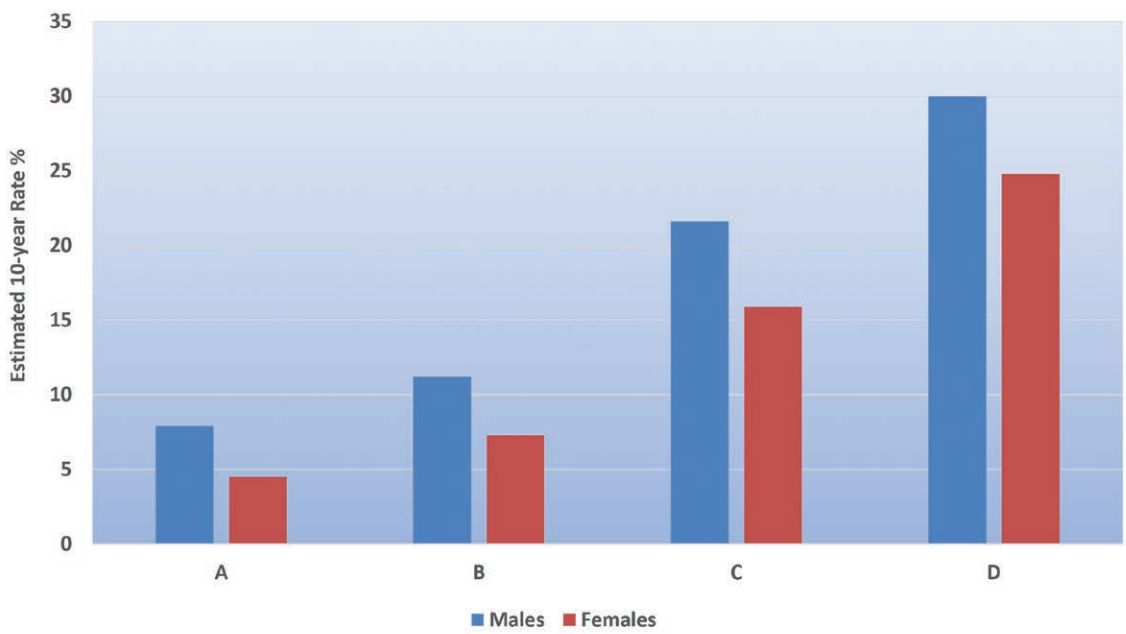


Chart 13-19. Hospital discharges (*International Classification of Diseases, 9th Revision*) for the 10 leading diagnostic groups (United States, 2014).
Source: Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality, and National Heart, Lung, and Blood Institute.



	A	B	C	D
Age	50-54	50-54	50-54	50-54
HDL Cholesterol, mg/dL	45-49	45-49	35-44	35-44
Total Cholesterol, mg/dL	160-199	200-239	200-239	200-239
Systolic BP mm/Hg, no treatment	120-129	130-139	130-139	130-139
Smoker	No	No	No	Yes
Diabetes	No	No	Yes	Yes

Chart 13-20. Estimated average 10-year cardiovascular disease risk in adults 50 to 54 years of age according to levels of various risk factors (FHS).
BP indicates blood pressure; FHS, Framingham Heart Study; and HDL, high-density lipoprotein.
Data derived from D'Agostino et al.[53]

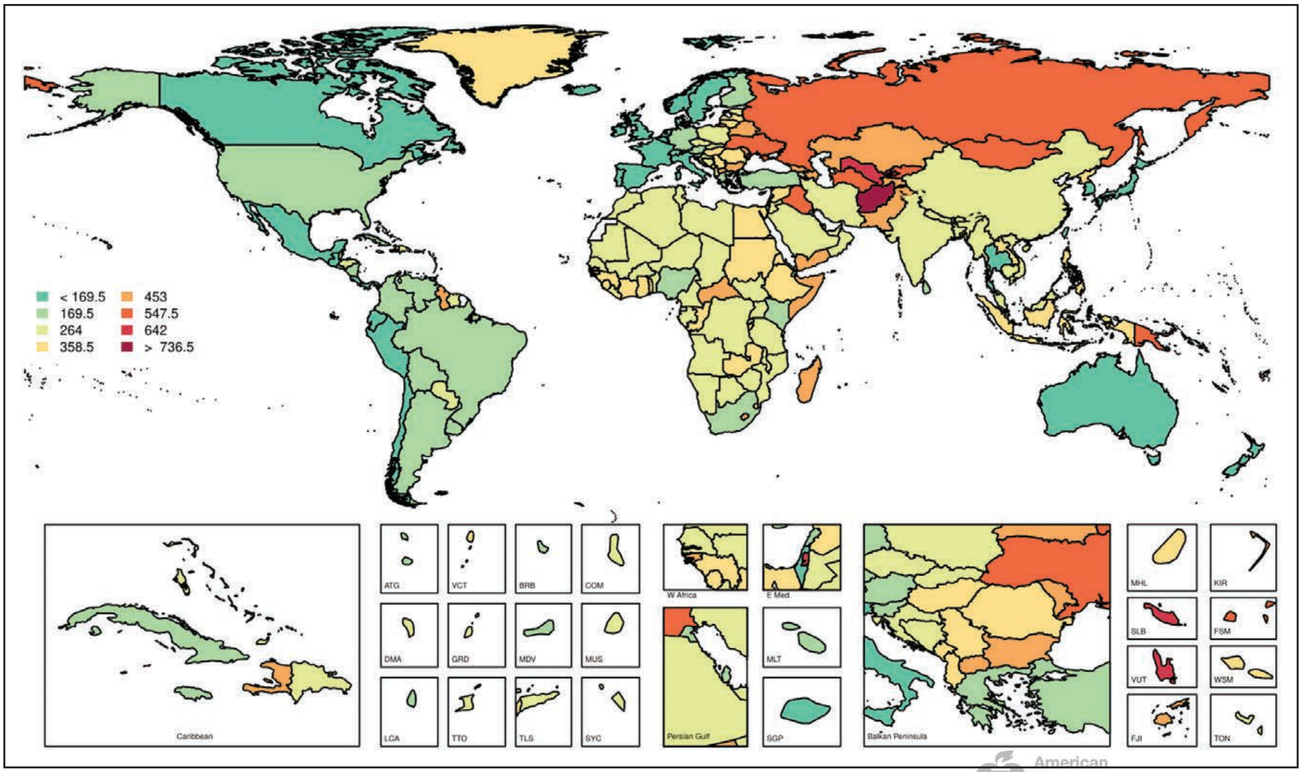


Chart 13-21. Age-standardized global mortality rates of cardiovascular diseases per 100 000, both sexes, 2016.

Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.

Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[46] Printed with permission. Copyright © 2017, University of Washington.

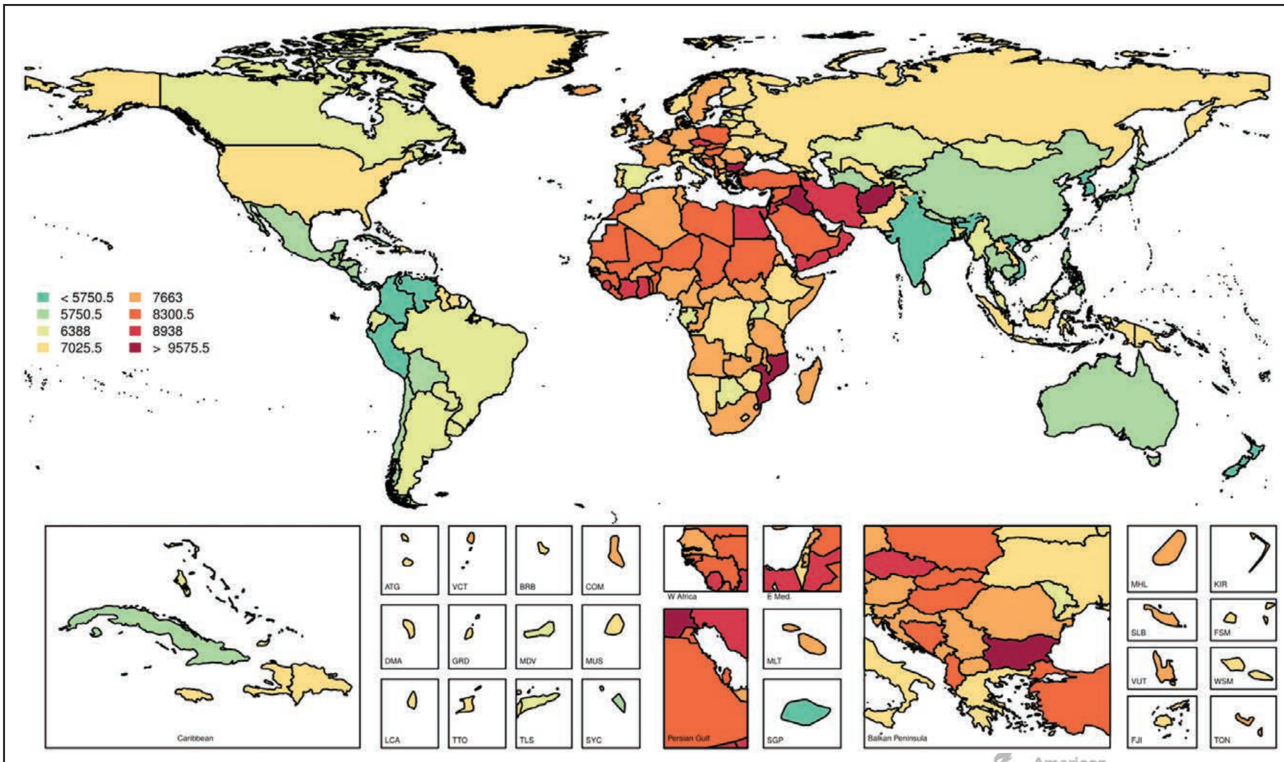


Chart 13-22. Age-standardized global prevalence rates of cardiovascular diseases per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[46] Printed with permission. Copyright © 2017, University of Washington.

REFERENCES

1. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee.. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
2. National Center for Health Statistics. Centers for Disease Control and Prevention website. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2016. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed May 21, 2018.
3. Kochanek KD, Murphy SL, Xu JQ, Arias E. Mortality in the United States, 2016. NCHS Data Brief No. 293. Hyattsville, MD: National Center for Health Statistics; December 2017. https://www.cdc.gov/nchs/data/databriefs/db293.pdf. Accessed June 18, 2018.
4. Roth GA, Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, Morozoff C, Naghavi M, Mokdad AH, Murray CJL. Trends and Patterns of Geographic Variation in Cardiovascular Mortality Among US Counties, 1980-2014. *JAMA*. 2017;317:1976–1992. doi: 10.1001/jama.2017.4150
5. Centers for Disease Control and Prevention website. National Ambulatory Medical Care Survey: 2015 State and National Summary Tables. https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2015_namcs_web_tables.pdf. Accessed June 14, 2018.
6. Centers for Disease Control and Prevention website. National Hospital Ambulatory Medical Care Survey: 2015 Emergency Department Summary Tables. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2015_ed_web_tables.pdf. Accessed June 14, 2018.
7. Centers for Disease Control and Prevention website. Disability and Health: Data & Statistics: Healthcare Cost Data. https://www.cdc.gov/ncbddd/disabilityandhealth/data-highlights.html. Accessed May 23, 2017.
8. Centers for Disease Control and Prevention (CDC). Prevalence and most common causes of disability among adults: United States, 2005. *MMWR Morb Mortal Wkly Rep*. 2009;58:421–426.
9. Courtney-Long EA, Carroll DD, Zhang QC, Stevens AC, Griffin-Blake S, Armour BS, Campbell VA. Prevalence of disability and disability type among adults: United States, 2013. *MMWR Morb Mortal Wkly Rep*. 2015;64:777–783.
10. RTI International. Projections of Cardiovascular Disease Prevalence and Costs: 2015–2035: Technical Report [report prepared for the American Heart Association]. Research Triangle Park, NC: RTI International; November 2016. RTI project number 021480.003.001.001. https://healthmetrics.heart.org/wp-content/uploads/2017/10/Projections-of-Cardiovascular-Disease.pdf. Accessed November 10, 2018.
11. Roth GA, Johnson CO, Abate KH, et al. The burden of cardiovascular diseases among US states, 1990–2016. *JAMA Cardiol*. 2018;3:375–389. doi: 10.1001/jamacardio.2018.0385
12. Fryar CD, Chen TC, Li X. Prevalence of uncontrolled risk factors for cardiovascular disease: United States, 1999–2010. *NCHS Data Brief*. 2012;(103):1–8.
13. Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, Murray CJ, Ezzati M. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors [published correction appears in PLoS Med. 2011;8:10.1371/annotation/0ef47acd-9dcc-4296-a897-872d182cde57]. *PLoS Med*. 2009;6:e1000058. doi: 10.1371/journal.pmed.1000058
14. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ*. 2017;357:j2099. doi: 10.1136/bmj.j2099
15. Lisabeth LD, Beiser AS, Brown DL, Murabito JM, Kelly-Hayes M, Wolf PA. Age at natural menopause and risk of ischemic stroke:

the Framingham Heart Study. *Stroke*. 2009;40:1044–1049. doi: 10.1161/STROKEAHA.108.542993
16. Losina E, Hyle EP, Borre ED, Linas BP, Sax PE, Weinstein MC, Rusu C, Ciaranello AL, Walensky RP, Freedberg KA. Projecting 10-year, 20-year, and lifetime risks of cardiovascular disease in persons living with human immunodeficiency virus in the United States. *Clin Infect Dis*. 2017;65:1266–1271. doi: 10.1093/cid/cix547
17. Miller RG, Mahajan HD, Costacou T, Sekikawa A, Anderson SJ, Orchard TJ. A contemporary estimate of total mortality and cardiovascular disease risk in young adults with type 1 diabetes: the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care*. 2016;39:2296–2303. doi: 10.2337/dc16-1162
18. Ramsay SE, Morris RW, Whincup PH, Subramanian SV, Papacosta AO, Lennon LT, Wannamethee SG. The influence of neighbourhood-level socioeconomic deprivation on cardiovascular disease mortality in older age: longitudinal multilevel analyses from a cohort of older British men. *J Epidemiol Community Health*. 2015;69:1224–1231. doi: 10.1136/jech-2015-205542
19. Gebreab SY, Davis SK, Symanzik J, Mensah GA, Gibbons GH, Diez-Roux AV. Geographic variations in cardiovascular health in the United States: contributions of state- and individual-level factors. *J Am Heart Assoc*. 2015;4:e001673. doi: 10.1161/JAHA.114.001673
20. Yang Q, Cogswell ME, Flanders WD, Hong Y, Zhang Z, Loustalot F, Gillespie C, Merritt R, Hu FB. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. *JAMA*. 2012;307:1273–1283. doi: 10.1001/jama.2012.339
21. Guasch-Ferré M, Liu X, Malik VS, Sun Q, Willett WC, Manson JE, Rexrode KM, Li Y, Hu FB, Bhupathiraju SN. Nut consumption and risk of cardiovascular disease. *J Am Coll Cardiol*. 2017;70:2519–2532. doi: 10.1016/j.jacc.2017.09.035
22. Mensah GA, Brown DW, Croft JB, Greenlund KJ. Major coronary risk factors and death from coronary heart disease: baseline and follow-up mortality data from the Second National Health and Nutrition Examination Survey (NHANES II). *Am J Prev Med*. 2005;29(5 Suppl 1):68–74. doi: 10.1016/j.amepre.2005.07.030
23. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, Greenland P, Van Horn L, Tracy RP, Lloyd-Jones DM. Lifetime risks of cardiovascular disease. *N Engl J Med*. 2012;366:321–329. doi: 10.1056/NEJMoa1012848
24. Terry DF, Pencina MJ, Vasan RS, Murabito JM, Wolf PA, Hayes MK, Levy D, D'Agostino RB, Benjamin EJ. Cardiovascular risk factors predictive for survival and morbidity-free survival in the oldest-old Framingham Heart Study participants. *J Am Geriatr Soc*. 2005;53:1944–1950. doi: 10.1111/j.1532-5415.2005.00465.x
25. Gooding HC, Ning H, Gillman MW, Shay C, Allen N, Goff DC Jr, Lloyd-Jones D, Chiuve S. Application of a Lifestyle-Based Tool to Estimate Premature Cardiovascular Disease Events in Young Adults: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *JAMA Intern Med*. 2017;177:1354–1360. doi: 10.1001/jamainternmed.2017.2922
26. Wu H, Flint AJ, Qi Q, van Dam RM, Sampson LA, Rimm EB, Holmes MD, Willett WC, Hu FB, Sun Q. Association between dietary whole grain intake and risk of mortality: two large prospective studies in US men and women. *JAMA Intern Med*. 2015;175:373–384. doi: 10.1001/jamainternmed.2014.6283
27. Appelman Y, van Rijn BB, Ten Haaf ME, Boersma E, Peters SA. Sex differences in cardiovascular risk factors and disease prevention. *Atherosclerosis*. 2015;241:211–218. doi: 10.1016/j.atherosclerosis.2015.01.027
28. Olives C, Myerson R, Mokdad AH, Murray CJ, Lim SS. Prevalence, awareness, treatment, and control of hypertension in United States counties, 2001-2009. *PLoS One*. 2013;8:e60308. doi: 10.1371/journal.pone.0060308
29. Hozawa A, Folsom AR, Sharrett AR, Chambless LE. Absolute and attributable risks of cardiovascular disease incidence in relation to optimal and borderline risk factors: comparison of African American with white subjects—Atherosclerosis Risk in Communities Study. *Arch Intern Med*. 2007;167:573–579. doi: 10.1001/archinte.167.6.573
30. Centers for Disease Control and Prevention (CDC). Vital signs: avoidable deaths from heart disease, stroke, and hypertensive disease—United States, 2001–2010. *MMWR Morb Mortal Wkly Rep*. 2013;62:721–727.
31. Schoenborn CA, Adams PF, Peregoy JA. Health behaviors of adults: United States, 2008–2010. *Vital Health Stat 10*. 2013;(257):1–184.
32. Pearson-Stuttard J, Bandosz P, Rehm CD, Penalvo J, Whitsel L, Gaziano T, Conrad Z, Wilde P, Micha R, Lloyd-Williams F, Capewell S, Mozaffarian D, O'Flaherty M. Reducing US cardiovascular disease burden and disparities through national and targeted dietary policies: a modelling study. *PLoS Med*. 2017;14:e1002311. doi: 10.1371/journal.pmed.1002311
33. Eamranond PP, Legedza AT, Diez-Roux AV, Kandula NR, Palmas W, Siscovick DS, Mukamal KJ. Association between language and risk factor levels among Hispanic adults with hypertension, hypercholesterolemia, or diabetes. *Am Heart J*. 2009;157:53–59. doi: 10.1016/j.ahj.2008.08.015
34. Daviglus ML, Talavera GA, Avilés-Santa ML, Allison M, Cai J, Criqui MH, Gellman M, Giachello AL, Gouskova N, Kaplan RC, LaVange L, Penedo F, Perreira K, Pirzada A, Schneiderman N, Wassertheil-Smoller S, Sorlie PD, Stamler J. Prevalence of major cardiovascular risk factors and cardiovascular diseases among Hispanic/Latino individuals of diverse backgrounds in the United States. *JAMA*. 2012;308:1775–1784. doi: 10.1001/jama.2012.14517
35. Chow CK, Islam S, Bautista L, Rumboldt Z, Yusufali A, Xie C, Anand SS, Engert JC, Rangarajan S, Yusuf S. Parental history and myocardial infarction risk across the world: the INTERHEART Study. *J Am Coll Cardiol*. 2011;57:619–627. doi: 10.1016/j.jacc.2010.07.054
36. Lloyd-Jones DM, Nam BH, D'Agostino RB Sr, Levy D, Murabito JM, Wang TJ, Wilson PW, O'Donnell CJ. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *JAMA*. 2004;291:2204–2211. doi: 10.1001/jama.291.18.2204
37. Murabito JM, Pencina MJ, Nam BH, D'Agostino RB Sr, Wang TJ, Lloyd-Jones D, Wilson PW, O'Donnell CJ. Sibling cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults. *JAMA*. 2005;294:3117–3123. doi: 10.1001/jama.294.24.3117
38. Yeboah J, Young R, McClelland RL, Delaney JC, Polonsky TS, Dawood FZ, Blaha MJ, Miedema MD, Sibley CT, Carr JJ, Burke GL, Goff DC Jr, Psaty BM, Greenland P, Herrington DM. Utility of nontraditional risk markers in atherosclerotic cardiovascular disease risk assessment. *J Am Coll Cardiol*. 2016;67:139–147. doi: 10.1016/j.jacc.2015.10.058
39. Valerio L, Peters RJ, Zwinderman AH, Pinto-Sietsma SJ. Association of family history with cardiovascular disease in hypertensive individuals in a multiethnic population. *J Am Heart Assoc*. 2016;5:e004260. doi: 10.1161/JAHA.116.004260
40. Lee DS, Pencina MJ, Benjamin EJ, Wang TJ, Levy D, O'Donnell CJ, Nam BH, Larson MG, D'Agostino RB, Vasan RS. Association of parental heart failure with risk of heart failure in offspring. *N Engl J Med*. 2006;355:138–147. doi: 10.1056/NEJMoa052948
41. Fox CS, Parise H, D'Agostino RB Sr, Lloyd-Jones DM, Vasan RS, Wang TJ, Levy D, Wolf PA, Benjamin EJ. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. *JAMA*. 2004;291:2851–2855. doi: 10.1001/jama.291.23.2851
42. Olsson C, Granath F, Ståhle E. Family history, comorbidity and risk of thoracic aortic disease: a population-based case-control study. *Heart*. 2013;99:1030–1033. doi: 10.1136/heartjnl-2013-303654
43. Murabito JM, Nam BH, D'Agostino RB Sr, Lloyd-Jones DM, O'Donnell CJ, Wilson PW. Accuracy of offspring reports of parental cardiovascular disease history: the Framingham Offspring Study. *Ann Intern Med*. 2004;140:434–440.
44. Ganesh SK, Arnett DK, Assimes TL, Assimes TL, Basson CT, Chakravarti A, Ellinor PT, Engler MB, Goldmuntz E, Herrington DM, Hershberger RE, Hong Y, Johnson JA, Kittner SJ, McDermott DA, Meschia JF, Mestroni L, O'Donnell CJ, Psaty BM, Vasan RS, Ruel M, Shen WK, Terzic A, Waldman SA; on behalf of the American Heart Association Council on Functional Genomics and Translational Biology; American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Basic Cardiovascular Sciences; American Heart Association Council on Cardiovascular Disease in the Young; American Heart Association Council on Cardiovascular and Stroke Nursing; American Heart Association Stroke Council. Genetics and genomics for the prevention and treatment of cardiovascular disease: update: a scientific statement from the American Heart Association [published correction appears in *Circulation*. 2014;129:e398]. *Circulation*. 2013;128:2813–2851. doi: 10.1161/01.cir.0000437913.98912.1d
45. Mosca L, Hammond G, Mochari-Greenberger H, Towfighi A, Albert MA; on behalf of the American Heart Association Cardiovascular Disease and Stroke in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Cardiovascular Nursing, Council on High Blood Pressure Research, and Council on Nutrition, Physical Activity and Metabolism. Fifteen-year trends in awareness of heart disease in women: results of a 2012 American Heart Association national survey. *Circulation*. 2013;127:1254–1263. doi: 10.1161/CIR.0b013e318287cf2f
46. Global Burden of Disease Study 2016. Global Burden of Disease Study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and

Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed May 1, 2018.

47. Global Status Report on Noncommunicable Diseases 2014. Geneva, Switzerland: World Health Organization; 2014. http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf. Accessed September 2, 2016.
48. Bloom DE, Cafiero ET, Jane´-Llopis E, Abrahams-Gessel S, Bloom LR, Fathima S, Feigl AB, Gaziano T, Mowafi M, Pandya A, Prettner K, Rosenberg L, Seligman B, Stein AZ, Weinsteain C. The Global Economic Burden of Non-communicable Diseases. Geneva, Switzerland: World Economic Forum; 2011.
49. World Health Organization (WHO) website. Cardiovascular diseases (CVDs). Fact sheet No. 317. http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed April 10, 2015.
50. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, Murray CJ. Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation*. 2015;132:1667–1678. doi: 10.1161/CIRCULATIONAHA.114.008720
51. Smith SC Jr, Collins A, Ferrari R, Holmes DR Jr, Logstrup S, McGhie DV, Ralston J, Sacco RL, Stam H, Taubert K, Wood DA, Zoghbi WA. Our time: a call to save preventable death from cardiovascular disease (heart disease and stroke). *Circulation*. 2012;126:2769–2775. doi: 10.1161/CIR.0b013e318267e99f
52. Kontis V, Mathers CD, Rehm J, Stevens GA, Shield KD, Bonita R, Riley LM, Poznyak V, Beaglehole R, Ezzati M. Contribution of six risk factors to achieving the 25×25 non-communicable disease mortality reduction target: a modelling study. *Lancet*. 2014;384:427–437. doi: 10.1016/S0140-6736(14)60616-4
53. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753. doi: 10.1161/CIRCULATIONAHA.107.699579

14. STROKE (CEREBROVASCULAR DISEASE)

ICD-9 430 to 438; ICD-10 I60 to I69. See Table 14-1 and Charts 14-1 through 14-16

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Abbreviations Used in Chapter 14

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACR	albumin-creatinine ratio
AF	atrial fibrillation
AHA	American Heart Association
AHI	apnea-hypopnea index
ARIC	Atherosclerosis Risk in Communities study
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation
AVAIL	Adherence Evaluation After Ischemic Stroke Longitudinal
BASIC	Brain Attack Surveillance in Corpus Christi
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CAD	coronary artery disease
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CLRD	chronic lower respiratory disease
CREST	Carotid Revascularization Endarterectomy Versus Stenting Trial
CRP	C-reactive protein
CVD	cardiovascular disease
DALY	disability-adjusted life-year
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
DM	diabetes mellitus
DVT	deep vein thrombosis
ECG	electrocardiogram
ED	emergency department
eGFR	estimated glomerular filtration rate
EPIC	European Prospective Investigation Into Cancer and Nutrition
ESCAPE	Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times
EXTEND-IA	Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial
FHS	Framingham Heart Study
FINRISK	Finnish Population Survey on Risk Factors for Chronic, Noncommunicable Diseases
FUTURE	Follow-up of TIA and Stroke Patients and Unelucidated Risk Factor Evaluation
GBD	Global Burden of Disease
GCNKSS	Greater Cincinnati/Northern Kentucky Stroke Study
GFR	glomerular filtration rate
GWAS	genome wide association study
GWTG	Get With The Guidelines
HBP	high blood pressure
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HIV	human immunodeficiency virus

(Continued)

Abbreviations Used in Chapter 14 Continued

HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
ICD-10	*International Classification of Diseases, 10th Revision*
ICH	intracerebral hemorrhage
IMT	intima-media thickness
IQ	intelligence quotient
IQR	interquartile range
IRR	incidence rate ratio
LDL	low-density lipoprotein
LDLC	low-density lipoprotein cholesterol
MEPS	Medical Expenditure Panel Survey
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
MIDAS	Myocardial Infarction Data Acquisition System
MONICA	Monitoring Trends and Determinants of Cardiovascular Disease
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
MRI	magnetic resonance imaging
MUFA	monounsaturated fatty acid
NAMCS	National Ambulatory Medical Care Survey
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institutes of Neurological Disorders and Stroke
NIS	National (Nationwide) Inpatient Sample
NOMAS	Northern Manhattan Study
ONTARGET	Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial
OR	odds ratio
OSA	obstructive sleep apnea
PA	physical activity
PAR	population attributable risk
PE	pulmonary embolism
PREVAIL	Prevention of VTE After Acute Ischemic Stroke With LMWH Enoxaparin
PREVEND	Prevention of Renal and Vascular End-Stage Disease
PROFESS	Prevention Regimen for Effectively Avoiding Second Stroke
RCT	randomized controlled trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
REVASCAT	Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset
RR	relative risk
SAH	subarachnoid hemorrhage
SBP	systolic blood pressure
SD	standard deviation
SES	socioeconomic status
SHS	Strong Heart Study
SNP	single-nucleotide polymorphism
SPRINT	Systolic Blood Pressure Intervention Trial
SPS3	Secondary Prevention of Small Subcortical Strokes
STOP	Stroke Prevention Trial in Sickle Cell Anemia
SVT	supraventricular tachycardia
SWIFT PRIME	Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment
TC	total cholesterol
TIA	transient ischemic attack
tPA	tissue-type plasminogen activator
VTE	venous thromboembolism

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Stroke Prevalence (See Table 14-1 and Chart 14-1)

- Stroke prevalence estimates may differ slightly between studies because each study selects and recruits a sample of participants to represent the target study population (eg, state, region, or country).
- An estimated 7.0 million Americans ≥20 years of age self-report having had a stroke (extrapolated to 2016 by use of NHANES 2013–2016 data). Overall stroke prevalence during this period was an estimated 2.5% (NHANES, NHLBI tabulation; Table 14-1).
- Prevalence of stroke in the United States increases with advancing age in both males and females (Chart 14-1).
- According to data from the 2016 BRFSS (CDC)[1]:
  - 2.9% of males and 2.8% of females ≥18 years of age had a history of stroke; 2.7% of NH whites, 4.1% of NH blacks, 1.2% of Asian/Pacific Islanders, 2.3% of Hispanics (of any race), 5.3% of American Indian/Alaska Natives, and 4.9% of other races or multiracial people had a history of stroke.
  - Stroke prevalence in adults is 2.9% in the United States, with the lowest prevalence in South Dakota (1.9%) and the highest prevalence in Mississippi (4.5%).
- Over the time period 2006 to 2010, data from BRFSS show that the overall self-reported stroke prevalence did not change. Older adults, blacks, people with lower levels of education, and people living in the southeastern United States had higher stroke prevalence.[2]
- Analysis of temporal trends in age-, sex- and race/ethnicity-specific stroke prevalence rates from 2006 to 2010, according to BRFSS, revealed that stroke prevalence remained stable in individuals aged 18 to 44 and 45 to 64 years but had a declining trend among individuals ≥65 years old across the study period (−1.2%, *P*=0.09). From 2006 to 2010, stroke prevalence declined in males (−3.6%, *P*<0.01) while remaining stable in females across the study period, such that in more recent years, stroke prevalence was similar in both males and females. From 2006 to 2010, there were no statistically significant temporal trends in stroke prevalence by race/ethnicity.[2]
- The prevalence of stroke-related symptoms was found to be relatively high in a general population free of a prior diagnosis of stroke or TIA, which suggests that stroke may be underdiagnosed or that other conditions mimic stroke, or both. On the basis of data from 18 462 participants enrolled in a national cohort study, 17.8% of the population >45 years of age reported at least 1 symptom. Stroke symptoms were more likely among blacks than whites, among those with lower income and lower educational attainment, and among those with fair to poor perceived health status. Symptoms also were more likely in participants with higher Framingham stroke risk scores (REGARDS, NINDS).[3]
- Projections show that by 2030, an additional 3.4 million US adults aged ≥18 years, representing 3.9% of the adult population, will have had a stroke, a 20.5% increase in prevalence from 2012. The highest increase (29%) is projected to be in white Hispanic males.[4]
- With the aging of the US population, prevalence of stroke survivors is projected to increase, especially among elderly females.[5]

Stroke Incidence (See Table 14-1 and Chart 14-2)

- Each year, ≈795 000 people experience a new or recurrent stroke (Table 14-1). Approximately 610 000 of these are first attacks, and 185 000 are recurrent attacks (GCNKSS, NINDS, and NHLBI; GCNKSS and NINDS data for 1999 provided July 9, 2008; estimates compiled by NHLBI).
- Of all strokes, 87% are ischemic and 10% are ICH strokes, whereas 3% are SAH strokes (GCNKSS, NINDS, 1999).
- On average, every 40 seconds, someone in the United States has a stroke (AHA computation based on the latest available data).

Temporal Trends

- In the NIS, from 1995 to the period 2011 to 2012, rates of hospitalization for acute ischemic stroke almost doubled for males aged 18 to 34 and 35 to 44 years.[6] Hospitalization rates for ICH and SAH remained stable, however, with the exception of declines among males and NH black patients aged 45 to 54 with SAH (see Stroke in the Young).
- In the multicenter ARIC study of black and white adults, stroke incidence rates decreased from 1987 to 2011. The decreases varied across age groups but were similar across sex and race.[7]
- Data from the BASIC Project for the time period 2000 through 2010 demonstrated that ischemic stroke rates declined significantly in people aged ≥60 years but remained largely unchanged over time in those aged 45 to 59 years.
  - Rates of stroke decline did not differ significantly for NH whites and Mexican Americans overall in any age group; however, ethnic disparities in stroke rates persist between Mexican Americans and NH whites in the

45- to 59-year-old and 60- to 74-year-old age groups.[8]
- — Data from the BASIC Project showed that the age-, sex-, and ethnicity-adjusted incidence of ICH decreased from 2000 to 2010, from an annual incidence rate of 5.21 per 10 000 (95% CI, 4.36–6.24) to 4.30 per 10 000 (95% CI, 3.21–5.76).[9]

- Analysis of data from the FHS suggests that stroke incidence is declining over time in this largely white cohort. Data from 1950 to 1977, 1978 to 1989, and 1990 to 2004 showed that the age-adjusted incidence of first stroke per 1000 person-years in each of the 3 periods was 7.6, 6.2, and 5.3 in males and 6.2, 5.8, and 5.1 in females, respectively. Lifetime risk for incident stroke at 65 years of age decreased significantly in the latest data period compared with the first, from 19.5% to 14.5% in males and from 18.0% to 16.1% in females.[10] Data from the Tromsø Study found that changes in cardiovascular risk factors accounted for 57% of the decrease in ischemic stroke incidence for the time period from 1995 to 2012.[11]

Race/Ethnicity

- Annual age-adjusted incidence for first-ever stroke was higher in black individuals than white individuals in data collected in 1993 to 1994, 1999, and 2005 for each of the following stroke types: ischemic stroke, ICH, and SAH (Chart 14-2).
- In the national REGARDS cohort, in 27 744 participants followed up for 4.4 years (2003–2007), the overall age- and sex-adjusted black/white IRR was 1.51, but for ages 45 to 54 years, it was 4.02, whereas for those ≥85 years of age, it was 0.86.[12] Similar trends for decreasing black/white IRR with older age were seen in the GCNKSS.[13]
- The BASIC Project (NINDS) demonstrated an increased incidence of stroke among Mexican Americans compared with NH whites in a community in southeast Texas. The crude 3-year cumulative incidence (2000–2002) was 16.8 per 1000 in Mexican Americans and 13.6 per 1000 in NH whites. Specifically, Mexican Americans had a higher cumulative incidence of ischemic stroke than NH whites at younger ages (45–59 years of age: RR, 2.04 [95% CI, 1.55–2.69]; 60–74 years of age: RR, 1.58 [95% CI, 1.31–1.91]) but not at older ages (≥75 years of age: RR, 1.12 [95% CI, 0.94–1.32]). Mexican Americans also had a higher incidence of ICH and SAH than NH whites after adjustment for age.[14]
- The age-adjusted incidence of first ischemic stroke per 1000 was 0.88 in whites, 1.91 in blacks, and 1.49 in Hispanics according to data from NOMAS (NINDS) for 1993 to 1997. Among blacks, compared with whites, the RR of intracranial atherosclerotic stroke was 5.85 (95% CI, 1.82–18.73); extracranial atherosclerotic stroke, 3.18 (95% CI, 1.42–7.13); lacunar stroke, 3.09 (95% CI, 1.86–5.11); and cardioembolic stroke, 1.58 (95% CI, 0.99–2.52). Among Hispanics compared with whites, the relative rate of intracranial atherosclerotic stroke was 5.00 (95% CI, 1.69–14.76); extracranial atherosclerotic stroke, 1.71 (95% CI, 0.80–3.63); lacunar stroke, 2.32 (95% CI, 1.48–3.63); and cardioembolic stroke, 1.42 (95% CI, 0.97–2.09).[15]
- Among 4507 American Indian or Alaska Native participants without a prior stroke in the SHS from 1989 to 1992, the age- and sex-adjusted incidence of stroke through 2004 was 6.79 per 100 person-years, with 86% of incident strokes being ischemic.[16]
- In the REGARDS study, the increased risk of ICH with age differed between blacks and whites: there was a 2.25-fold (95% CI, 1.63–3.12) increase per decade older age in whites but no age association with ICH risk in blacks (HR, 1.09 [95% CI, 0.70–1.68] per decade older age).[17]

Sex

- Each year, ≈55 000 more females than males have a stroke (GCNKSS, NINDS).[18]
- Females have a higher lifetime risk of stroke than males. In the FHS, lifetime risk of stroke among those 55 to 75 years of age was 1 in 5 for females (95% CI, 20%–21%) and ≈1 in 6 for males (95% CI, 14%–17%).[19]
- Age-specific incidence rates are substantially lower in females than males in younger and middle-age groups, but these differences narrow so that in the oldest age groups, incidence rates in females are approximately equal to or even higher than in males.[5,20–24]
- In the GCNKSS, sex-specific incidence rates between 1993 to 1994 and 2010 declined significantly for males but not for females. This trend was seen for all strokes and ischemic stroke but not for hemorrhagic stroke.[25]

TIA: Prevalence, Incidence, and Prognosis

- In a nationwide survey of US adults, the estimated prevalence of self-reported physician-diagnosed TIA increased with advancing age and was 2.3% overall, which translates to ≈5 million people. The true prevalence of TIA is likely to be greater, because many patients who experience neurological symptoms consistent with a TIA fail to report them to their healthcare provider.[26]
- A 2013 survey study of nearly 600 000 people in China led to a neurologist-confirmed TIA

prevalence of 1.03 per 1000 people, with a slightly higher prevalence in females (1.15) than males (0.92).[27]

- In an Italian community-based registry (2007 to 2009), the crude TIA incidence rate was 0.52 per 1000, and in a population-based registry from Dijon, France (2013–2015), the incidence was 0.61 per 1000.[28] In China, 2013 TIA incidence was 0.24 per 1000 person-years.[27]
- Incidence of TIA increases with age and varies by sex and race/ethnicity. Males, blacks, and Mexican Americans have higher rates of TIA than their female and NH white counterparts.[14,29] Conversely, in China, incidence was slightly higher in females (0.26 per 1000 person-years) than males (0.21).[27]
- Approximately 12% of all strokes are heralded by a TIA.[30]
- TIAs confer a substantial short-term risk of stroke, hospitalization for CVD events, and death. Of 1707 TIA patients evaluated in the EDs of Kaiser Permanente Northern California from 1997 to 1998, 180 (11%) experienced a stroke within 90 days, and 91 (5%) had a stroke within 2 days. Predictors of stroke included age >60 years, DM, focal symptoms of weakness or speech impairment, and symptoms that lasted >10 minutes.[31]
- Meta-analyses of cohorts of patients with TIA have shown the short-term risk of stroke after TIA to be ≈3% to 10% at 2 days and 9% to 17% at 90 days.[32,33]
- Individuals who have a TIA and survive the initial high-risk period have a 10-year stroke risk of roughly 19% and a combined 10-year stroke, MI, or vascular death risk of 43% (4% per year).[34]
- In the GCNKSS, the 1-year mortality rate after a TIA was 12%.[29]
- In the community-based Oxford Vascular Study, among patients with TIA, disability levels increased from 14% (modified Rankin scale >2) before the TIA to 23% at 5 years after the TIA (*P*=0.002). In this same study, the 5-year risk of institutionalization after TIA was 11%.[35]
- In a meta-analysis of 47 studies,[36] it was estimated that approximately one-third of TIA patients have an acute lesion present on diffusion-weighted MRI and thus would be classified as having had a stroke under a tissue-based case definition[37,38]; however, substantial between-study heterogeneity was noted.

Recurrent Stroke

- In the North Dublin Population Stroke Study, the cumulative 2-year stroke recurrence rate was 10.8%, and case fatality was 38.6%.[39]
- Children with arterial ischemic stroke, particularly those with arteriopathy, remain at high risk for recurrent arterial ischemic stroke despite increased use of antithrombotic agents. The cumulative stroke recurrence rate was 6.8% (95% CI, 4.6%–10%) at 1 month and 12% (95% CI, 8.5%–15%) at 1 year. The 1-year recurrence rate was 32% (95% CI, 18%–51%) for moyamoya, 25% (95% CI, 12%–48%) for transient cerebral arteriopathy, and 19% (95% CI, 8.5%–40%) for arterial dissection.[40]
- A meta-analysis of 13 studies derived from hospital-based or community-based stroke registries found a pooled cumulative stroke recurrence risk of 3.1% (95% CI, 1.7%–4.4%) at 30 days, 11.1% (95% CI, 9.0%–13.3%) at 1 year, 26.4% (95% CI, 20.1%–32.8%) at 5 years, and 39.2% (95% CI, 27.2%–51.2%) at 10 years.[41] There was a temporal reduction in the 5-year risk of stroke recurrence from 32% to 16.2%, but substantial differences across studies in terms of case mix and definition of stroke recurrence were reported.
- Among 6700 patients with first-ever ischemic stroke or ICH who survived the first 28 days in the Northern Sweden MONICA stroke registry from 1995 to 2008, the cumulative risk of recurrence was 6% at 1 year, 16% at 5 years, and 25% at 10 years.[42] The risk of stroke recurrence decreased 36% between 1995 to 1998 and 2004 to 2008. Approximately 62% of all recurrent strokes after ICH (63 of 101) were ischemic.
- Approximately 10% of participants with a prior stroke in the REGARDS study had a recurrent stroke during a mean follow-up of 6.8 years.[43] Although black participants aged 45 to 75 years had an increased risk of incident stroke compared with white participants, there were no significant black/white differences in risk of recurrent stroke.
- Using data for 12 392 patients aged 18 to 45 years who were hospitalized with ischemic or hemorrhagic stroke and included in the 2013 National Readmissions Database, the rate of recurrent stroke per 100 000 index hospitalizations was 1814.0 at 30 days, 2611.1 at 60 days, and 2913.3 at 90 days.[44] Among patients without vascular risk factors at the index stroke (ie, hypertension, hypercholesterolemia, DM, smoking, AF/atrial flutter), rates per 100 000 hospitalizations were 1461.9 at 30 days, 2203.6 at 60 days, and 2534.9 at 90 days. DM was associated with greater risk of recurrent stroke in multivariable analyses (HR, 1.5 [95% CI, 1.22–1.84]).
- In a meta-analysis of 34 studies published through the end of 2016 and including a total of 73 184 patients with either ischemic stroke or TIA, the

annual risk of recurrent stroke was 4.26% (95% CI, 3.43%–5.09%).[45] Risk of stroke recurrence decreased with longer follow-up duration but did not vary over time or according to type of ischemic event. Risk was higher in RCTs (4.58% [95% CI, 3.26%–5.91%]) and hospital-based studies (4.54% [95% CI, 3.35%–5.72%]) than in community-based studies (2.55% [95% CI, 0.50%–4.60%]). The annual risk was 0.77% (95% CI, 0.45%–1.10%) for fatal stroke and 2.92% (95% CI, 2.22%–3.62%) for nonfatal stroke.

Stroke Mortality (See Table 14-1 and Charts 14-3 through 14-6)

See "Factors Influencing the Decline in Stroke Mortality: A Statement From the American Heart Association/American Stroke Association"[46] for more in-depth coverage of factors contributing to the decline in stroke mortality over the past several decades.

- In 2016[47,48]:
  - On average, every 3 minutes 42 seconds, someone died of a stroke.
  - Stroke accounted for ≈1 of every 19 deaths in the United States.
  - When considered separately from other CVDs, stroke ranks fifth among all causes of death, behind diseases of the heart, cancer, CLRD, and unintentional injuries/accidents.
  - The number of deaths with stroke as an underlying cause was 142 142 (Table 14-1); the age-adjusted death rate for stroke as an underlying cause of death was 37.3 per 100 000, whereas the age-adjusted rate for any mention of stroke as a cause of death was 62.6 per 100 000.
  - Approximately 62% of stroke deaths occurred outside of an acute care hospital.
  - In 2016, NH black males and females had higher age-adjusted death rates for stroke than NH white, NH Asian, NH Indian or Alaska Native, and Hispanic males and females in the United States (Chart 14-3).
  - More females than males die of stroke each year because of a larger number of elderly females than males. Females accounted for 58% of US stroke deaths in 2016.
- Conclusions about changes in stroke death rates from 2006 to 2016 are as follows[47]:
  - The age-adjusted stroke death rate decreased 16.7% (from 44.8 per 100 000 to 37.3 per 100 000), whereas the actual number of stroke deaths increased 3.7% (from 137 119 deaths to 142 142 deaths).
  - The decline in age-adjusted stroke death rates for males and females was similar (−17.0% and −16.9%, respectively).
  - Crude stroke death rates declined most among people aged 65 to 74 years (−19.9%; from 94.9 to 76.0 per 100 000), 75 to 84 years (−20.5%; from 333.9 to 265.5 per 100 000), and ≥85 years (−14.0%; from 1131.7 to 972.9 per 100 000). By comparison, crude stroke death rates declined more modestly among those aged 25 to 34 years (0%; 1.3 and 1.3 per 100 000), 35 to 44 years (−9.8%; 5.1 to 4.6 per 100 000), 45 to 54 years (−14.4%; 14.6 to 12.5 per 100 000), and 55 to 64 years (−9.7%; 32.9 and 29.7 per 100 000). Despite the improvements noted since 2006, there has been a recent flattening or increase in death rates among all age groups (Charts 14-4 and 14-5).
  - Age-adjusted stroke death rates declined by ≈14% or more among all racial/ethnic groups; however, in 2016, rates remained higher among NH blacks (51.9 per 100 000; change since 2006: −19.3%) than among NH whites (36.1 per 100 000; −15.9%), NH Asians/Pacific Islanders (31.0 per 100 000; −21.5%), NH American Indians/Alaska Natives (30.7 per 100 000; −20.7%), and Hispanics (32.1 per 100 000; −13.7%).
- There are substantial geographic disparities in stroke mortality, with higher rates in the southeastern United States, known as the "stroke belt" (Chart 14-6). This area is usually defined to include the 8 southern states of North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. These geographic differences have existed since at least 1940, and despite some minor shifts, they persist.[49] Historically, the overall average stroke mortality has been ≈30% higher in the stroke belt than in the rest of the nation and ≈40% higher in the stroke "buckle" (North Carolina, South Carolina and Georgia).[46]
- The risk of dementia is also increased in the Southeastern United States, the geographic area of excess stroke risk.[50,51]
- More recent analyses of the geographic disparities determined that stroke risks are highest for residents of the stroke belt who were born and resided in the Southeast for the first 2 decades of their life.[52]
- On the basis of pooled data from several large studies, the probability of death within 1 year or 5 years after a stroke was highest in individuals ≥75 years of age (Charts 14-7 and 14-8). The probability of death within 1 year of a stroke was lowest

in black males aged 45 to 64 years (Chart 14-7). The probability of death within 5 years of a stroke was lowest for white males aged 45 to 64 years (Chart 14-9).

- In examining trends in stroke mortality by US census divisions from 1999 to 2007 for people ≥45 years of age, the rate of decline varied by geographic region and racial/ethnic group. Among black and white females and white males, rates declined by ≥2% annually in every census division, but among black males, rates declined little in the East and West South Central divisions.[53]
- On the basis of national death statistics for the time period 1990 to 2009, stroke mortality rates among American Indian and Alaska Native people were higher than among whites for both males and females in contract health services delivery area counties in the United States and were highest in the youngest age groups (35–44 years old). Stroke mortality rates and the rate ratios for American Indians/Alaska Natives to whites varied by region, with the lowest in the Southwest and the highest in Alaska. Starting in 2001, rates among American Indian/Alaska Native people decreased in all regions.[54]
- Data from the ARIC study (1987–2011; 4 US cities) showed that the cumulative all-cause mortality rate after a stroke was 10.5% at 30 days, 21.2% at 1 year, 39.8% at 5 years, and 58.4% at the end of 24 years of follow-up. Mortality rates were higher after an incident hemorrhagic stroke (67.9%) than after ischemic stroke (57.4%). Age-adjusted mortality after an incident stroke decreased over time (absolute decrease of 8.1 deaths per 100 strokes after 10 years), which was mainly attributed to the decrease in mortality among those aged ≤65 years (absolute decrease of 14.2 deaths per 100 strokes after 10 years).[7]
- Data from the BASIC Project showed there was no change in ICH case fatality or long-term mortality from 2000 to 2010 in a South Texas community. Yearly age-, sex-, and ethnicity-adjusted 30-day case fatality ranged from a low of 28.3% (95% CI, 19.9%–40.3%) in 2006 to 46.5% (95% CI, 35.5%–60.8%) in 2008.[9]
- Projections of stroke mortality from 2012 to 2030 differ based on what factors are included in the forecasting.[55] Conventional projections that only incorporate expected population growth and aging reveal that the number of stroke deaths in 2030 may increase by ≈50% compared with the number of stroke deaths in 2012. However, if previous stroke mortality trends are also incorporated into the forecasting, the number of stroke deaths among the entire population is projected to remain stable through 2030, with potential increases among the population aged ≥65 years. Moreover, the trend-based projection method reveals that the disparity in stroke deaths among NH blacks compared with NH whites could increase from an RR of 1.10 (95% CI, 1.08–1.13) in 2012 to 1.30 (95% CI, 0.45–2.44) in 2030.[55]

Stroke Risk Factors

For prevalence and other information on any of these specific risk factors, refer to the specific risk factor chapters.

- In analyses using data from the GBD Study, ≈90% of the stroke risk could be attributed to modifiable risk factors, such as HBP, obesity, hyperglycemia, hyperlipidemia, and renal dysfunction, and 74% could be attributed to behavioral risk factors, such as smoking, sedentary lifestyle, and an unhealthy diet.[56] Globally, 29% of the risk of stroke was attributable to air pollution.

High BP
(See Chapter 8 for more information.)

- BP is a powerful determinant of risk for both ischemic stroke and intracranial hemorrhage. The evidence-based 2017 "ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults" recommends intensive BP control for primary and secondary stroke prevention. The guideline proposes a target BP of <130/80 mm Hg.[57] The recommendations are supported by an extensive evidence document accompanying the guideline.[58]
- In a recent meta-analysis, 9 trials showed high-strength evidence that BP control to <150/90 mm Hg reduces stroke (RR, 0.74 [95% CI, 0.65–0.84]), and 6 trials yielded low- to moderate-strength evidence that lower targets (≤140/85 mm Hg) are associated with significant decreases in stroke (RR, 0.79 [95% CI, 0.59–0.99]).[59]
- A recent special report identified the highly significant and global implications of the hypertension treatment and control clinical guidelines on stroke risk reduction around the world.[60]
  - — There was agreement across meta-analyses that intensive BP lowering appears to be most beneficial for reduction in risk of stroke.[61–63]
  - — Median SBP declined 16 mm Hg between 1959 and 2010 for different age groups in association with large accelerated reductions in stroke mortality.[46] In a meta-analysis of clinical trials, antihypertensive therapy was associated with an average decline of 41% (95% CI, 33%–48%) in stroke incidence

with SBP reductions of 10 mm Hg or DBP reductions of 5 mm Hg.[64]

- Three recent additional meta-analyses[65–67] were consistent with the results of the aforementioned studies; the more intense BP-lowering strategy was associated with a significant reduction in the cumulative risk of stroke. Taken together, the evidence from these meta-analyses suggests that SBP <130 mm Hg may be most clinically advantageous BP target in the prevention of stroke.
- Risk prediction models identify elevated BP as a key parameter in the assessment of cardiovascular and stroke risk.[68]
  - — People with DM with BP <120/80 mm Hg have approximately half the lifetime risk of stroke of diabetics with hypertension. The treatment and lowering of BP among hypertensive individuals with DM was associated with a significant reduction in stroke risk.[69,70]
  - — A review identified the benefit of intense BP reduction and reduced stroke outcome risks in recent clinical trials.[71] Combined results from SPRINT and ACCORD demonstrated that intensive BP control (<120 mm Hg) compared with standard treatment (<140 mm Hg) resulted in a significantly lower risk of stroke (RR, 0.75 [95% CI, 0.58–0.97]).[69]
- Cross-sectional baseline data from the SPS3 trial showed that more than half of all patients with symptomatic lacunar stroke had uncontrolled hypertension at 2.5 months after stroke.[72]
- A meta-analysis of 19 prospective cohort studies (including 762 393 participants) found that prehypertension is associated with incident stroke. The risk is particularly noted in those with BP values in the higher prehypertension range.[73]
- Several studies have shown significantly lower rates of recurrent stroke with lower BPs. Most recently, the BP-reduction component of the SPS3 trial showed that targeting an SBP <130 mm Hg (versus a higher group at 130–149 mm Hg) was likely to reduce recurrent stroke by ≈20% (HR, 0.81 [95% CI, 0.64–1.03]; *P*=0.08) and significantly reduced ICH by two-thirds (HR, 0.37 [95% CI, 0.14–0.89]; *P*=0.03) compared with an SBP goal of 130 to 149 mm Hg.[74]
- Results from the SPS3 study showed the lowest risk of events was observed at an SBP of 120 to 128 mm Hg and a DBP of 65 to 70 mm Hg.[75]
- In the Ethnic/Racial Variations of Intracerebral Hemorrhage study, both treated and untreated hypertension conferred a greater risk of ICH among blacks (treated: OR, 3.02 [95% CI, 2.16–4.22]; untreated: OR, 12.46 [95% CI, 8.08–19.20]) and Hispanics (treated: OR, 2.50 [95% CI, 1.73–3.62]; untreated: OR, 10.95 [95% CI, 6.58–18.23]) compared with whites (treated: OR, 1.57 [95% CI, 1.24–1.98]; untreated: OR, 8.79 [95% CI, 5.66–13.66]), as well as among blacks compared with whites and Hispanics (*P* for interaction <0.0001).[76]
- In the SPS3 trial, black participants were more likely to have SBP ≥150 mm Hg at both study entry (40%) and end-study visit (17%; mean follow-up, 3.7 years) than whites (9%) and Hispanics (11%) at end-study visit.[77]

Diabetes Mellitus
(See Chapter 9 for more information.)

- DM increases ischemic stroke incidence at all ages, but this risk is most prominent (risk ratio >5) before 65 years of age in both blacks and whites. Overall, ischemic stroke patients with DM are younger, more likely to be black, and more likely to have HBP, MI, and high cholesterol than nondiabetic patients.[78]
- The association between DM and stroke risk differs between sexes. A systematic review of 64 cohort studies representing 775 385 individuals and 12 539 strokes revealed that the pooled, fully adjusted RR of stroke associated with DM was 2.28 (95% CI, 1.93–2.69) in females and 1.83 (95% CI, 1.60–2.08) in males. Compared with males with DM, females with DM had a 27% greater RR for stroke when baseline differences in other major cardiovascular risk factors were taken into account (pooled ratio of RR, 1.27 [95% CI, 1.10–1.46]; I^2=0%).[79]
- Prediabetes, defined as impaired glucose tolerance or a combination of impaired fasting glucose and impaired glucose tolerance, may be associated with a higher future risk of stroke, but the RRs are modest. A meta-analysis of 15 prospective cohort studies including 760 925 participants revealed that when prediabetes was defined as fasting glucose of 110 to 125 mg/dL (5 studies), the adjusted RR for stroke was 1.21 (95% CI, 1.02–1.44; *P*=0.03).[80]
- DM is an independent risk factor for stroke recurrence; a meta-analysis of 18 studies involving 43 899 participants with prior stroke revealed higher stroke recurrence in patients with DM than in those without (HR, 1.45 [95% CI, 1.32–1.59]).[81]
- A Swedish population-based stroke registry of 12 375 first-ever stroke patients 25 to 74 years old who were followed up to 23 years found that patients with DM at stroke onset (21%) had a higher risk of death than patients without DM (adjusted HR, 1.67 [95% CI, 1.58–1.76]).[82] The reduced survival of stroke patients with DM was more pronounced in females (*P*=0.02) and younger individuals (*P*<0.001).

- In a meta-analysis of 11 RCTs that included 56 161 patients with type 2 DM and 1835 stroke cases, those who were randomized to intensive glucose control did not have a reduction in stroke risk compared with those with conventional glucose control (RR, 0.94 [95% CI, 0.84–1.06]; *P*=0.33; I^2 *P*=0.20); however, there was a 10% reduction in all MI (RR, 0.90 [95% CI, 0.820.98]; *P*=0.02; I^2 *P*=0.20).[83]
- A meta-analysis of 40 RCTs of BP lowering among 100 354 participants with DM revealed a lower risk of stroke (combined RR, 0.73 [95% CI, 0.64–0.83]; absolute risk reduction, 4.06 [95% CI, 2.53–5.40]).[84]
- A subsequent meta-analysis of 28 RCTs involving 96 765 participants with DM revealed that a decrease in SBP by 10 mm Hg was associated with a lower risk of stroke (RR from 21 studies, 0.74 [95% CI, 0.66–0.83]). Significant interactions were observed, with lower RRs (RR, 0.71 [95% CI, 0.63–0.80]) observed among trials with mean baseline SBP ≥140 mm Hg and no significant associations among trials with baseline SBP <140 mm Hg (RR, 0.90 [95% CI, 0.69–1.17]). The associations between BP lowering and stroke risk reduction were present for both the achieved SBP of <130 mm Hg and the ≥130 mm Hg stratum.[85]
- The ACCORD study showed that in patients with type 2 DM, targeting SBP to <120 mm Hg did not reduce the rate of cardiovascular events compared with subjects in whom the SBP target was <140 mm Hg, except for the end point of stroke, for which intensive therapy reduced the risk of any stroke (HR, 0.59 [95% CI, 0.39–0.89]) and nonfatal stroke (HR, 0.63 [95% CI, 0.41–0.96]).[70]
- ONTARGET revealed that in both patients with and without DM, the adjusted risk of stroke continued to decrease down to achieved SBP values of 115 mm Hg, whereas there was no benefit for other fatal or nonfatal cardiovascular outcomes below an SBP of 130 mm Hg.[86]
- In NOMAS, duration of DM was associated with ischemic stroke risk (adjusted HR per year with DM, 1.03 [95% CI, 1.02–1.04]).[87]
- The ATRIA Study demonstrated that the duration of DM is a stronger predictor of ischemic stroke than glycemic control for patients with DM and AF.[88] Duration of DM ≥3 years was associated with an increased rate of ischemic stroke (HR, 1.74 [95% CI, 1.10–2.76]) compared with a duration of <3 years.

Disorders of Heart Rhythm (See Chapter 16 for more information.)

- AF is a powerful risk factor for stroke, independently increasing risk ≈5-fold throughout all ages. The percentage of strokes attributable to AF increases steeply from 1.5% at 50 to 59 years of age to 23.5% at 80 to 89 years of age.[89,90]
- An analysis from the FHS demonstrated that the risk of stroke associated with AF declined by 73% in the 50 years from 1958 to 2007.[91] However, analysis from the Olmsted County, MN, database suggests that AF-associated stroke risk has not changed over the past decade (from 2000 to 2010).[92]
- Because AF is often asymptomatic[93,94] and likely frequently undetected clinically,[95] the stroke risk attributed to AF could be substantially underestimated.[96] Screening for AF in patients with cryptogenic stroke or TIA by use of outpatient telemetry for 21 to 30 days has resulted in an AF detection rate of 12% to 23%.[95–97]
- In an RCT among patients with cryptogenic stroke, the cumulative incidence of AF detected with an implantable cardiac monitor was 30% by 3 years. Approximately 80% of the first AF episodes were asymptomatic.[98]
- Among 2580 participants ≥65 years of age with hypertension in whom a cardiac rhythm device that included an atrial lead was implanted, 35% developed subclinical tachyarrhythmias (defined as an atrial rate ≥190 beats per minute that lasted ≥6 minutes). These subclinical events were associated with a 2.5-fold increased risk of ischemic stroke or systemic embolism. The authors estimated that subclinical atrial tachyarrhythmias were associated with a 13% PAR for stroke or systemic embolism.[99]
- An analysis of patients from the Veterans Administration showed that among patients with device-documented AF, the presence of relatively brief amounts of AF raised the short-term risk of stroke 4- to 5-fold. This risk was highest in the initial 5 to 10 days after the episode of AF and declined rapidly after longer periods.[100]
- Important risk factors for stroke in the setting of AF include advancing age, hypertension, HF, DM, previous stroke or TIA, vascular disease, renal dysfunction, and female sex.[84,101–104] Additional biomarkers, including high levels of troponin and BNP, are associated with an increased risk of stroke in the setting of AF in models adjusted for well-established clinical characteristics.[105]
- In patients with AF on anticoagulation, presence of persistent AF versus paroxysmal AF is associated with higher risk of stroke.[106,107]
- A significant obesity paradox has been noted for stroke risk among AF patients in a meta-analysis of RCTs with newer oral anticoagulant trials such that overweight to obese participants had lower

risk of stroke and systemic embolism.[108] However, this relationship was not observed in the observational studies.[109]

- Other cardiac arrhythmias and ECG findings associated with an increased risk of stroke include paroxysmal SVT; short, irregular SVTs without P waves; short-run atrial tachyarrhythmia (episodes of supraventricular ectopic beats <5 seconds); PR interval prolongation >200 ms; abnormal P-wave axis (any value outside 0° to 75° using 12-lead ECGs); elevated P-wave terminal force; and maximal P-wave area.[110]
- Left atrial enlargement is associated with AF, causing the 2 conditions to often coexist. A systematic review of 9 cohort studies including 67 875 participants revealed that those with left atrial enlargement in the setting of sinus rhythm had stroke rates ranging from 0.64 to 2.06 per 100 person-years. Two studies found potential indications of modification by sex, with only positive associations observed in females.[111]

High Blood Cholesterol and Other Lipids (See Chapter 7 for more information.)

- Overall, the association of each cholesterol subfraction with total stroke has shown inconsistent results, and the data are limited on associations with specific ischemic stroke subtypes. Further research is needed to identify the association of cholesterol with ischemic stroke subtypes, as well as the association of lobar versus deep ICH.[112–116] For clarity, results for different types of cholesterol (TC, subfractions) are described in this section.
- An association between TC and ischemic stroke has been found in some prospective studies[117–119] but not others.[112,113,116] In the Women's Pooling Project, including those <55 years of age without CVD, TC was associated with an increased risk of stroke at the highest quintile (mean cholesterol 7.6 mmol/L) in black (RR, 2.58 [95% CI, 1.05–6.32]) but not white (RR, 1.47 [95% CI, 0.57–3.76]) females.[114] An association of elevated TC with risk of stroke was noted to be present in those 40 to 49 years old and 50 to 59 years old but not in other age groups in the Prospective Studies Collaboration.[115] In a recent meta-analysis of data from 61 cohorts, TC was only weakly associated with risk of stroke, with no significant difference between males and females (HR [95% CI] for ischemic stroke per 1 mmol/L higher TC: 1.01 [0.98–1.05] in females and 1.03 [1.00–1.05] in males).[120]
- Elevated TC is inversely associated in multiple studies with hemorrhagic stroke. In a meta-analysis of 23 prospective cohort studies, 1 mmol higher TC was associated with a 15% lower risk of hemorrhagic stroke (HR, 0.85 [95% CI, 0.80–0.91]).[121]
- Data from the Honolulu Heart Program/NHLBI found that in Japanese males 71 to 93 years of age, low concentrations of HDL-C were more likely to be associated with a future risk of thromboembolic stroke than were high concentrations.[122] However, a meta-analysis of 23 studies performed in the Asia-Pacific region showed no significant association between low HDL-C and stroke risk,[123] although another meta-analysis without geographic restriction demonstrated a protective association of HDL-C with stroke.[116] A Finnish study of 27 703 males and 30 532 females followed up for >20 years for ischemic stroke found an independent inverse association of HDL-C with the risks of total and ischemic stroke in females.[113] In the CHS, higher HDL-C was associated with a lower risk of ischemic stroke in males but not in females.[124] In the SHS, a possible interaction was noted between DM status and HDL-C for risk of stroke such that higher HDL-C was protective against stroke risk in patients with DM (HR per 1-SD higher HDL-C, 0.72 [95% CI, 0.53–0.97]) but not in those without DM (HR per 1-SD higher HDL-C, 0.93 [95% CI, 0.69–1.26]).[125] In a recent meta-analysis, no significant association was observed between HDL-C levels and risk of hemorrhagic stroke.[121]
- Data from the Dallas Heart Study suggest that higher HDL-C efflux capacity is strongly associated with lower risk of stroke.[126]
- In an analysis by the Emerging Risk Factors Collaboration of individual records on 302 430 people without initial vascular disease from 68 long-term prospective studies, HR for ischemic stroke was 1.12 (95% CI, 1.04–1.20) for non–HDL-C in analyses using the lowest quantile as the referent group[127] and 0.93 (95% CI, 0.84–1.02) for HDL-C. In the Women's Health Study, LDL-C was associated with an increased risk of stroke,[117] and LDL-C may have a stronger association for large-artery atherosclerotic subtype.[128] In a pooled analysis of CHS and ARIC, low LDLC (<158.8 mg/dL) was associated with an increased risk of ICH.[129]
- Among 13 951 patients in the Copenhagen Heart Study followed up for 33 years for ischemic stroke, increasing stepwise levels of nonfasting triglycerides were associated with increased risk of ischemic stroke in both males and females,[130] although in ARIC, the Physician's Health Study, and the SHS, there was no association.[125,131,132] In the Rotterdam Study (N=9068), increasing quartiles of serum triglycerides were associated with a reduced risk of ICH.[133]

- A mendelian randomization study of lipid genetics suggested an increased risk of large-artery ischemic stroke with increased LDL and a lower risk of small-vessel ischemic stroke with increased HDL.[134]

Smoking/Tobacco Use (See Chapter 3 for more information.)

- Current smokers have a 2 to 4 times increased risk of stroke compared with nonsmokers or those who have quit for >10 years.[135,136]
- Cigarette smoking is a risk factor for ischemic stroke and SAH.[135–137]
- Smoking is perhaps the most important modifiable risk factor in preventing SAH, with the highest PAR (38%–43%) of any SAH risk factor.[138]
- In a large Danish cohort study, among people with AF, smoking was associated with a higher risk of ischemic stroke/arterial thromboembolism or death, even after adjustment for other traditional risk factors.[139]
- Although some studies have reported a dose-response relationship between smoking and risk of stroke across old and young age groups,[137,140] a recent meta-analysis of 141 cohort studies showed that low cigarette consumption (≈1 cigarette per day) carries a risk of developing stroke as large as 50% of that of high cigarette consumption (≈20 cigarette per day).[141] This is much higher than what would be predicted from a linear or log-linear dose-response relationship between smoking and risk of stroke.[141]
- A meta-analysis that compared pooled data of almost 4 million smokers and nonsmokers found a similar risk of stroke associated with current smoking in females and males.[142]
- Discontinuation of smoking has been shown to reduce stroke risk across sex, race, and age groups.[140,142]
- Smoking may impact the effect of other stroke risk factors on stroke risk. For example, a synergistic effect on the risk of stroke appears to exist between smoking and SBP[143] and oral contraceptives.[144,145]
- Exposure to secondhand smoke, also termed passive smoking or secondhand tobacco smoke, is a risk factor for stroke.
  - Meta-analyses have estimated a pooled RR of 1.25 for exposure to spousal smoking (or nearest equivalent) and risk of stroke. A dose-response relationship between exposure to secondhand smoke and stroke risk was also reported.[146,147]
  - Data from REGARDS found that after adjustment for other stroke risk factors, the risk of overall stroke was 30% higher among nonsmokers who had secondhand smoke exposure during adulthood (95% CI, 2%–67%).[148]
  - Data from another large-scale prospective cohort study of females in Japan showed that secondhand tobacco smoke exposure at home during adulthood was associated with an increased risk of stroke mortality in those aged ≥80 years (HR, 1.24 [95% CI, 1.05–1.46]). Overall, the increased risk was most evident for SAH (HR, 1.66 [95% CI, 1.02–2.70]) in all age groups.[149]
  - A study using NHANES data found that individuals with a prior stroke have a greater odds of having been exposed to secondhand smoke (OR, 1.46 [95% CI, 1.05–2.03]), and secondhand smoke exposure was associated with a 2-fold increase in mortality among stroke survivors compared with stroke survivors without the exposure (age-adjusted mortality rate: 96.4±20.8 versus 56.7±4.8 per 100 person-years; P=0.026).[150]
- The FINRISK study found a strong association between current smoking and SAH compared with nonsmokers (HR, 2.77 [95% CI, 2.22–3.46]) and reported a dose-dependent and cumulative association with SAH risk that was highest in females who were heavy smokers.[151]
- Use of smokeless tobacco is associated with an increased risk of fatal stroke.
  - In recent meta-analyses of studies from Europe, North America, and Asia, adult ever-users of smokeless tobacco had a higher risk of fatal stroke (OR, 1.39 [95% CI, 1.29–1.49]).[152,153]
  - No association has been reported between use of smokeless tobacco and nonfatal stroke.[152]

Physical Inactivity (See Chapter 4 for more information.)

- Over a mean follow-up of 17 years, the ARIC study found a significant trend among African-Americans toward reduced incidence of stroke with increasing level of PA; a similar trend was observed for whites in the study, although it was not statistically significant. Data from this study showed that although the highest levels of activity were most protective, even modest levels of PA appeared to be beneficial.[154]
- Among individuals >80 years of age in NOMAS, physical inactivity was associated with higher risk of stroke (physical inactivity versus PA: HR, 1.60 [95% CI, 1.05–2.42]).[155]
- In the CHS, a greater amount of leisure-time PA (across quintiles, P_{trend}=0.001), as well as exercise

intensity (categories: high, moderate, low versus none, P_{trend}<0.001), were both associated with lower risk of stroke among individuals >65 years of age. The relation between greater PA and lower risk of stroke was even observed in individuals ≥75 years of age.[155a]

- In the Cooper Center Longitudinal Study of participants who underwent evaluation at the Cooper Clinic in Dallas, TX, investigators found that cardiorespiratory fitness in mid-life as measured by exercise treadmill testing was inversely associated with risk of stroke in older age, including in models that were adjusted for the interim development of stroke risk factors such as DM, hypertension, and AF.[156]
- Similarly, a prospective study of young Swedish males demonstrated that the highest compared with the lowest tertile of fitness (HR, 1.70 [95% CI, 1.50–1.93]) and lower muscle strength (HR, 1.39 [95% CI, 1.27–1.53]) were associated with higher risk of stroke over 42 years of follow-up.[157]
- Several recent prospective studies found associations of PA and stroke risk in females.
  - In the Million Women Study, a prospective cohort study among females in England and Scotland, over an average follow-up of 9 years, self-report of any PA at baseline was associated with reduced risk of any stroke, as well as stroke subtypes; however, more frequent or strenuous activity was not associated with increased protection against stroke.[158]
  - Similarly, a low level of leisure-time PA was associated with a 1.5 times higher risk of stroke and a 2.4 times higher risk of fatal stroke compared with intermediate to high levels of activity in a cohort of ≈1500 Swedish females followed up for up to 32 years.[159]
  - The EPIC-Heidelberg cohort included 25 000 males and females and identified stroke outcomes over a mean of 13 years of follow-up. Among females, participation in any level of PA was associated with a nearly 50% reduction in stroke risk compared with inactivity; no similar pattern was seen for males.[160]
- A dose-response effect was seen for total number of hours spent walking per week, and increased walking time was associated with reduced risk of incident stroke among 4000 males in the British Regional Heart Study. Those reporting ≥22 hours of walking per week had one-third the risk of incident stroke as those who walked <4 hours per week. No clear association between stroke and walking speed or distance walked was seen in this study.[161]
- Recent studies have also demonstrated a significant association between sedentary time duration and risk of CVD including stroke, independent of PA levels.[162,163] In the REGARDS study, screen time >4 h/d was associated with 37% higher risk (HR, 1.37 [95% CI, 1.10–1.71]) of stroke over a 7-year follow-up.[164]
- In a population-based study of 74 913 Japanese people aged 50 to 79 years and without histories of CVD or cancer, there was a nonlinear dose-response relationship between daily total PA and stroke risk. Individuals with moderate levels of total PA had the lowest risk of total stroke (HR, 0.83 [95% CI, 0.75–0.93]), hemorrhagic stroke (HR, 0.79 [95% CI, 0.66–0.94]), and ischemic stroke (HR, 0.79 [95% CI, 0.69–0.90]). The associations of total PA level with hemorrhagic stroke showed a U or J shape, and that with ischemic stroke showed a L shape.[165]

Nutrition
(See Chapter 5 for more information.)

- Adherence to a Mediterranean-style diet that was higher in nuts and olive oil was associated with a reduced risk of stroke (diet with nuts: HR, 0.54 [95% CI, 0.35–0.82]; diet with olive oil: HR, 0.65 [95% CI, 0.44–0.95]; Mediterranean diets combined versus control: HR, 0.58 [95% CI, 0.42–0.82]) in an RCT conducted in Spain.[165a]
- In the Nurses Health and Health Professionals Follow-up Studies, each 1-serving increase in sugar-sweetened soda beverage was associated with a 13% increased risk of ischemic stroke, and each 1-serving increase in low-calorie or diet soda was associated with a 7% increased risk of ischemic stroke and a 27% increased risk of hemorrhagic stroke.[166]
- A meta-analysis of >94 000 people with 34 817 stroke events demonstrated that eating ≥5 servings of fish per week versus eating <1 serving per week was associated with a 12% reduction in stroke risk; however, these results were not consistent across all cohort studies.[167]
- According to registry data from Sweden, people eating ≥7 servings of fruits and vegetables per day had a 19% reduced risk of stroke compared with those eating only 1 serving per day among people who did not have hypertension.[168] Results from 2 prospective cohorts from Sweden, comprising 74 404 males and females 45 to 83 years of age free of stroke at baseline, found that high adherence to the modified DASH diet is associated with a reduced risk of ischemic stroke (RR, 0.86 [95% CI, 0.78–0.94] for the highest versus lowest quartile of diet adherence).[169]
- A Nordic diet, including fish, apples and pears, cabbages, root vegetables, rye bread, and

oatmeal, was associated with a decreased risk of stroke among 55 338 males and females (HR, 0.86 [95% CI, 0.76–0.98] for high versus low diet adherence).[170]

- A meta-analysis of case-control, prospective cohort studies and an RCT investigating the association between olive oil consumption and the risk of stroke (N=38 673 participants) revealed a reduction in stroke risk (RR, 0.74 [95% CI, 0.60–0.92]).[171]
- A meta-analysis of 10 prospective cohort studies including 314 511 nonoverlapping individuals revealed that higher MUFA intake was not associated with risk of overall stroke (RR, 0 .86 [95% CI, 0.74–1.00]) or risk of ischemic stroke (RR, 0.92 [95% CI, 0.79–1.08]) but was associated with a reduced risk of hemorrhagic stroke (RR, 0.68 [95% CI, 0.49–0.96]).[172]
- A meta-analysis of prospective cohort studies evaluating the impact of dairy intake on CVD noted that total dairy intake and calcium from dairy were associated with an inverse summary RR estimate for stroke (0.91 [95% CI, 0.83–0.99] and 0.69 [95% CI, 0.60–0.81], respectively).[173]
- A meta-analysis of 20 prospective cohort studies of the association between nut consumption and cardiovascular outcomes (N=467 389) revealed no association between nut consumption and stroke (2 studies; RR, 1.05 [95% CI, 0.69–1.61]) but did find an association with stroke mortality (3 studies; RR, 0.83 [95% CI, 0.69–1.00]).[174]
- A meta-analysis of 8 prospective studies (N=410 921) revealed no significant association between consumption of refined grains and risk of stroke.[175] A second meta-analysis[176] of 8 prospective studies (N=468 887) revealed that a diet that contained greater amounts of legumes was not associated with a lower risk of stroke; however, a diet with greater amounts of nuts was associated with lower risk of stroke (summary RR, 0.90 [95% CI, 0.81–0.99]). Sex significantly modified the effects of nut consumption on stroke risk, and high nut intake was associated with reduced risk of stroke in females (summary RR, 0.85 [95% CI, 0.75–0.97]) but not in males (summary RR, 0.95 [95% CI, 0.82–1.11]).[176]
- A meta-analysis of 21 studies (N=13 033) evaluating the effect of vitamin D on cardiovascular outcomes revealed that vitamin D supplementation was not associated with a lower risk of stroke (HR, 1.07 [95% CI, 0.91–1.29]).[177]
- A meta-analysis of 14 cohorts (N=333 250) revealed that potassium intake is associated with lower risk of stroke (RR, 0.80 [95% CI, 0.72–0.90]). In addition, the dose-response analysis showed that for every 1 g/d (25.6 mmol/d) increase in potassium intake, there was a 10% reduction in stroke risk (RR, 0.90 [95% CI, 0.84–0.96]).[178]
- A systematic meta-analysis from 19 independent cohort samples from 13 studies determined a higher salt intake was associated with greater risk of stroke (pooled RR, 1.23 [95% CI, 1.06 to 1.43]), with no significant evidence of publication bias.[179]
- A meta-analysis of 8 studies (N=280 174) indicated an inverse association between flavonol intake and stroke (summary RR, 0.86 [95% CI, 0.75–0.99]). An increase in flavonol intake of 20 mg/d was associated with a 14% decrease in the risk for developing stroke (summary RR, 0.86 [95% CI, 0.77–0.96]). Subgroup analyses suggested an inverse association between highest flavonol intake and stroke risk among males (summary RR, 0.74 [95% CI, 0.56–0.97]) but not females (summary RR, 0.99 [95% CI, 0.85–1.16]).[180]
- In a population of Chinese adults, folate therapy combined with enalapril was associated with a significant reduction in ischemic stroke risk (HR, 0.76 [95% CI, 0.64–0.91]). Although the US population is not as likely to be at risk of folate deficiency because of folate fortification of grains, this study demonstrates the importance of adequate folate levels for stroke prevention.[181]
- A study using Framingham data found that recent consumption and an increased cumulative intake of artificially sweetened soft drinks was associated with a higher risk of stroke, with the strongest association observed for ischemic stroke; no association was observed for sugary beverages or sugar-sweetened soft drinks.[182]

Family History and Genetics

- Ischemic stroke is a heritable disease; family history of stroke is associated with increased risk of ischemic stroke, stroke subtypes, and carotid atherosclerosis.[183]
- In the Family Heart Study, the adjusted ORs of stroke for a positive paternal and maternal history of stroke were 2.0 and 1.4, respectively, with similar patterns seen in African Americans and European Americans.[184]
- Heritability of stroke appears to play a larger role in strokes that occur in younger people.[185]
- Genetic factors appear to be more important in large-artery and small-vessel stroke than in cryptogenic or cardioembolic stroke.[185]
- Genetic studies have identified genetic variants associated with risk of ischemic stroke, with distinct genetic associations[186] for different stroke subtypes.
  — For example, variants in the paired-like homeodomain transcription factor 2 (*PITX2*)

gene discovered through an unbiased genome-wide approach for AF have been shown to be associated with cardioembolic stroke.[187]
    — Variants in the *HDAC9* gene have been associated with large-artery stroke, as have variants in the chromosome 9p21 locus originally identified through a genome-wide approach for CAD.[188,189]
- The largest multiethnic GWAS of stroke conducted to date reports 32 genetic loci, including 22 not previously reported.[190] These novel loci point to a major role of cardiac mechanisms beyond established sources of cardioembolism. Approximately half of the stroke genetic loci share genetic associations with other vascular traits, most notably BP. The identified loci were also enriched for targets of antithrombotic drugs, including alteplase and cilostazol.
- Some genetic loci were subtype specific. For example, *EDNRA* and *LINC01492* were exclusively associated with large-artery stroke. But shared genetic influences between stroke subtypes were also evident. For example, *SH2B3* showed shared influence on large-artery and small-vessel stroke and *ABO* on large-artery and cardioembolic stroke; *PMF1-SEMA4A* has been associated with both nonlobar ICH and ischemic stroke
- A recent GWAS focused on small-vessel stroke from the International Stroke Consortium identified a novel association with a region on chromosome 16q24.2.[191]
- Studies have also identified genetic loci unique to non-European ethnicity populations. For example, one study of African Americans from MESA found that variants within the *SERGEF* gene were associated with carotid artery IMT, as well as with stroke.[192]
- Low-frequency genetic variants (ie, allele frequency <5%) may also contribute to risk of large- and small-vessel stroke. *GUCY1A3*, for example, with an allele frequency in the lead SNP of 1.5%, was associated with large-vessel stroke.[193] The gene encodes the α1-subunit of soluble guanylyl cyclase, which plays a role both in nitric oxide–induced vasodilation and platelet inhibition, and has been associated with early MI.
- The gene *GCH1*, also with an allele frequency of only 1.5%, was associated with small-vessel stroke. This gene encodes GTP cyclohydrolase 1, which plays a role in endothelial nitric oxide synthase.[194] Rare variants thus may account for some of the unexplained heritability in stroke risk.
- Monogenic forms of ischemic stroke have much higher risk associated with the underlying genetic variant but are rare.[195]
    — For example, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), an autosomal dominant disease presenting with stroke, progressive cognitive impairment, and characteristic bilateral involvement of the anterior temporal white matter and external capsule, is caused by mutations in the *NOTCH3* gene on chromosome 19q12.[196]
    — Other monogenic causes of stroke include Fabry disease, sickle cell disease, homocystinuria, Marfan syndrome, vascular Ehlers-Danlos syndrome (type IV), pseudoxanthoma elasticum, retinal vasculopathy with cerebral leukodystrophy and systemic manifestations, and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS).[186]
- ICH also appears to have a genetic component, with heritability estimates of 34% to 74% depending on the subtype.[197] A GWAS of ICH suggests that 15% of this heritability is attributable to genetic variants in the apolipoprotein E (*APOE*) gene and 29% is attributable to non-*APOE* genetic variants.[197]
- Genetic variants that predispose to hypertension also have been associated with ICH risk.[185] The other strongest genes associated with ICH are *PMF1* and *SLC25A44*, which have been linked to ICH with small-vessel disease.[198,199]

Kidney Disease
(See Chapter 11 for more information.)

- A meta-analysis of 21 studies including >280 000 patients showed a 43% (RR, 1.43 [95% CI, 1.31–1.57]) increased incident stroke risk among patients with a GFR <60 mL·min^{-1}·1.73 m^{-2}.[200]
- A meta-analysis showed that a higher albuminuria level confers greater stroke risk, providing evidence that albuminuria is strongly linked to stroke risk, and suggested that people with elevated levels of urinary albumin excretion could benefit from more intensive vascular risk reduction.[201]
- A meta-analysis showed stroke risk increases linearly and additively with declining GFR (RR per 10 mL·min^{-1}·1.73 m^{-2} decrease in GFR, 1.07 [95% CI, 1.04–1.09]) and increasing albuminuria (RR per 25 mg/mmol increase in ACR, 1.10 [95% CI, 1.01–1.20]), which indicates that CKD staging might also be a useful clinical tool to identify people who might benefit most from interventions to reduce stroke risk.[202]
- A pooled analysis of 4 prospective community-based cohorts (ARIC, MESA, CHS, and PREVEND)

including 29 595 participants showed that low eGFR (45 mL·min^{-1}·1.73 m^{-2}) was significantly associated with increased risk of ischemic stroke (HR, 1.30 [95% CI, 1.01–1.68]) but not hemorrhagic stroke (HR, 0.92 [95% CI, 0.47–1.81]) compared with normal GFR (95 mL·min^{-1}·1.73 m^{-2}). A high ACR of 300 mg/g was associated with both ischemic stroke (HR, 1.62 [95% CI, 1.27–2.07]) and hemorrhagic stroke (HR, 2.57 [95% CI, 1.37–4.83]) compared with 5 mg/g.[203]

- Proteinuria and albuminuria are better predictors of stroke risk than eGFR in patients with kidney disease.[204]
- Among 232 236 patients in the GWTG–Stroke registry, admission eGFR (in mL·min^{-1}·1.73 m^{-2}) was inversely associated with mortality and poor functional outcomes. After adjustment for potential confounders, lower eGFR was associated with increased mortality, with the highest mortality among those with eGFR <15 without dialysis (OR, 2.52 [95% CI, 2.07–3.07]) compared with eGFR ≥60. Lower eGFR was also associated with decreased likelihood of being discharged home.[205]
- In a Chinese stroke registry, low eGFR (<60 mL·min^{-1}·1.73 m^{-2}) compared with eGFR ≥90 mL·min^{-1}·1.73 m^{-2} was similarly associated with increased mortality among patients with and without hypertension, but there was an interaction between eGFR and hypertension for the effect on functional outcomes. In 5082 patients without hypertension, the risk of a poor functional outcome (defined as modified Rankin Scale score of 3–6) was approximately twice as high for those with low eGFR (adjusted OR, 2.14 [95% CI, 1.45–3.16]). In 1378 patients with previously diagnosed hypertension, the magnitude of risk of a poor functional outcome associated with low eGFR was less (adjusted OR, 1.30 [95% CI, 1.11–1.52]; *P* for interaction 0.046).[206]

Risk Factor Issues Specific to Females

See the "Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association" for more in-depth coverage of stroke risk factors unique to females.[207]

- On average, females are ≈4 years older at stroke onset than males (≈75 years compared with 71 years).[208]
- In the setting of AF, females have a significantly higher risk of stroke than males.[209–213]
- In the UK Million Women Study, there was a U-shaped relationship between age at menarche and risk of incident stroke.[214] Compared with females experiencing menarche at 13 years of age, both those experiencing menarche at age ≤10 years and those experiencing menarche at age ≥17 years had an increased risk of stroke (RR, 1.16 [95% CI, 1.09–1.24] and RR, 1.13 [95% CI, 1.03 -1.24], respectively).
- In a recent meta-analysis of 32 studies, females who experienced menopause before age 45 years had an increased risk of stroke compared with females 45 years or older at menopause onset (OR, 1.23 [95% CI, 0.98–1.53]). This association was not observed for stroke mortality (OR, 0.99 [95% CI, 0.92–1.07]).[215]
- Overall, randomized clinical trial data indicate that the use of estrogen plus progestin, as well as estrogen alone, increases stroke risk in postmenopausal, generally healthy females and provides no protection for postmenopausal females with established CHD[216–219] and recent stroke or TIA.[220]
- In a nested case-control study of the United Kingdom's General Practice Research Database, stroke risk was not increased for users of low-dose (≤50 µg) estrogen patches (RR, 0.81 [95% CI, 0.62–1.05]) but was increased for users of high-dose (>50 µg) patches (RR, 1.89 [95% CI, 1.15–3.11]) compared with nonusers.[221]
- Migraine with aura is associated with ischemic stroke in younger females, particularly if they smoke or use oral contraceptives. The combination of all 3 factors increases the risk ≈9-fold compared with females without any of these factors.[222,223]
- The peripartum period extending from 2 days before to 1 day after delivery and, to a lesser extent, up to 6 weeks postpartum is associated with an increased risk of ischemic stroke and ICH.[224]
- In the Baltimore-Washington Cooperative Young Stroke Study, the risk of ischemic stroke or ICH during pregnancy and the first 6 weeks after giving birth was 2.4 times greater than for nonpregnant females of similar age and race. The excess risk of stroke (all types except SAH) attributable to the combined pregnancy/postpregnancy period was 8.1 per 100 000 pregnancies.[225]
- Analyses of the US NIS from 1994 to 1995 and from 2006 to 2007 showed a temporal increase in the proportion of pregnancy hospitalizations that were associated with a stroke, with a 47% increase for antenatal hospitalizations and an 83% increase for postpartum hospitalizations. Increases in the prevalence of HD and hypertensive disorders accounted for almost all the increase in postpartum stroke hospitalizations but not the antenatal stroke hospitalizations.[117]
- Preeclampsia is a risk factor for ischemic stroke remote from pregnancy.[176] The increase in stroke risk related to preeclampsia could be mediated by

later risk of hypertension and DM.[226] A case-control study of females aged 12 to 55 years admitted to New York State hospitals found several factors increased the risk of pregnancy-associated stroke in females with preeclampsia, including infections present on admission (OR, 3.0 [95% CI, 1.6–5.8]), prothrombotic states (OR, 3.5 [95% CI, 1.3–9.2]), coagulopathies (OR, 3.1 [95% CI, 1.3–7.1]), and chronic hypertension (OR, 3.2 [95% CI, 1.8–5.5]).[227]

- Among people living with HIV, females had a higher incidence of stroke or TIA than males, especially at younger ages.[228] Compared with HIV-uninfected females, females living with HIV had a 2-fold higher incidence of ischemic stroke.[229]

Sleep-Disordered Breathing and Sleep Duration (See Chapter 12 for more information)

- Sleep-disordered breathing is associated with stroke risk. In a 2017 meta-analysis including 16 cohort studies (N=24 308 individuals), severe OSA was associated with a doubling in stroke risk (RR, 2.15 [95% CI, 1.42–3.24]). Severe OSA was independently associated with stroke risk among males, but not females, in stratified analyses. Neither mild nor moderate OSA was associated with stroke risk.[230]
- OSA is also common after stroke.[219,231,232] In a 2017 meta-analysis that included 43 studies, the prevalence of OSA (AHI >10) after stroke and TIA ranged from 24% to 92%, with a pooled estimate of 59%.[233] The proportion of cerebrovascular disease patients with severe OSA (AHI>30) ranged from 8% to 64%.
- In the BASIC Project, Mexican Americans had a higher prevalence of poststroke sleep-disordered breathing, defined as an AHI ≥10, than NH whites after adjustment for confounders (prevalence ratio, 1.21 [95% CI, 1.01–1.46]).[231]
- Also in the BASIC Project, acute infarction involving the brainstem (versus no brainstem involvement) was associated with increased odds of sleep-disordered breathing, defined as an AHI ≥10, with OR 3.76 (95% CI, 1.44–9.81) after adjustment for demographics, risk factors, and stroke severity.[234] In this same study, ischemic stroke subtype was not found to be associated with the presence or severity of sleep-disordered breathing.[235]
- OSA is associated with higher poststroke mortality[236–238] and worse functional outcome.[239]
- Sleep duration is also associated with stroke risk. In a meta-analysis of 11 studies, long sleep, mostly defined as self-reported sleep of ≥8 to 9 hours per night, was associated with incident stroke, with an HR of 1.45 (95% CI, 1.30–1.62) after adjustment for demographics, vascular risk factors, and comorbidities.[240] In this same meta-analysis, short sleep, defined as sleep ≤5 to 6 hours per night, was also associated with incident stroke (HR, 1.15 [95% CI, 1.07–1.24]) after adjustment for similar factors.
- In a 2017 meta-analysis that included 20 reports related to stroke outcomes, there was an approximate U-shaped association between sleep duration and stroke risk, with the lowest risk at a sleep duration of ≈6 to 7 hours daily. Both short and long sleep duration were associated with increased stroke risk of stroke. For every hour of sleep reduction below 7 hours, after adjustment for other risk factors, the pooled RR was 1.05 (95% CI, 1.01–1.09) and for each 1-hour increment of sleep above 7 hours, the RR was 1.18 (95% CI, 1.14–1.21).[241]
- In a meta-analysis of 10 studies, a J-shaped relationship was reported between sleep duration and stroke risk, with the lowest risk among those with a sleep duration of 6 to 7 h/d.[242]

Psychosocial Factors

- Depression was associated with a nearly 2-fold increased odds of stroke after adjustment for age, SES, lifestyle, and physiological risk factors (OR, 1.94 [95% CI, 1.37–2.74]) in a cohort of 10 547 females aged 47 to 52 years who were followed up for 12 years as part of the Australian Longitudinal Study on Women's Health.[243]
- A meta-analysis of 28 prospective cohort studies comprising 317 540 participants with a follow-up period that ranged from 2 to 29 years found that depression was associated with an increased risk of total stroke (pooled HR, 1.45 [95% CI, 1.29–1.63]), fatal stroke (pooled HR, 1.55 [95% CI, 1.25–1.93]), and ischemic stroke (pooled HR, 1.25 [95% CI, 1.11–1.40]).[244]
- A meta-analysis of 14 studies found a 33% (95% CI, 17%–50%) increased risk of total stroke for those with general or work stress and those who experienced stressful life events, although there was significant statistical heterogeneity between studies.[245] Among 10 studies reporting sex-specific analyses, 6 of 7 showed a positive association, with a pooled HR of 1.24 (95% CI, 1.12–1.36 for males); 3 studies reporting results for females only showed a pooled HR of 1.90 (95% CI, 1.40–2.56), and 1 case-control study showed no difference by sex.
- In a meta-analysis that included 46 studies (30 on psychological factors, 13 on vocational factors, 10 on interpersonal factors, and 2 on behavioral factors), the risk of stroke increased by 39%

with psychological factors (HR, 1.39 [95% CI, 1.27–1.51]), 35% with vocational factors (HR, 1.35 [95% CI, 1.20–1.51]), and 16% with interpersonal factors (HR, 1.16 [95% CI 1.03–1.31]); there was no significant relationship with behavior factors (HR, 0.94 [95% CI 0.20–4.31]).[246]

- Among 13 930 ischemic stroke cases and 28 026 controls in the NINDS Stroke Genetics Network, each 1-SD increase in the Psychiatric Genomics Consortium polygenic risk score for major depressive disorder was associated with a 3% increase in the odds of ischemic stroke (OR, 1.03 [95% CI, 1.00–1.05]) for those of European ancestry and an 8% increase (OR, 1.08 [95% CI, 1.04–1.13]) for those of African ancestry.[247] The risk score was associated with increased odds of small-artery occlusion in both ancestry samples (European: OR, 1.08 [95% CI, 1.03–1.13]; African: OR, 1.09 [95% CI, 1.01–1.19]), cardioembolic stroke in those of European ancestry (OR, 1.04 [95% CI 1.00–1.08]), and large-artery atherosclerosis in those of African ancestry (OR, 1.12 [95% CI, 1.01–1.25]).

Awareness of Stroke Warning Signs and Risk Factors

- Knowledge on stroke risk factors and symptoms is limited in children; stroke knowledge is lowest for those living in communities with greater economic need and sociodemographic distress and lower school performance.[248]
- A study of CVD awareness performed by the AHA among females in the United States who were >75 years old (N=1205) showed that low proportions of females identified severe headache (23%), unexplained dizziness (20%), and vision loss/changes (18%) as stroke warning symptoms.[249]
- In a single-center study of 144 stroke survivors, Hispanics scored lower on a test of stroke symptoms and the appropriate response to those symptoms than NH whites (72.5% versus 79.1% of responses correct) and were less often aware of tPA as a treatment for stroke (91.5% versus 79.2%).[250]
- In the 2009 BRFSS (N=132 604), 25% of males versus 21% of females had low stroke symptom knowledge scores (correct response to 0–4 of the 7 survey questions).[251] Sudden confusion or difficulty speaking and sudden numbness or weakness of the face, arm, or leg were the most commonly correctly identified stroke symptoms, whereas sudden headache was the least; 60% of females and 58% of males incorrectly identified sudden chest pain as a stroke symptom.
- In a study of patients with AF, there was a lack of knowledge about stroke subtypes, common symptoms of stroke, and the increased risk of stroke associated with AF.[252] Only 68% of patients without a prior stroke history were able to identify the most common symptoms of stroke.
- Among 2975 stroke/TIA cases in the GCNKSS, symptoms of weakness, decreased level of consciousness, speech/language abnormalities, and dizziness increased the odds that 9-1-1 was called for emergency transport to the hospital, independent of age, prior stroke, location of patients, stroke subtype, stroke severity, and prestroke disability. Numbness and vision disturbances were associated with decreased odds of calling 9-1-1; headache was not associated with 9-1-1 use.[253]

Complications and Recovery (See Charts 14-7 through 14-9)

- Stroke is a leading cause of serious long-term disability in the United States (Survey of Income and Program Participation, a survey of the US Census Bureau).[254] Approximately 3% of males and 2% of females reported that they were disabled because of stroke.
- In data from the NIS (2010 to 2012), among 395 411 stroke patients, 6.2% had a palliative care encounter. There was wide variability in use of palliative care, with higher use among patients who were older, female, and white; for those with hemorrhagic stroke; and for those at larger, nonprofit hospitals.[255]
- Stroke was among the top 18 diseases contributing to years lived with disability in 2010; of these 18 causes, only the age-standardized rates for stroke increased significantly between 1990 and 2010 (*P*<0.05).[256]
- Common complications after stroke include both short-term complications, such as seizures, DVT, PE, urinary infection, aspiration pneumonia, decubitus ulcers, and constipation, as well as chronic sequelae including pain syndromes, pseudobulbar affect, depression and anxiety, cognitive impairment and dementia, epilepsy, gait instability, and falls and fractures.
- Among 1075 patients undergoing rehabilitation after stroke in a Polish cohort, at least 1 complication was reported by 77% of patients, and 20% experienced ≥3 complications.[257] Urinary tract infection (23.2%), depression (18.9%), falls (17.9%), unstable hypertension (17.6%), and shoulder pain (14.9%) were the most common complications.
- DVT and PE are well-known complications of stroke, particularly in the acute phase. The

incidence of DVT is lower now than in older studies because of the use of prophylactic treatment with subcutaneous heparin and pneumatic compression boots. In the PREVAIL trial, among 1762 ischemic stroke patients unable to walk without assistance, the incidence of symptomatic DVT was ≤1% in patients treated with either enoxaparin or unfractionated heparin.[258] PE occurred in only 1 of 666 patients (0.2%) treated with enoxaparin and 6 of 669 patients (1%) treated with unfractionated heparin.

- The risk of VTE ranged from 16% to 30% for those with severe strokes (NIHSS score ≥14) to 8% to 14% for those with mild and moderate strokes (NIHSS score <14) in PREVAIL.
- In a meta-analysis that included 7 studies, the incidence density of late-onset poststroke seizure (ie, seizure occurring at least 14 days after a stroke) was 1.12 (95% CI, 0.95–1.32) per 100 person-years.[259]
- In the PROFESS trial, among 15 754 participants with ischemic stroke, 1665 patients (10.6%) reported new chronic poststroke pain, including 431 (2.7%) with central poststroke pain, 238 (1.5%) with peripheral neuropathic pain, 208 (1.3%) with pain from spasticity, and 136 (0.9%) with pain from shoulder subluxation.[260] Chronic pain was associated with greater dependence (OR, 2.16 [95% CI, 1.82–2.56]).
- Patients with stroke are at increased risk of fractures compared with those with TIA or no stroke history. In the Ontario Stroke Registry, which included 23 751 stroke and 11 240 TIA patients, the risk of low-trauma fractures was 5.7% during the 2 years after stroke, compared with 4.8% in those with TIA and 4.1% in age- and sex-matched control subjects.[261] The risk among stroke survivors compared with healthy control subjects was ≈50% higher (adjusted HR for those with stroke versus control subjects, 1.47 [95% CI 1.35–1.60]).
- Chronic insomnia occurred in 16% of stroke survivors in an Australian cohort. Insomnia was associated with depression, anxiety, disability, and failure to return to work.[262]
- In a meta-analysis of 8 studies with data available on constipation after stroke, which included 1385 participants, the pooled incidence of constipation was 48% (95% CI, 33%–63%).[263]
- Among 190 mild to moderately disabled survivors >6 months after stroke, aged 40 to 84 years, the prevalence of sarcopenia (loss of muscle mass) ranged between 14% and 18%, which was higher than for control subjects matched on age, sex, race, and BMI.[264]
- Patients with stroke are at increased risk of depression. Approximately one-third of stroke survivors develop poststroke depression, and the frequency is highest in the first year after a stroke.[265] Suicidality is also increased after stroke.[266]
- A 2014 meta-analysis involving 61 studies (N=25 488) revealed depression in 33% (95% CI, 26%–39%) of patients at 1 year after stroke, with a decline at 1 to 5 years to 25% (95% CI, 16%–33%) and to 23% (95% CI, 14%–31%) at 5 years.[267]
- Poststroke depression is associated with higher mortality. A meta-analysis of 13 studies involving 59 598 individuals revealed a pooled OR for mortality at follow-up of 1.22 (95% CI, 1.02–1.47).[268] Cognitive impairment and dementia are common after stroke, with the incidence increasing with duration of follow-up. In 2 prospective studies, 11% to 23% of patients with incident lacunar stroke developed vascular dementia during 3-year follow-up.[269] Vascular dementia may develop annually in 3% to 5% of patients with lacunar stroke.[270]
- Twelve RCTs (N=1121 subjects) suggested that antidepressant medications might be effective in treating poststroke depression, with a beneficial effect of antidepressants on remission (pooled OR for meeting criteria for depression: 0.47 [95% CI, 0.22–0.98]) and response, measured as a >50% reduction in mood scores (pooled OR, 0.22 [95% CI, 0.09–0.52]).[271]
- Seven trials (N=775 subjects) suggested that brief psychosocial interventions could be useful and effective in treatment of poststroke depression.[271–275]
- A meta-analysis of 8 RCTs assessing the efficacy of preventive pharmacological interventions among 776 initially nondepressed stroke patients revealed that the likelihood of developing poststroke depression was reduced among subjects receiving active pharmacological treatment (OR, 0.34 [95% CI, 0.22–0.53]), especially after a 1-year treatment (OR, 0.31 [95% CI, 0.18–0.56]) and with the use of a selective serotonin reuptake inhibitor (OR, 0.37 [95% CI, 0.22–0.61]). All studies excluded those with aphasia or significant cognitive impairment, which limits their generalizability.[276]
- Five RCTs (N=1078 subjects) suggested that psychosocial therapies could prevent the development of poststroke depression; however, the studies were limited by heterogeneity in design, analysis, inclusion and exclusion criteria, inadequate concealment of randomization, and high numbers of dropouts.[271,277]

- Of 127 Swedish survivors assessed for cognition at 10 years after stroke, poststroke cognitive impairment was found in 46% using a Mini–Mental State Examination threshold of <27, and in 61% using a Montreal Cognitive Assessment threshold of <25.[278] Data from prospective studies provide evidence that after an initial period of recovery, function, cognition, and quality of life decline over several years after stroke, even in the absence of definite new clinical strokes.[279–281] In NOMAS, 210 of 3298 participants had an ischemic stroke during follow-up and had functional assessments using the Barthel index before and after stroke.[281] Among those with Medicaid or no insurance, in a fully adjusted model, the slope of functional decline increased after stroke compared with before stroke (*P*=0.04), with a decline of 0.58 Barthel index points per year before stroke (*P*=0.02) and 1.94 Barthel index points after stroke (*P*=0.001). There was no effect among those with private insurance or Medicare.
- In the REGARDS prospective cohort, 515 of 23 572 participants ≥45 years of age without baseline cognitive impairment underwent repeated cognitive testing.[282] Incident stroke was associated with a short-term decline in cognitive function as well as accelerated and persistent cognitive decline over 6 years. Participants with stroke had faster declines in global cognition and executive function, but not in new learning and verbal memory, compared with prestroke slopes, in contrast to those without stroke. The rate of incident cognitive impairment also increased compared with the prestroke rate (OR, 1.23 per year [95% CI, 1.10–1.38]).
- In a meta-analysis of 14 longitudinal studies with at least 2 assessments of cognitive function after stroke, there was a trend toward significant deterioration in cognition in stroke survivors in 8 studies, although cognitive stability was found in 3 studies and improvement in 3 studies.[283] Follow-up time tended to be shorter in studies without evidence of decline.
- Stroke also appears to accelerate natural age-related functional decline. In the CHS, 382 of 5888 participants (6.5%) had ischemic stroke during follow-up with ≥1 disability assessments afterwards. The annual increase in disability before stroke (0.06 points on the Barthel index per year [95% CI, 0.002–0.12]) more than tripled after stroke (0.15 additional points per year [95% CI, 0.004–0.30]). Notably, the annual increase in disability before MI (0.04 points per year) did not change significantly after MI (0.02 additional points per year [95% CI, −0.07 to 0.11]).[284]
- In the multicenter AVAIL registry, among 1444 patients, depression was associated with worsening function during the first year after stroke. Those whose depression resolved were less likely to have functional decline over time than those without depression.[285]
- In CHS, among 509 participants with recovery data, prestroke walking speed and grip strength were associated with poststroke declines in both cognition and activities of daily living.[286] Inflammatory biomarkers (CRP, interleukin 6) were associated with poststroke cognitive decline among males, and frailty was associated with decline in activities of daily living among females.
- In data from 2011, 19% of Medicare patients were discharged to inpatient rehabilitation facilities, 25% were discharged to skilled nursing facilities, and 12% received home health care.[287]
- The 30-day readmission rate for Medicare fee-for-service beneficiaries with ischemic stroke in 2006 was 14.4%.[288]
- The 30-day hospital readmission rate after discharge from post-acute rehabilitation for stroke was 12.7% among fee-for-service Medicare patients. The mean rehabilitation length of stay for stroke was 14.6 days.[289]
- After stroke, females often have greater disability than males. For example, an analysis of community-living adults (>65 years of age) found that females were half as likely to be independent in activities of daily living after stroke, even after controlling for age, race, education, and marital status.[290]
- A meta-analysis of >25 studies examining sex differences in long-term outcomes among stroke survivors found that females had worse functional recovery and greater long-term disability and handicap. However, confidence in these conclusions was limited by the quality of the studies and variability in the statistical approach to confounding.[291]
- A national study of inpatient rehabilitation after first stroke found that blacks were younger, had a higher proportion of hemorrhagic stroke, and were more disabled on admission. Compared with NH whites, blacks and Hispanics also had a poorer functional status at discharge but were more likely to be discharged to home rather than to another institution, even after adjustment for age and stroke subtype. After adjustment for the same covariates, compared with NH whites, blacks also had less improvement in functional status per inpatient day.[292]
- Blacks were less likely to report independence in activities of daily living and instrumental activities of daily living than whites 1 year after stroke after

controlling for stroke severity and comparable rehabilitation use.[293]

- In a study of 90-day poststroke outcomes among ischemic stroke patients in the BASIC Project, Mexican Americans scored worse on neurological, functional, and cognitive outcomes than NH whites after multivariable adjustment.[294]
- Hospital characteristics also predict functional outcomes after stroke. In an analysis of the AVAIL study, which included 2083 ischemic stroke patients enrolled from 82 US hospitals participating in GWTG–Stroke, patients treated at teaching hospitals (OR, 0.72 [95% CI, 0.54–0.96]) and certified primary stroke centers (OR, 0.69 [95% CI, 0.53–0.91]) had lower rates of 3-month death or dependence.[295]
- In a survey among 391 stroke survivors, the vast majority (87%) reported unmet needs in at least 1 of 5 domains (activities and participation, environmental factors, body functions, post-acute care, and secondary prevention).[296] The greatest area of unmet need was in secondary prevention (71% of respondents). Older age, greater functional ability, and reporting that the general practitioner was the most important health professional providing care were associated with fewer unmet needs, and depression and receipt of community services after stroke were associated with more unmet needs.
- Stroke also takes its toll on caregivers. In a meta-analysis of 12 studies that included 1756 caregivers, the pooled prevalence of depressive symptoms among caregivers was 40% (95% CI, 30%–51%). Symptoms of anxiety were present in 21% (95% CI, 12%–36%).[297]

Stroke in Children

- On the basis of pathogenic differences, pediatric strokes are typically classified as either perinatal (occurring at ≤28 days of life and including in utero strokes) or (later) childhood. Presumed perinatal strokes are diagnosed in children with no symptoms in the newborn period presenting with hemiparesis or other neurological symptoms later in infancy.
- The prevalence of perinatal strokes is 29 per 100 000 live births, or 1 per 3500 live births in the 1997 to 2003 Kaiser Permanente of Northern California population.[298]
- A history of infertility, preeclampsia, prolonged rupture of membranes, and chorioamnionitis are independent maternal risk factors for perinatal arterial ischemic stroke.[263] However, maternal health and pregnancies are normal in most cases.[299]
- Diagnostic delays are more common in ischemic than hemorrhagic stroke in children, with a median time from symptom onset to diagnostic neuroimaging of 3 hours for hemorrhagic and 24 hours for ischemic stroke in a population-based study from the south of England.[300]
- The most common cause of arterial ischemic stroke in children is a cerebral arteriopathy, found in more than half of all cases.[301,302] Childhood arteriopathies are heterogeneous and can be difficult to distinguish from a partially thrombosed artery in the setting of a cardioembolic stroke; incorporation of clinical data and serial vascular imaging is important for diagnosis.[303]
- In a retrospective population-based study in northern California, 7% of childhood ischemic strokes and 2% of childhood hemorrhagic strokes were attributable to congenital heart defects. Congenital heart defects increased a child's risk of stroke 19-fold (OR, 19 [95% CI, 4.2–83]). The majority of children with stroke related to congenital heart defects were outpatients at the time of the stroke.[304] In a single-center Australian study, infants with cyanotic congenital heart defects undergoing palliative surgery were the highest-risk group to be affected by arterial ischemic stroke during the periprocedural period; stroke occurred in 22 per 2256 cardiac surgeries (1%).[305]
- In another study of the northern Californian population, adolescents with migraine had a 3-fold increased odds of ischemic stroke compared with those without migraine (OR, 3.4 [95% CI, 1.2–9.5]); younger children with migraine had no significant difference in stroke risk.[306]
- In a post hoc analysis, head or neck trauma in the prior week was a strong risk factor for childhood arterial ischemic stroke (adjusted OR, 36 [95% CI, 5–281]), present in 10% of cases.[307]
- Exposure to minor infection in the prior month was also associated with stroke and was present in one-third of cases (adjusted OR, 3.9 [95% CI, 2.0–7.4]).[307] The effect of infection on pediatric stroke risk is short-lived, lasting for days; 80% of infections preceding childhood stroke are respiratory.[308] A prospective study of 326 children with arterial stroke revealed that serologic evidence of acute herpesvirus infection doubled the odds of childhood arterial ischemic stroke, even after adjustment for age, race, and SES (OR, 2.2 [95% CI, 1.2–4.0]; P=0.007).[309] Among 187 cases with acute and convalescent blood samples, 85 (45%) showed evidence of acute herpesvirus infection; herpes simplex virus 1 was found most often. Most infections were asymptomatic.
- Thrombophilias (genetic and acquired) are risk factors for childhood stroke, with summary ORs

ranging from 1.6 to 8.8 in a meta-analysis.[310] In contrast, a population-based, controlled study suggested a minimal association between perinatal stroke and thrombophilia,[311] and therefore, routine testing is not recommended in very young children.

- In a prospective Swiss registry,[312] atherosclerotic risk factors were less common in children with arterial ischemic stroke than in young adults; the most common of these factors in children was hyperlipidemia (15%). However, an analysis of the NIS suggests a low but rising prevalence of these factors among US adolescents and young adults hospitalized for ischemic stroke (1995 versus 2008).[313]
- Compared with girls, US boys have a 25% increased risk of ischemic stroke and a 34% increased risk of ICH, whereas a study in the United Kingdom found no sex difference in childhood ischemic stroke.[314] Compared with white children, black children in both the United States and United Kingdom have a >2-fold risk of stroke.[315] The increased risk among blacks is not fully explained by the presence of sickle cell disease, nor is the excess risk among boys fully explained by trauma.[315]
- The excess ischemic stroke mortality in US black children compared with white children has diminished since 1998 when the STOP trial was published, which established a method for primary stroke prevention in children with sickle cell disease.[316]
- Among young adult survivors of childhood stroke, 37% had a normal modified Rankin score, 42% had mild deficits, 8% had moderate deficits, and 15% had severe deficits.[317] Concomitant involvement of the basal ganglia, cerebral cortex, and posterior limb of the internal capsule predicts a persistent hemiparesis.[318]
- Survivors of childhood arterial ischemic stroke have, on average, low-normal cognitive performance,[319,320] with poorest performance in visual-constructive skills, short-term memory, and processing speed. Younger age at stroke and seizures, but not laterality of stroke (left versus right), predict worse cognitive outcome.[320]
- Compared with referent children with asthma, childhood stroke survivors have greater impairments in adaptive behaviors, social adjustment, and social participation, even if their IQ is normal.[321] Severity of disability after perinatal stroke correlates with maternal psychosocial outcomes such as depression and quality of life.[322]
- Despite current treatment, at least 1 of 10 children with ischemic or hemorrhagic stroke will have a recurrence within 5 years.[323,324] Of 355 children with stroke followed up prospectively as part of a multicenter study with a median follow-up of 2 years, the cumulative stroke recurrence rate was 6.8% (95% CI, 4.6%–10%) at 1 month and 12% (95% CI, 8.5%–15%) at 1 year.[42] The sole predictor of recurrence was the presence of an arteriopathy, which increased the risk of recurrence 5-fold compared with an idiopathic acute ischemic stroke (HR, 5.0 [95% CI, 1.8–14]). In a retrospective cohort, with a cerebral arteriopathy, the 5-year recurrence risk was as high as 60% among children with abnormal arteries on vascular imaging.[325] The recurrence risk after perinatal stroke, however, was negligible.[325]
- Among 59 long-term survivors of pediatric brain aneurysms, 41% developed new or recurrent aneurysm during a median follow-up of 34 years; of those, one-third developed multiple aneurysms.[326]
- More than 25% of survivors of perinatal ischemic strokes develop delayed seizures within 3 years; those with larger strokes are at higher risk.[327] The cumulative risk of delayed seizures after later childhood stroke is 13% at 5 years and 30% at 10 years.[328] Children with acute seizures (within 7 days of their stroke) have the highest risk for delayed seizures, >70% by 5 years after the stroke.[329] In survivors of ICH in childhood, 13% developed delayed seizures and epilepsy within 2 years.[330] Elevated intracranial pressure requiring short-term intervention at the time of acute ICH is a risk factor for delayed seizures and epilepsy.
- Pediatric stroke teams and stroke centers[331] are developing worldwide. In a study of 124 children presenting to a children's hospital ED with stroke symptoms where a "stroke alert" was paged, 24% had a final diagnosis of stroke, 2% were TIAs, and 14% were other neurological emergencies, which underscores the need for prompt evaluation of children with "brain attacks."[332] Implementation of a pediatric stroke clinical pathway improved time to MRI from 17 hours to 4 hours at 1 center.[333]
- In a study of 111 pediatric stroke cases admitted to a single US children's hospital, the median 1-year direct cost of a childhood stroke (inpatient and outpatient) was ≈$50 000, with a maximum approaching $1 000 000. More severe neurological impairment after a childhood stroke correlated with higher direct costs of a stroke at 1 year and poorer quality of life in all domains.[334]
- A prospective study at 4 centers in the United States and Canada found that the median 1-year out-of-pocket cost incurred by the family of a child with a stroke was $4354 (maximum $38 666), which exceeded the median American household cash savings of $3650 at the time of

the study and represented 6.8% of the family's annual income.[335]

Stroke in the Young

- Approximately 10% of all strokes occur in individuals 18 to 50 years of age.[336]
- In the NIS, hospitalizations for acute ischemic stroke increased significantly for both males and females and for certain racial/ethnic groups among younger adults, aged 18 to 54 years.[6] From 1995 to 2011 through 2012, hospitalization rates almost doubled for males aged 18 to 34 and 35 to 44 years, with a 41.5% increase among males aged 35 to 44 years from 2003 to 2004 through 2011 to 2012. Hospitalization rates for ICH and SAH remained stable, however, with the exception of declines among males and NH black patients aged 45 to 54 years with SAH.
- In the NIS, the prevalence of stroke risk factors also increased from 2003 to 2004 through 2011 to 2012 among those hospitalized for stroke.[6] These increases in prevalence were seen among both males and females aged 18 to 64 years. Absolute increases in prevalence were seen for hypertension (range of absolute increase 4%–11%), lipid disorders (12%–21%), DM (4%–7%), tobacco use (5%–16%), and obesity (4%–9%).
- The prevalence of having 3 to 5 risk factors increased from 2003 to 2004 through 2011 to 2012, as well.[6] Among males, the prevalence of 3 or more risk factors among stroke patients increased from 9% to 16% at 18 to 34 years, 19% to 35% at 35 to 44 years, 24% to 44% at 45 to 54 years, and 26% to 46% at 55 to 64 years. Among females, the prevalence of ≥3 risk factors among stroke patients increased from 6% to 13% at 18 to 34 years, 15% to 32% at 35 to 44 years, 25% to 44% at 45 to 54 years, and 27% to 48% at 55 to 65 years (*P* for trend<0.001).
- In the 2005 GCNKSS study period, the sex-adjusted incidence rate of first-ever stroke was 48 per 100 000 (95% CI, 42–53) among whites aged 20 to 54 years compared with 128 per 100 000 (95% CI, 106–149) among blacks of the same age. Both races had a significant increase in the incidence rate from 1993 to 1994.[208] Similarly, other studies suggest an increase in the incidence of stroke in young adults. According to MIDAS 29, an administrative database containing hospital records of all patients discharged from nonfederal hospitals in New Jersey with a diagnosis of CVD or an invasive cardiovascular procedure, the rate of stroke more than doubled in patients aged 35 to 39 years, from 9.5 strokes per 100 000 person-years in the period 1995 to 1999 to 23.6 strokes per 100 000 person-years from 2010 to 2014 (rate ratio, 2.47 [95% CI, 2.07–2.96; *P*<0.0001).[337] Rates of stroke in those aged 40 to 44, 45 to 49, and 50 to 54 years also increased significantly. Strokes rates in those >55 years of age decreased during these time periods.
- Vascular risk factors are common among stroke patients aged 20 to 54 years. During 2005, in the biracial GCNKSS, hypertension prevalence was estimated at 52%, hyperlipidemia at 18%, DM at 20%, CHD at 12%, and current smoking at 46% among stroke patients 20 to 54 years of age.[208]
- In the FUTURE study, the 30-day case fatality rate among stroke patients 18 to 50 years of age was 4.5%. One-year mortality among 30-day survivors was 1.2% (95% CI, 0.0%–2.5%) for TIA, 2.4% (95% CI, 1.2%–3.7%) for ischemic stroke, and 2.9% (95% CI, 0.0%–6.8%) for ICH.[338]
- In the FUTURE study, after a mean follow-up of 13.9 years, 44.7% of young stroke patients had poor functional outcome, defined as a modified Rankin score >2. The strongest baseline predictors of poor outcome were female sex (OR, 2.7 [95% CI, 1.5–5.0]) and baseline NIHSS score (OR, 1.1 [95% CI, 1.1–1.2] per point increase).[339]

Stroke in Older Adults

- Stroke patients >85 years of age make up 17% of all stroke patients, and in this age group, stroke is more prevalent in females than in males.[340,341]
- Risk factors for stroke may be different in older adults. In the population-based multiethnic NOMAS cohort, the risk effect of physical inactivity was modified by age, and there was a significant risk only in stroke patients >80 years of age.[155] Also, the proportion of ischemic strokes attributable to AF increases with age and may reach 40% or higher in very elderly stroke patients.[342]
- Very elderly patients have a higher risk-adjusted mortality,[343] have greater disability,[343] have longer hospitalizations,[344] receive less evidence-based care,[251,252] and are less likely to be discharged to their original place of residence.[344,345]
- According to analyses from the US NIS, over the past decade, in-hospital mortality rates after stroke have declined for every age and sex group except males aged >84 years.[346]
- Over the period from 2010 to 2050, the number of incident strokes is expected to more than double, with the majority of the increase among the elderly (aged ≥75 years) and minority groups.[347]

- A Danish stroke registry reported on 39 centenarians (87% females; age range, 100–107 years) hospitalized with acute stroke. Although they had more favorable risk profiles than other age groups (lower prevalence of previous MI, stroke, and DM), their strokes were more severe and were associated with high 1-month mortality (38.5%).[348]

Organization of Stroke Care

- A study of 36 981 patients admitted with a primary diagnosis of ICH or SAH in New Jersey between 1996 and 2012 found that patients admitted to a comprehensive stroke center were more likely to have neurosurgical or endovascular treatments and had lower 90-day mortality (OR, 0.93 [95% CI, 0.89–0.97]) than patients admitted to other hospitals.[349]
- A Cochrane review of 28 trials involving 5855 participants concluded that stroke patients who receive organized inpatient care in a stroke unit had better outcomes, including decreased odds of mortality (median of 1 year; OR, 0.81 [95% CI, 0.69–0.94]), death or institutionalized care (0.78 [95% CI, 0.68–0.89]), and death or dependency (OR, 0.79 [95% CI, 0.68–0.90]), than patients treated in an alternative form of inpatient care. The findings were adjusted for patient age, sex, initial stroke severity, and stroke type.[350]
- A GWTG–Stroke study found differences in the quality measures and in-hospital outcomes among hospitals that received primary stroke center certification, depending on the different certification bodies (Joint Commission, Healthcare Facilities Accreditation Program, Det Norske Veritas, or state-based agencies).[351] State agency–certified hospitals had lower intravenous tPA utilization rates (OR, 0.76 [95% CI, 0.68–0.86]) and higher risk-adjusted in-hospital mortality rates (OR, 1.23 [95% CI, 1.07–1.41]) than Joint Commission–certified centers; Healthcare Facilities Accreditation Program–accredited hospitals were less likely to achieve door-to-needle times within 60 minutes (OR, 0.49 [95% CI, 0.31–0.77]) but had lower mortality rates (OR, 0.66 [95% CI, 0.47–0.92]).
- In analyses of 1 165 960 Medicare fee-for-service beneficiaries hospitalized between 2009 and 2013 for ischemic stroke, patients treated at primary stroke centers certified between 2009 and 2013 had lower in-hospital (OR, 0.89 [95% CI, 0.84–0.94]), 30-day (HR, 0.90 [95% CI, 0.89–0.91]), and 1-year (HR, 0.90 [95% CI, 0.89–0.91]) mortality than those treated at noncertified hospitals after adjustment for demographic and clinical factors.[352] Hospitals certified between 2009 and 2013 also had lower in-hospital and 30-day mortality than centers certified before 2009.
- Implementation of Target Stroke, a national quality improvement initiative to improve the timeliness of tPA administration, found that among 71 169 patients with acute ischemic stroke treated with tPA at 1030 GWTG–Stroke participating hospitals, participation in the program was associated with a decreased door-to-needle time, lower in-hospital mortality (OR, 0.89 [95% CI, 0.83–0.94]) and intracranial hemorrhage (OR, 0.83 [95% CI, 0.76–0.91]), and an increase in the percentage of patients discharged home (OR, 1.14 [95% CI, 1.09–1.19]).[353]

Hospital Discharges and Ambulatory Care Visits (See Table 14-1)

- From 2004 to 2014, the number of inpatient discharges from short-stay hospitals with stroke as the principal diagnosis remained stable, with 897 000 and 888 000 (Table 14-1), respectively (HCUP, NHLBI tabulation).
- In 2014, the average length of stay for discharges with stroke as the principal diagnosis was 4.7 days (HCUP, NHLBI tabulation).
- In 2015, there were 664 000 ED visits with stroke as the principal diagnosis, and in 2011, there were 209 000 outpatient visits with stroke as the first-listed diagnosis (NHAMCS, unpublished NHLBI tabulation). In 2015, physician office visits for a first-listed diagnosis of stroke totaled 2 506 000 (NAMCS, unpublished NHLBI tabulation).
- In 2014, males and females accounted for roughly the same number of inpatient hospital stays for stroke in the 18- to 44-year-old and 65- to 84-year-old age groups. Among people 45 to 64 years of age, 55.6% of stroke patients were males. Among those ≥85 years of age, females constituted 66.0% of all stroke patients (HCUP, NHLBI tabulation).
- Age-specific acute ischemic stroke hospitalization rates from 2000 to 2010 decreased for individuals aged 65 to 84 years (–28.5%) and ≥85 years (–22.1%) but increased for individuals aged 25 to 44 years (43.8%) and 45 to 64 years (4.7%). Age-adjusted acute ischemic stroke hospitalization rates were lower in females, and females had a greater rate of decrease from 2000 to 2010 than males (–22% versus –17.8%, respectively).[354]

- An analysis of the 2011 to 2012 NIS for acute ischemic stroke found that after risk adjustment, all racial/ethnic minorities except Native Americans had a significantly higher likelihood of length of stay ≥4 days than whites.[355]

Operations and Procedures (See Chart 14-10)

- In 2014, an estimated 86 000 inpatient endarterectomy procedures were performed in the United States. Carotid endarterectomy is the most frequently performed surgical procedure to prevent stroke (HCUP, NHLBI tabulation).
- Although rates of carotid endarterectomy decreased between 1997 and 2014 (Chart 14-10), the use of carotid stenting increased dramatically from 2004 to 2014 (HCUP, NHLBI tabulation).
- In-hospital mortality for carotid endarterectomy decreased steadily from 1993 to 2014 (HCUP, NHLBI tabulation).
- In the Medicare population, in-hospital stroke rate and mortality are similar for carotid endarterectomy and carotid stenting.[356,357]
- Similarly, a recent study from the NIS database demonstrated significant improvement in the in-hospital outcomes associated with carotid artery stenting over the past decade.[358]
- In the Medicare population, 30-day readmission rates and long-term risk of adverse clinical outcomes associated with carotid artery stenting were similar to those for carotid endarterectomy after adjustment for patient- and provider-level factors.[356,357,359,360]
- Evidence on comparative costs of carotid endarterectomy and stenting are mixed; whereas some studies found carotid stenting to be associated with significantly higher costs than carotid endarterectomy,[361] particularly among asymptomatic patients,[362] and that they might be less cost-effective in general,[363] CREST found that the overall cost of carotid stenting was not different from that of carotid endarterectomy (US $15 055 versus US $14 816).[364]
- The percentage of patients undergoing carotid endarterectomy within 2 weeks of the onset of stroke increased from 13% in 2007 to 47% in 2010.[365]
- Meta-analyses of 5 trials that investigated the efficacy of modern endovascular therapies for stroke (MR CLEAN, ESCAPE, SWIFT PRIME, EXTEND-IA and REVASCAT) have provided strong evidence to support the use of thrombectomy initiated within 6 hours of stroke onset, irrespective of patient age, NIHSS score, or receipt of intravenous thrombolysis.[366] Retrospective analyses of patient databases have found similar results.[367]
- Within a large telestroke network, of 234 patients who met the inclusion criteria, 51% were transferred for mechanical thrombectomy by ambulance and 49% by helicopter; 27% underwent thrombectomy. The median actual transfer time was 132 minutes (IQR, 103–165 minutes). Longer transfer time was associated with lower rates of thrombectomy, and transfer at night rather than during the day was associated with significantly longer delay. Metrics and protocols for more efficient transfer, especially at night, could shorten transfer times.[368]

Cost (See Table 14-1)

- In 2014 to 2015 (average annual):
  - The direct and indirect cost of stroke was $45.5 billion (MEPS, NHLBI tabulation; Table 14-1).
  - The estimated direct medical cost of stroke was $28.0 billion. This includes hospital outpatient or office-based provider visits, hospital inpatient stays, ED visits, prescribed medicines, and home health care.[369]
  - The mean expense per patient for direct care for any type of service (including hospital inpatient stays, outpatient and office-based visits, ED visits, prescribed medicines, and home health care) in the United States was estimated at $7902.[370]
- Between 2015 and 2035, total direct medical stroke-related costs are projected to more than double, from $36.7 billion to $94.3 billion, with much of the projected increase in costs arising from those ≥80 years of age.[371]
- The total cost of stroke in 2035 (in 2015 dollars) is projected to be $81.1 billion for NH whites, $32.2 billion for NH blacks, and $16.0 billion for Hispanics.[371]
- During 2001 to 2005, the average cost for outpatient stroke rehabilitation services and medications the first year after inpatient rehabilitation discharge was $11 145. The corresponding average yearly cost of medication was $3376, whereas the average cost of yearly rehabilitation service utilization was $7318.[372]
- In adjusted models that controlled for relevant covariates, the attributable 1-year cost of poststroke aphasia was estimated at $1703 in 2004 dollars.[373]

Social Determinants

- Adverse work conditions, including job loss and unemployment, have been linked to stroke risk. In a cohort of 21 902 Japanese males and 19 826 females followed up for 19 years, job loss (change in job status within the first 5 years of data collection) was associated with a >50% increase in incident stroke and a >2-fold increase in stroke mortality over follow-up.[374] Long work hours have also been linked to stroke. Meta-analytic findings from 24 cohort studies from the United States, Europe, and Australia revealed a dose-response relationship between working longer than 40 hours per week and incident stroke.[374a]
- In ARIC, having smaller social networks (ie, contact with fewer family members, friends, and neighbors) was linked to a 44% higher risk of incident stroke over the 18.6-year follow-up, even after controlling for demographics and other relevant risk factors.[375]
- Findings from MESA have documented linkages between other psychosocial factors, including depressive symptoms, chronic stress, and hostility, and incident stroke, with participants in the highest- versus lowest-scoring categories having a 1.5- to >2-fold increased risk of stroke over a median follow-up of 8.5 years.[376]

Global Burden of Stroke (See Charts 14-11 through 14-16)

Prevalence

- In 2016,[377]
  - — Global prevalence of cerebrovascular disease was 80.1 million people, whereas that of ischemic stroke was 67.6 million and that of hemorrhagic stroke was 15.3 million.
  - — Globally, there was a 2.7% increase in ischemic stroke prevalence from 2006 to 2016 and a 0.1% decrease from 1990 to 2016.
  - — Globally, there was a 1.7% decrease in hemorrhagic stroke prevalence from 2006 to 2016 and a 6.8% decrease from 1990 to 2016.
- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories.[377]
  - — Age-standardized prevalence rates of stroke are higher in Eastern Europe and East Asia (Chart 14-11).
  - — The prevalence of hemorrhagic stroke is high in Eastern Europe, Central Asia, and East Asia (Chart 14-12).
  - — Countries in Eastern Europe, Central Asia, and East Asia have the highest prevalence rates of ischemic stroke (Chart 14-13).

Incidence

- In 2010, there were an estimated 11.6 million incident ischemic strokes and 5.3 million incident hemorrhagic strokes; 63% of ischemic strokes and 80% of hemorrhagic strokes occurred in low- and middle-income countries.[378]
- Between 1990 and 2010[378]:
  - — Incidence of ischemic stroke was significantly reduced by 13% (95% CI, 6%–18%) in high-income countries. No significant change was seen in low- or middle-income countries.
  - — Incidence of hemorrhagic stroke decreased by 19% (95% CI, 1%–15%) in high-income countries. Rates increased by 22% (95% CI, 5%–30%) in low- and middle-income countries, with a 19% increase in those aged <75 years.

Mortality

- In 2016[377]:
  - — There were 5.5 million deaths attributable to cerebrovascular disease worldwide.
  - — The absolute number of cerebrovascular disease deaths worldwide increased 28.2% between 1990 and 2016; however, the age-standardized death rate decreased 36.2%.
  - — The absolute number of cerebrovascular disease deaths worldwide increased 5.1% between 2006 and 2016; however, the age-standardized death rate for the 10-year period decreased 21.0%.
  - — Globally, a total of 2.7 million individuals died of ischemic stroke, and 2.8 million died of hemorrhagic stroke.
- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories.[377]
  - — Eastern Europe, East Asia, and parts of Southeast Asia, Central Asia, and sub-Saharan Africa have the highest rates of stroke mortality (Chart 14-14).
  - — Hemorrhagic stroke mortality is highest in East Asia, the Pacific Islands, Southeast Asia, Central Asia, and parts of sub-Saharan Africa (Chart 14-15).
  - — Countries in Eastern Europe and central East Asia have among the highest mortality rates attributable to ischemic stroke (Chart 14-16).
- In 2010, 39.4 million DALYs were lost because of ischemic stroke and 62.8 million because of

hemorrhagic stroke (64% and 86%, respectively, in low- and middle-income countries).[378]

- In 2010, the mean age of stroke-related death in high-income countries was 80.4 years compared with 72.1 years in low- and middle-income countries.[379]
- Between 1990 and 2010, ischemic stroke mortality decreased 37% in high-income countries and 14% in low- and middle-income countries. Hemorrhagic stroke mortality decreased 38% in high-income countries and 23% in low- and middle-income countries.[378]

Table 14-1. Stroke

Population Group	Prevalence, 2013–2016: Age ≥20 y	New and Recurrent Attacks, All Ages	Mortality, 2016: All Ages*	Hospital Discharges, 2014: All Ages	Cost, 2014–2015
Both sexes	7 000 000 (2.5%)	795 000	142 142	888 000	$45.5 Billion
Males	3 200 000 (2.5%)	370 000 (46.5%)†	59 355 (41.8%)†	434 000	…
Females	3 800 000 (2.6%)	425 000 (53.5%)†	82 787 (58.2%)†	454 000	…
NH white males	2.4%	325 000‡	43 713	…	…
NH white females	2.5%	365 000‡	63 778	…	…
NH black males	3.1%	45 000‡	8115	…	…
NH black females	3.8%	60 000‡	10 074	…	…
Hispanic males	2.0%	…	4798	…	…
Hispanic females	2.2%	…	5485	…	…
NH Asian males	1.1%	…	2268§	…	…
NH Asian females	1.6%	…	2949§	…	…
NH American Indian or Alaska Native	…	…	632	…	…

Ellipses (…) indicate data not available; and NH, non-Hispanic.

*Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total stroke incidence or mortality that applies to males vs females.

‡Estimates include Hispanics and non-Hispanics. Estimates for whites include other nonblack races.

§Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander.

Sources: Prevalence: National Health and Nutrition Examination Survey 2013 to 2016 and National Heart, Lung, and Blood Institute (NHLBI). Percentages for racial/ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2016 US population. Incidence: Greater Cincinnati/Northern Kentucky Stroke Study/National Institutes of Neurological Disorders and Stroke data for 1999 provided on August 1, 2007. US estimates compiled by NHLBI. See also Kissela et al.[380] Data include children. Mortality: Centers for Disease Control and Prevention/National Center for Health Statistics, 2016 Mortality Multiple Cause-of-Death–United States. These data represent underlying cause of death only. Mortality for NH Asians includes Pacific Islanders. Hospital discharges: Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. Data include those inpatients discharged alive, dead, or status unknown. Cost: NHLBI. Data include estimated direct and indirect costs for 2014 to 2015 (average annual).

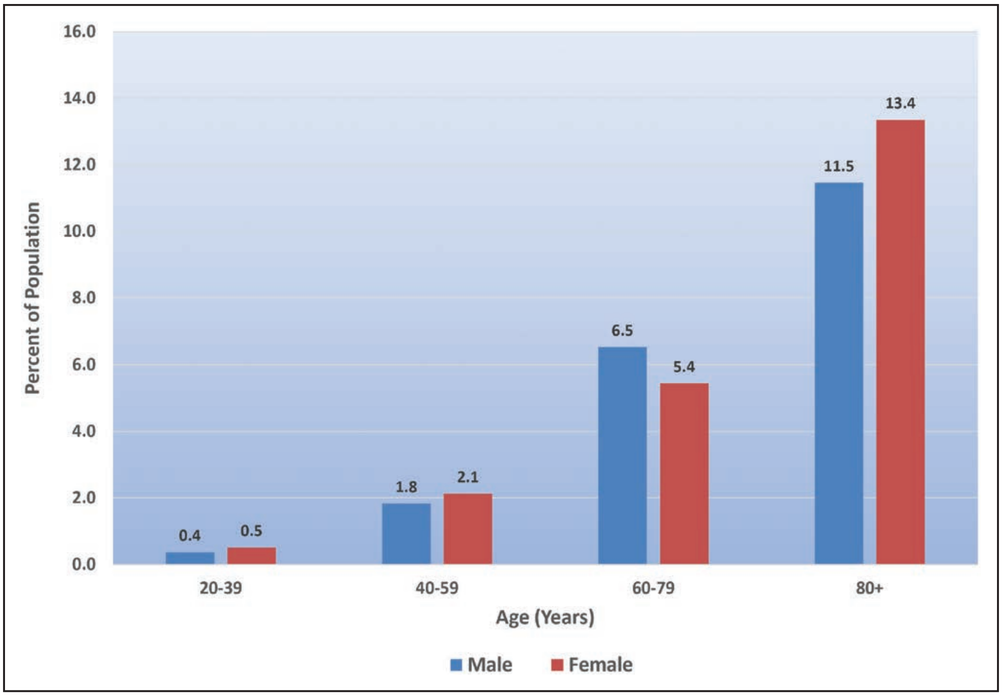

Chart 14-1. Prevalence of stroke by age and sex (NHANES, 2013–2016).
NHANES indicates National Health and Nutrition Examination Survey.
Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

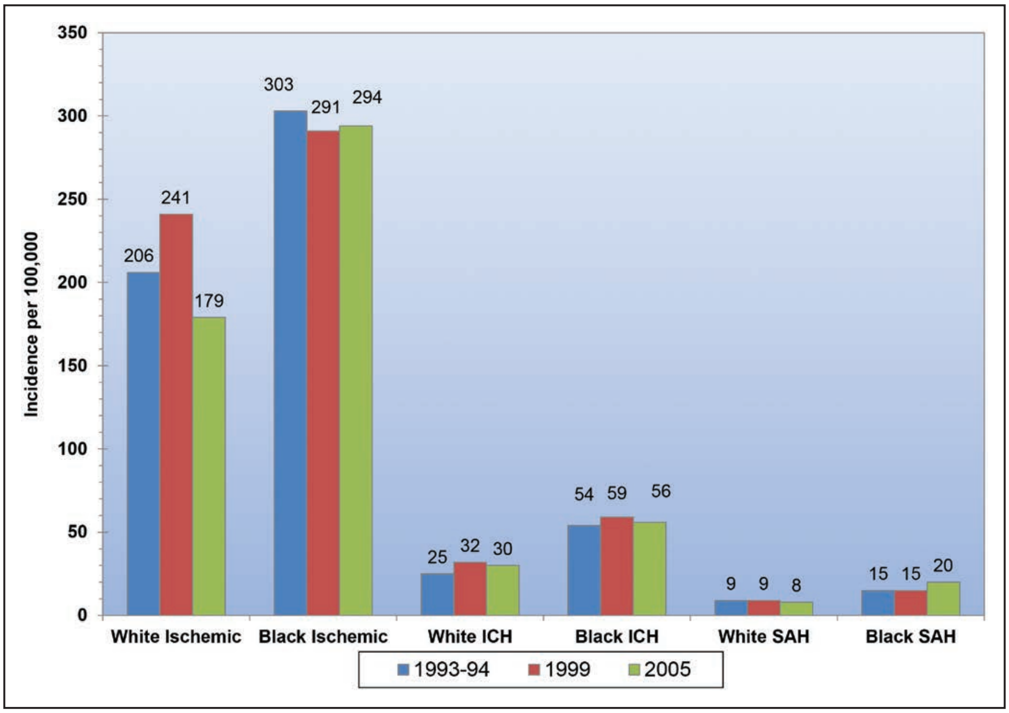

Chart 14-2. Annual age-adjusted incidence of first-ever stroke by race.
Hospital plus out-of-hospital ascertainment, 1993 to 1994, 1999, and 2005.
ICH indicates intracerebral hemorrhage; and SAH, subarachnoid hemorrhage.
Data derived from Kleindorfer et al.[18]

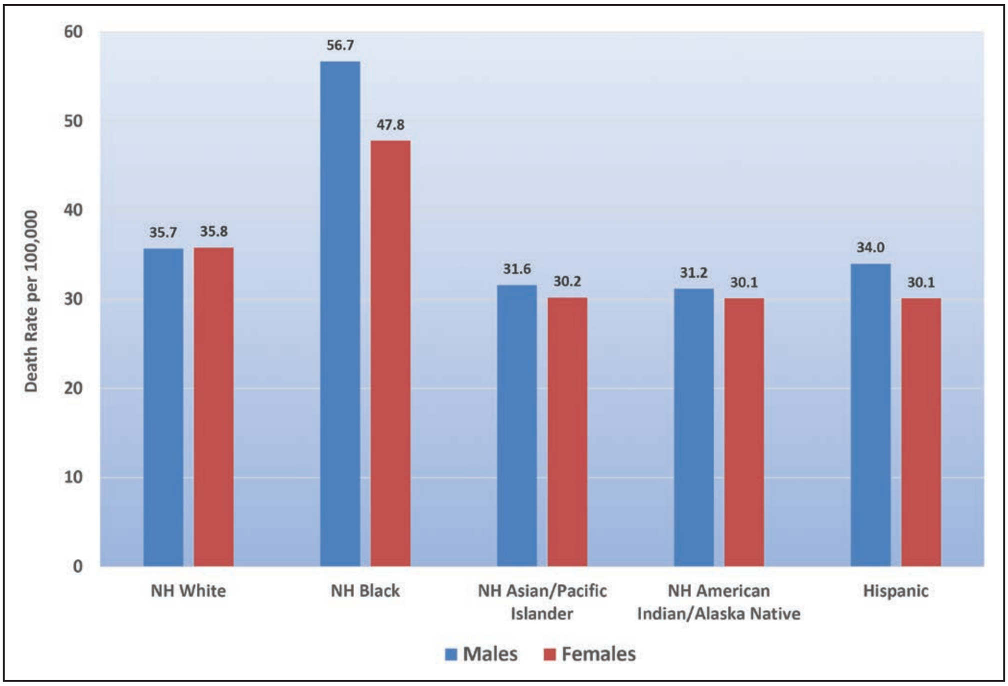

Chart 14-3. Age-adjusted death rates for stroke by sex and race/ethnicity, 2016.

Death rates for the American Indian or Alaska Native and Asian or Pacific Islander populations are known to be underestimated. Stroke includes *International Classification of Diseases, 10th Revision* codes I60 through I69 (cerebrovascular disease). Mortality for NH Asians includes Pacific Islanders.
NH indicates non-Hispanic.
Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

Chart 14-4. Crude stroke mortality rates among young US adults (aged 25–64 years), 2006 to 2016.

Source: Centers for Disease Control and Prevention.[47]

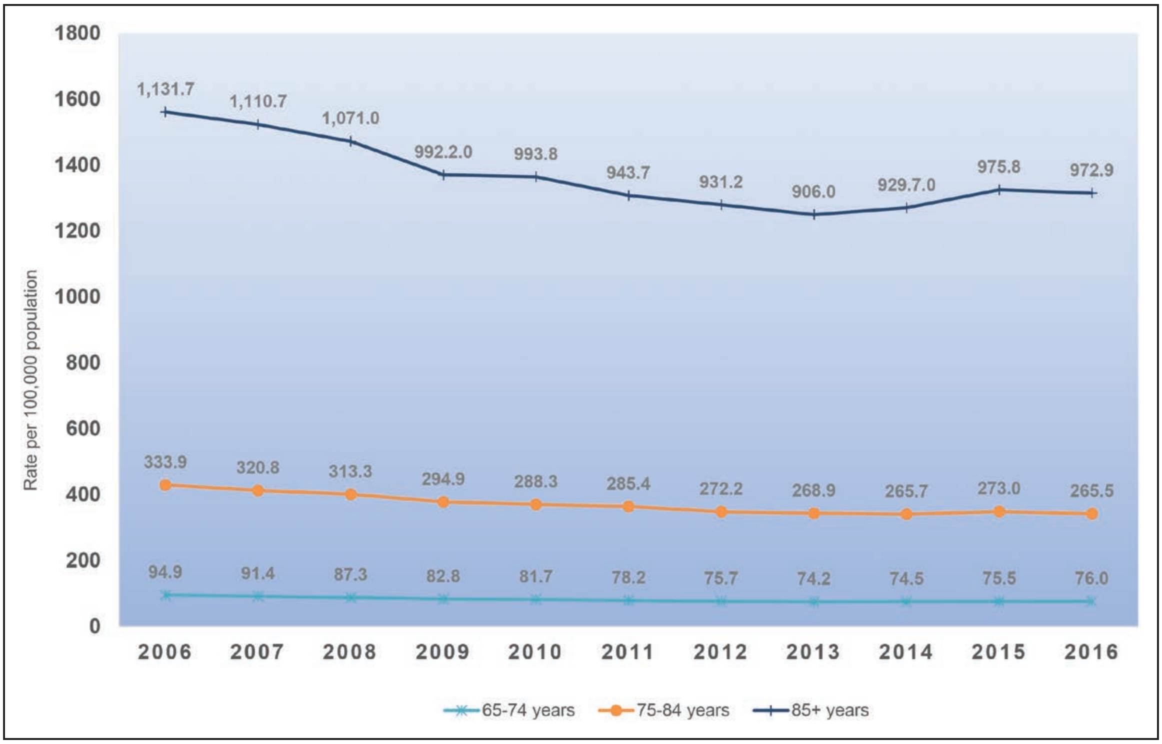

Chart 14-5. Crude stroke mortality rates among older US adults (aged ≥65 years), 2006 to 2016.
Source: Centers for Disease Control and Prevention.[47]

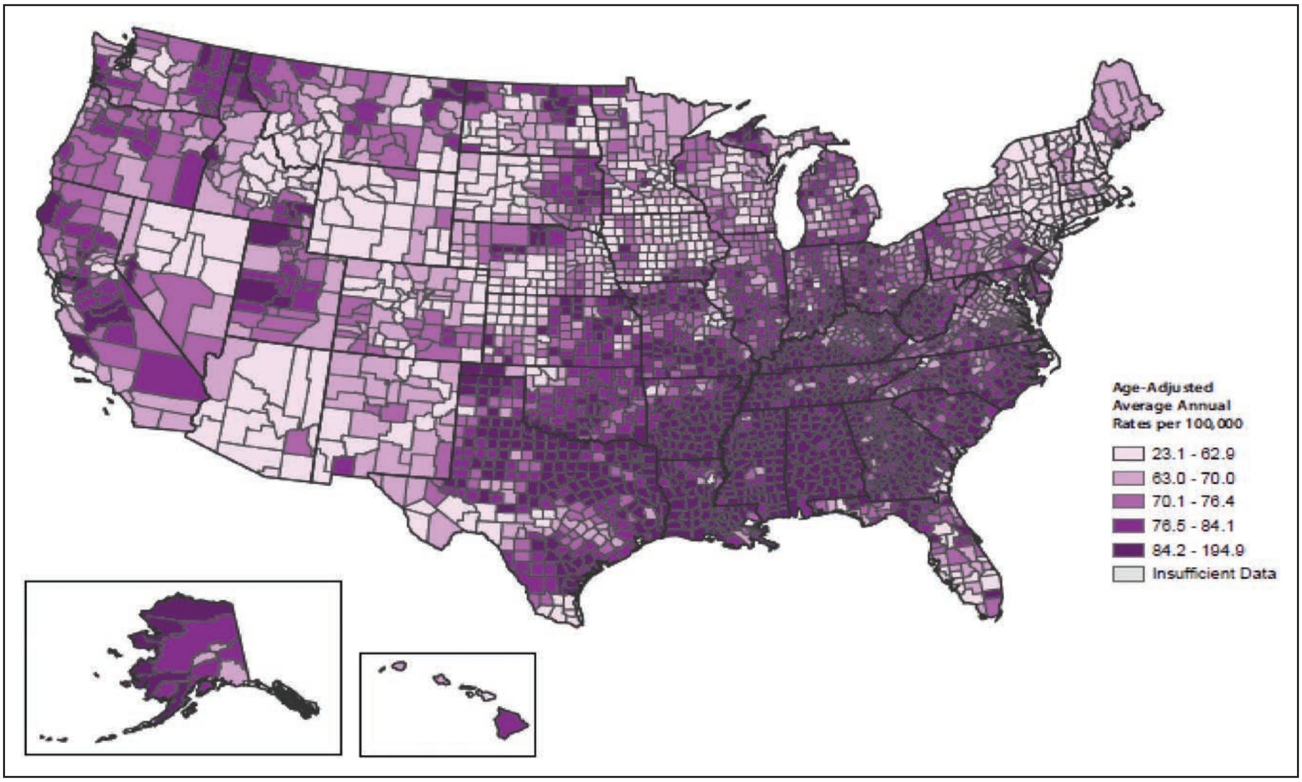

Chart 14-6. Stroke death rates, 2014 through 2016, all ages, by county.
Rates are spatially smoothed to enhance the stability of rates in counties with small populations. *International Classification of Diseases, 10th Revision* codes for stroke: I60 through I69.
Data source: National Vital Statistics System and National Center for Health Statistics.

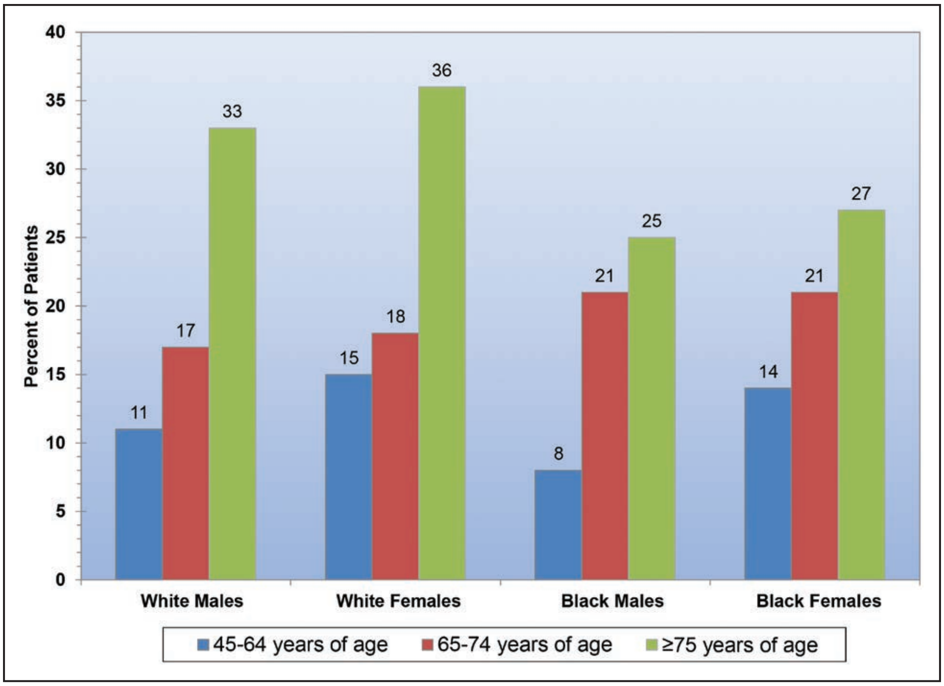

Chart 14-7. Probability of death within 1 year after first stroke.
Source: Pooled data from the Framingham Heart Study, Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis, Coronary Artery Risk Development in Young Adults, and Jackson Heart Study of the National Heart, Lung, and Blood Institute.

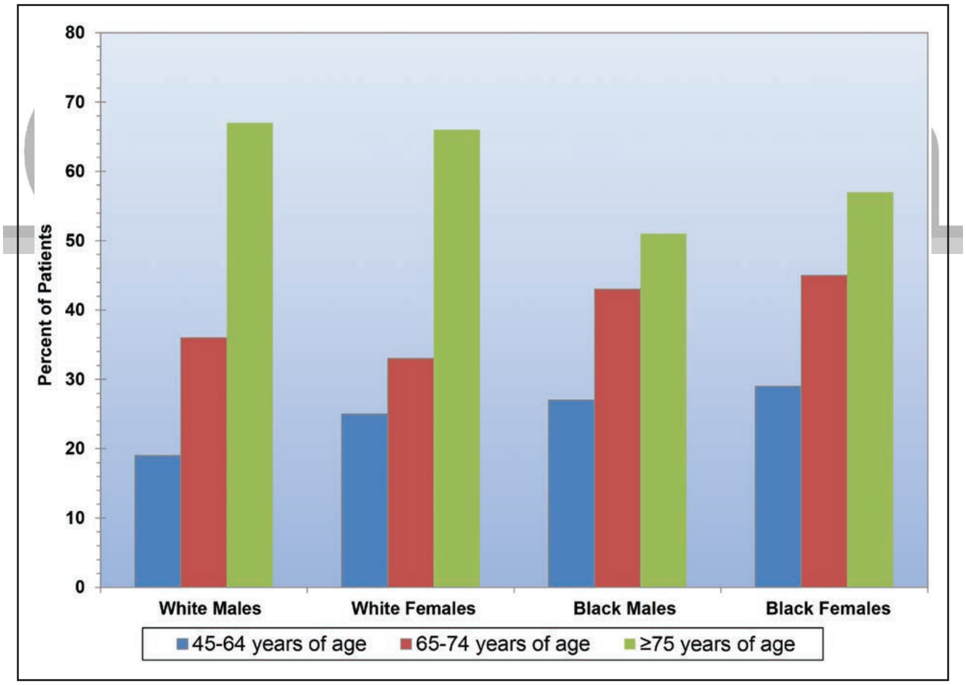

Chart 14-8. Probability of death within 5 years after first stroke.
Source: Pooled data from the Framingham Heart Study, Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis, Coronary Artery Risk Development in Young Adults, and Jackson Heart Study of the National Heart, Lung, and Blood Institute.

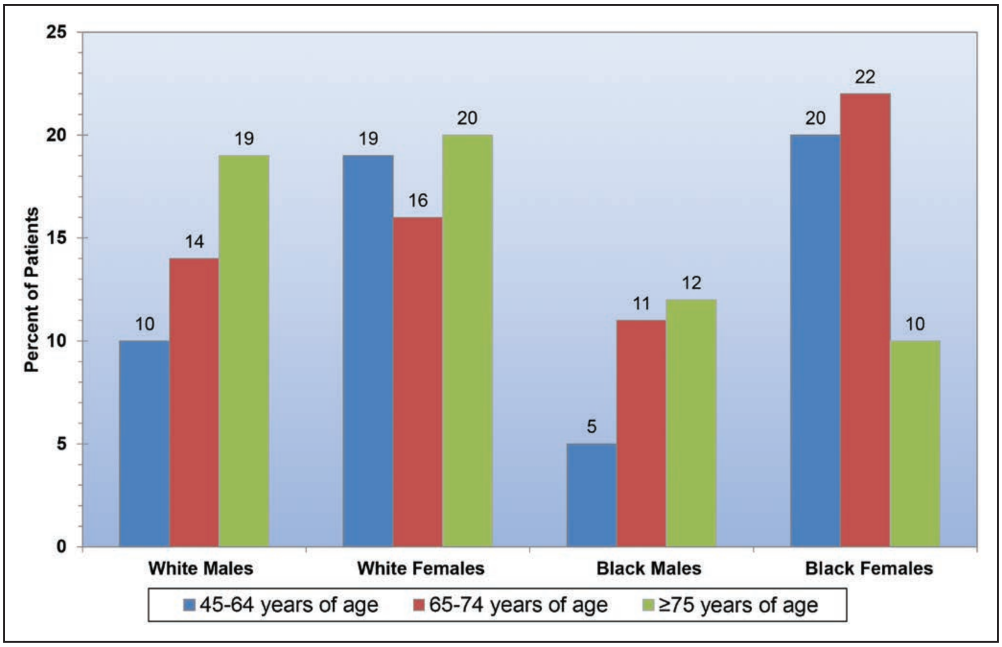

Chart 14-9. Probability of death with recurrent stroke in 5 years after first stroke.
Source: Pooled data from the Framingham Heart Study, Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis, Coronary Artery Risk Development in Young Adults, and Jackson Heart Study of the National Heart, Lung, and Blood Institute.

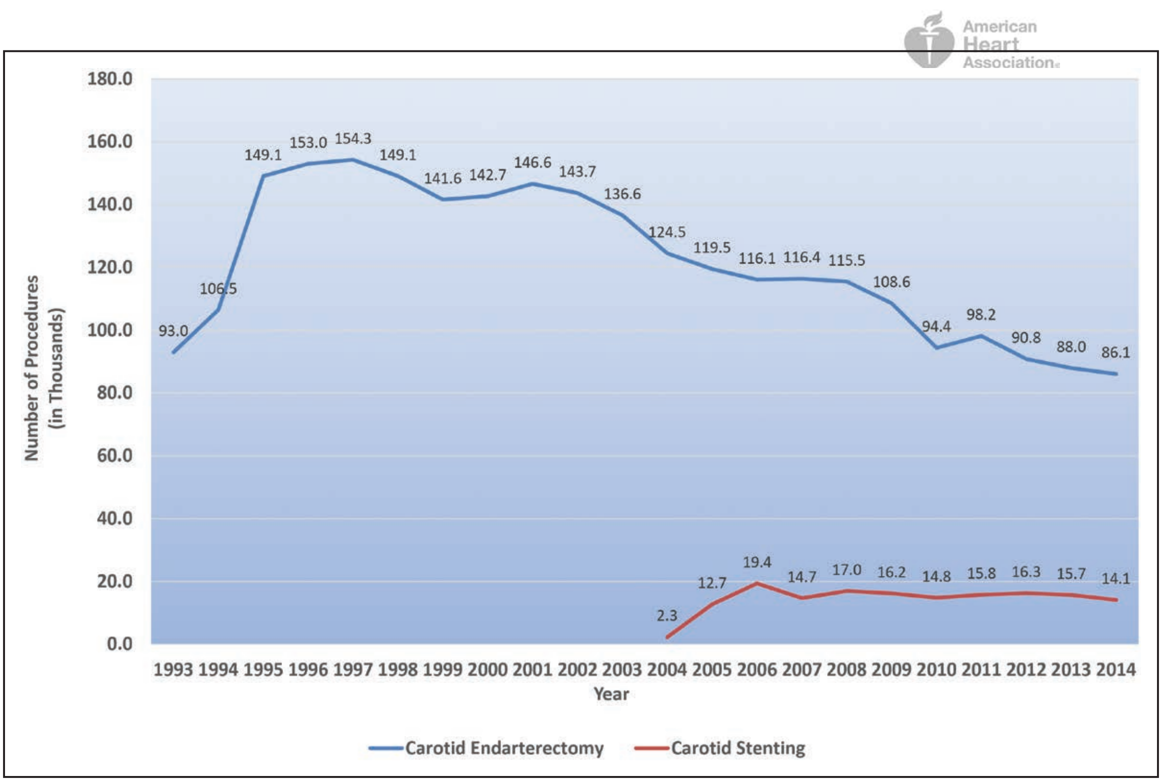

Chart 14-10. Trends in carotid endarterectomy and carotid stenting procedures (United States, 1993–2014).
Carotid endarterectomy: *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) 38.12 (all-listed); carotid stenting: *ICD-9-CM* 00.63 (all-listed).
Source: Nationwide Inpatient Sample, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality.

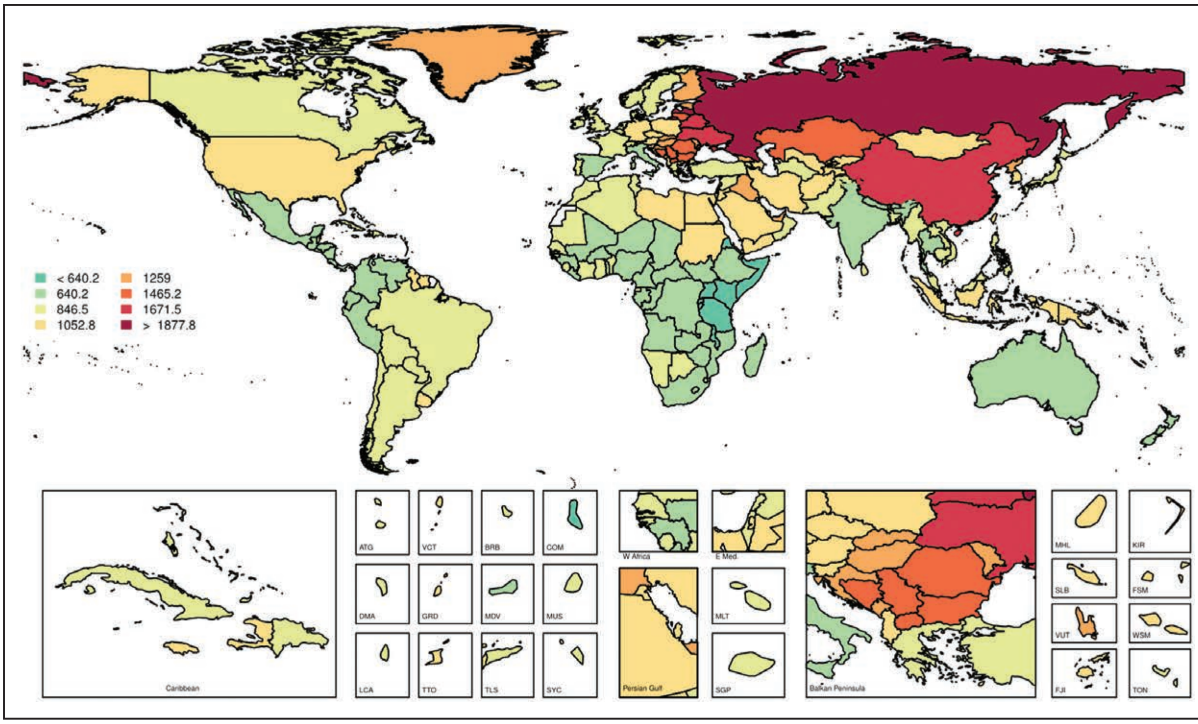

Chart 14-11. Age-standardized global prevalence rates of cerebrovascular disease per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[377] Printed with permission. Copyright © 2017, University of Washington.

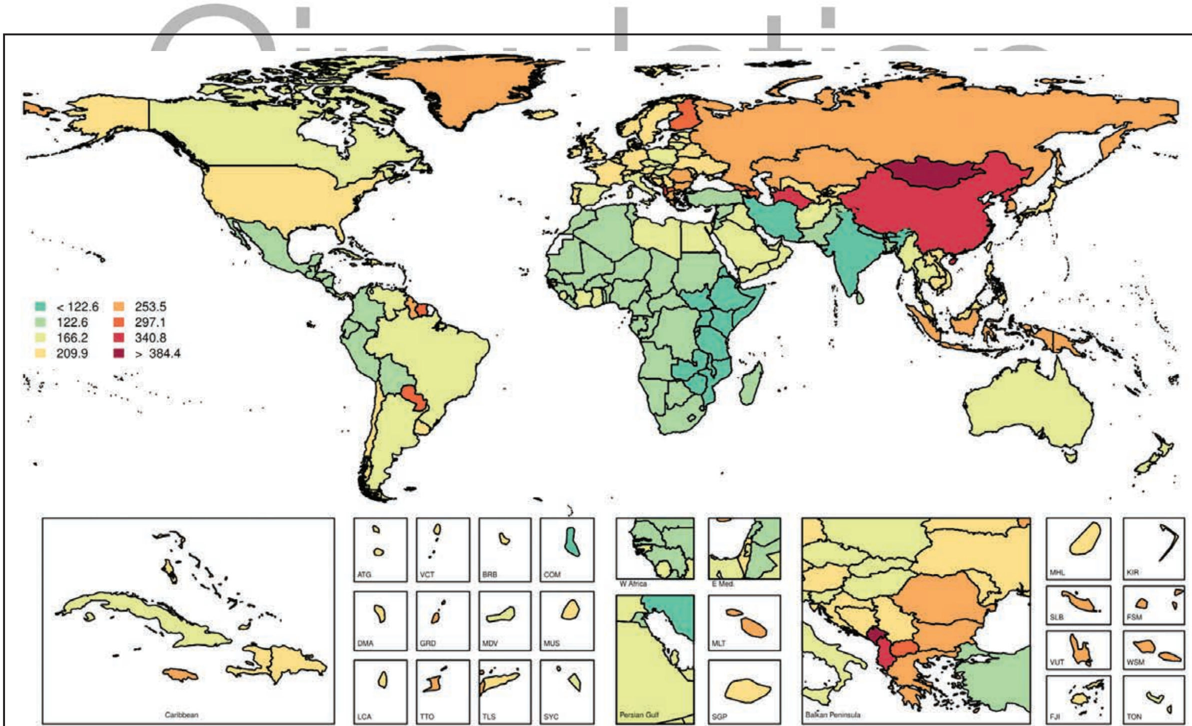

Chart 14-12. Age-standardized global prevalence rates of hemorrhagic stroke per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[377] Printed with permission. Copyright © 2017, University of Washington.

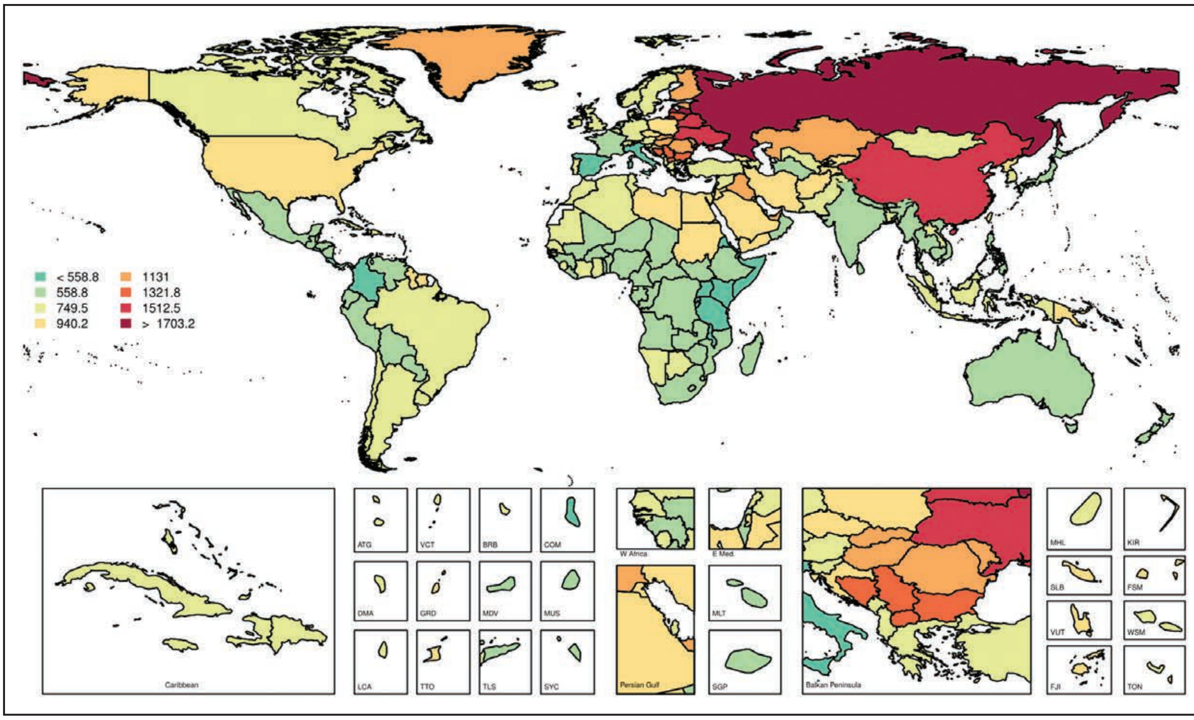

Chart 14-13. Age-standardized global prevalence rates of ischemic stroke per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[377] Printed with permission. Copyright © 2017, University of Washington.

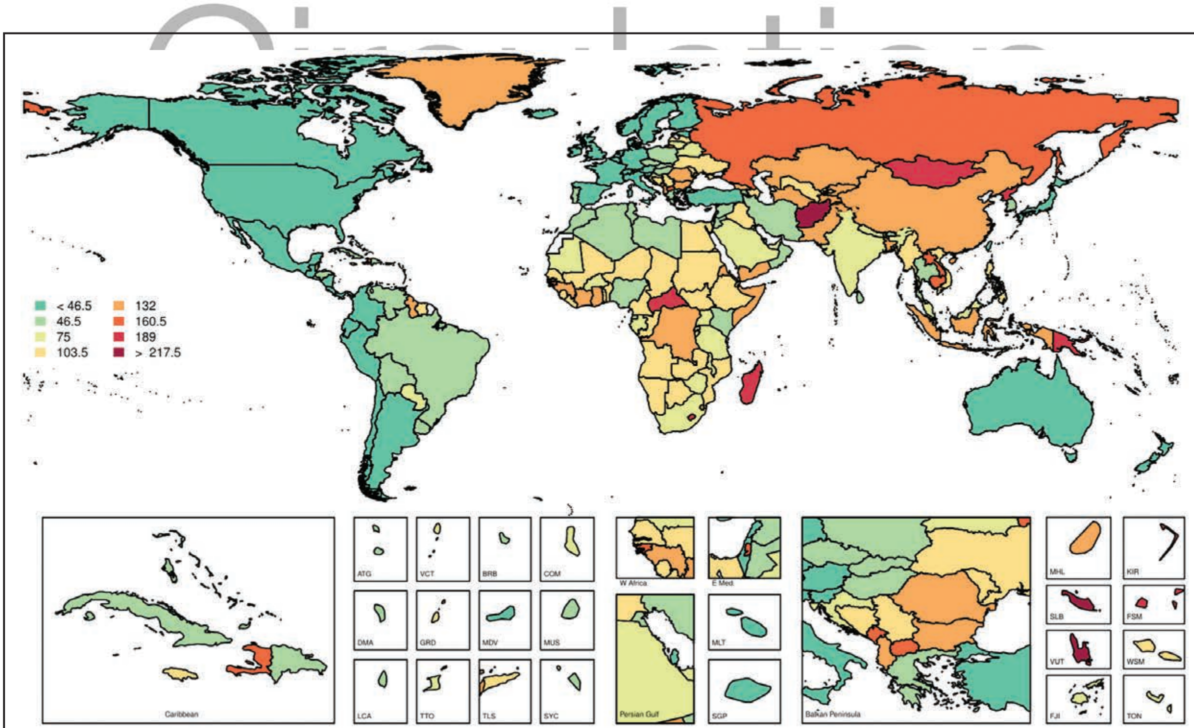

Chart 14-14. Age-standardized global mortality rates of cerebrovascular disease per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[377] Printed with permission. Copyright © 2017, University of Washington.

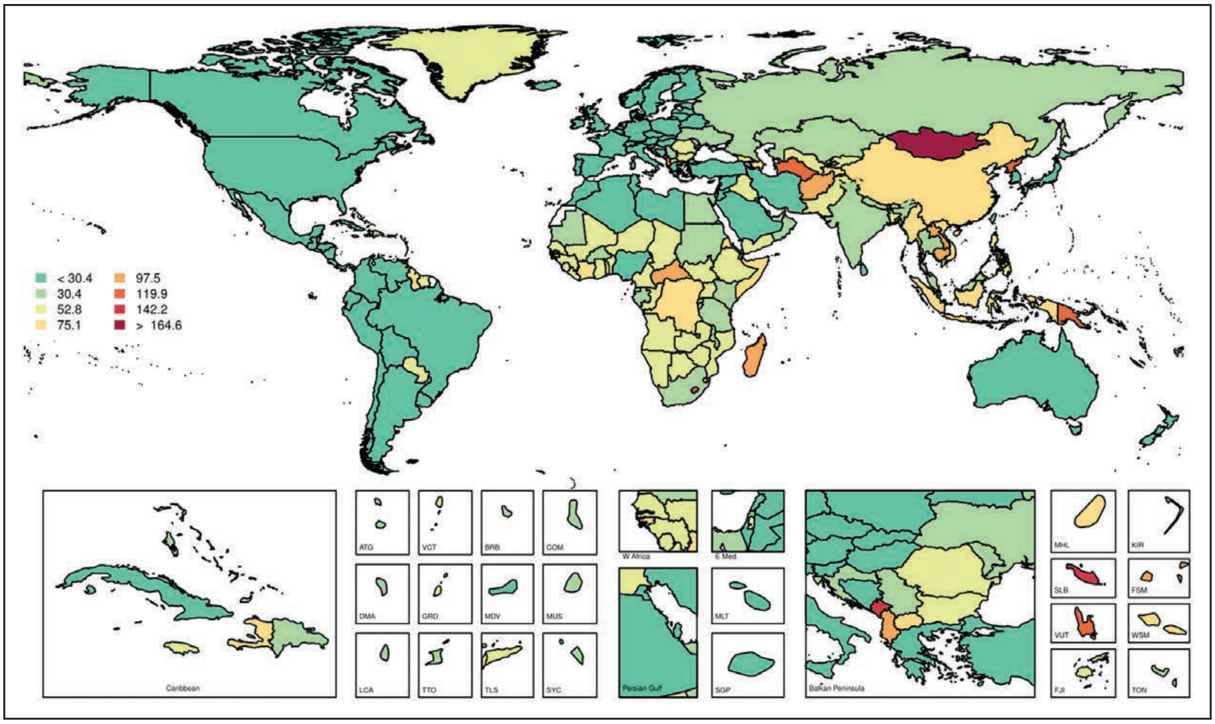

Chart 14-15. Age-standardized global mortality rates of hemorrhagic stroke per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[377] Printed with permission. Copyright © 2017, University of Washington.

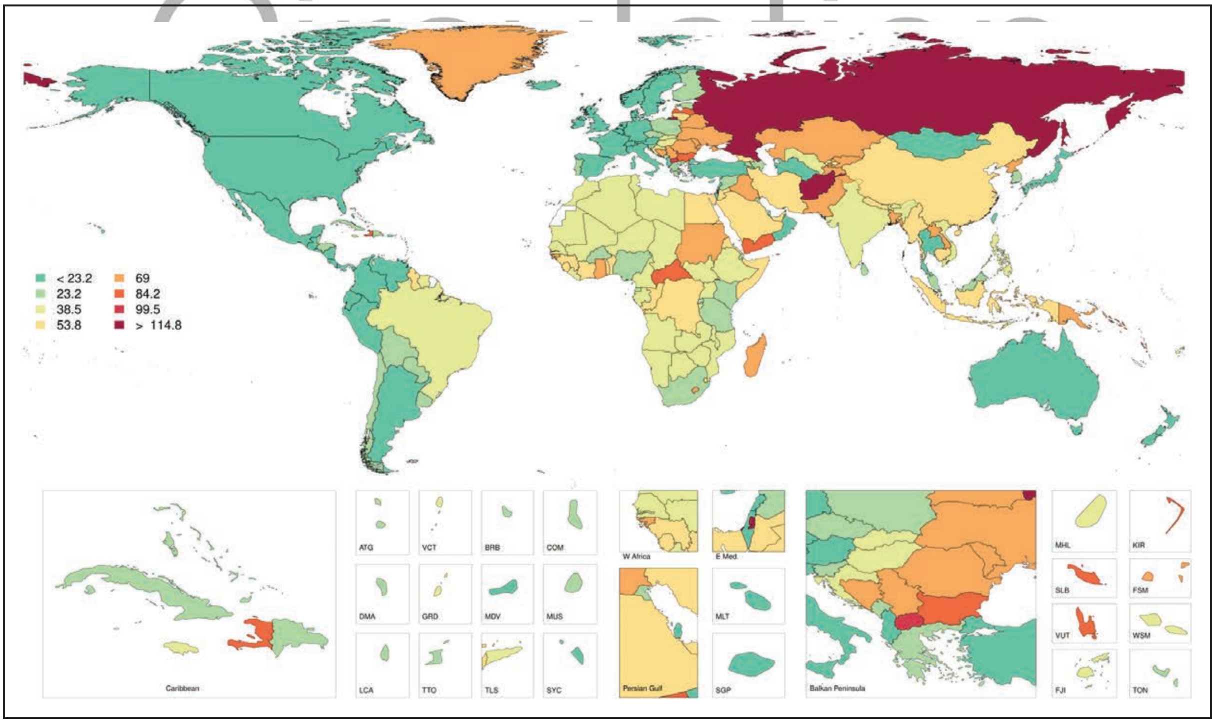

Chart 14-16. Age-standardized global mortality rates of ischemic stroke per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[377] Printed with permission. Copyright © 2017, University of Washington.

REFERENCES

1. 2016 BRFSS survey data and documentation. Centers for Disease Control and Prevention website. https://www.cdc.gov/brfss/annual_data/annual_2016.html. Accessed March 13, 2018.
2. Centers for Disease Control and Prevention. Prevalence of stroke: United States, 2006–2010. *MMWR Morb Mortal Wkly Rep*. 2012;61:379–382.
3. Howard VJ, McClure LA, Meschia JF, Pulley L, Orr SC, Friday GH. High prevalence of stroke symptoms among persons without a diagnosis of stroke or transient ischemic attack in a general population: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Arch Intern Med*. 2006;166:1952–1958. doi: 10.1001/archinte.166.18.1952
4. Ovbiagele B, Goldstein LB, Higashida RT, Howard VJ, Johnston SC, Khavjou OA, Lackland DT, Lichtman JH, Mohl S, Sacco RL, Saver JL, Trogdon JG; on behalf of the American Heart Association Advocacy Coordinating Committee and Stroke Council. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association [published correction appears in *Stroke*. 2015;46:e179]. *Stroke*. 2013;44:2361–2375. doi: 10.1161/STR.0b031829734f2
5. Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, Khatiwoda A, Lisabeth L. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol*. 2008;7:915–926. doi: 10.1016/S1474-4422(08)70193-5
6. George MG, Tong X, Bowman BA. Prevalence of cardiovascular risk factors and strokes in younger adults. *JAMA Neurol*. 2017;74:695–703. doi: 10.1001/jamaneurol.2017.0020
7. Koton S, Schneider AL, Rosamond WD, Shahar E, Sang Y, Gottesman RF, Coresh J. Stroke incidence and mortality trends in US communities, 1987 to 2011. *JAMA*. 2014;312:259–268. doi: 10.1001/jama.2014.7692
8. Morgenstern LB, Smith MA, Sánchez BN, Brown DL, Zahuranec DB, Garcia N, Kerber KA, Skolarus LE, Meurer WJ, Burke JF, Adelman EE, Baek J, Lisabeth LD. Persistent ischemic stroke disparities despite declining incidence in Mexican Americans. *Ann Neurol*. 2013;74:778–785. doi: 10.1002/ana.23972
9. Zahuranec DB, Lisabeth LD, Sánchez BN, Smith MA, Brown DL, Garcia NM, Skolarus LE, Meurer WJ, Burke JF, Adelman EE, Morgenstern LB. Intracerebral hemorrhage mortality is not changing despite declining incidence. *Neurology*. 2014;82:2180–2186. doi: 10.1212/WNL.0000000000000519
10. Carandang R, Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Kannel WB, Wolf PA. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. *JAMA*. 2006;296:2939–2946. doi: 10.1001/jama.296.24.2939
11. Vangen-Lønne AM, Wilsgaard T, Johnsen SH, Løchen ML, Njølstad I, Mathiesen EB. Declining incidence of ischemic stroke: what is the impact of changing risk factors? The Tromsø study 1995 to 2012. *Stroke*. 2017;48:544–550. doi: 10.1161/STROKEAHA.116.014377
12. Howard VJ, Kleindorfer DO, Judd SE, McClure LA, Safford MM, Rhodes JD, Cushman M, Moy CS, Soliman EZ, Kissela BM, Howard G. Disparities in stroke incidence contributing to disparities in stroke mortality. *Ann Neurol*. 2011;69:619–627. doi: 10.1002/ana.22385
13. Kleindorfer D, Broderick J, Khoury J, Flaherty M, Woo D, Alwell K, Moomaw CJ, Schneider A, Miller R, Shukla R, Kissela B. The unchanging incidence and case-fatality of stroke in the 1990s: a population-based study. *Stroke*. 2006;37:2473–2478. doi: 10.1161/01.STR.0000242766.65550.92
14. Morgenstern LB, Smith MA, Lisabeth LD, Risser JM, Uchino K, Garcia N, Longwell PJ, McFarling DA, Akuwumi O, Al-Wabil A, Al-Senani F, Brown DL, Moyé LA. Excess stroke in Mexican Americans compared with non-Hispanic whites: the Brain Attack Surveillance in Corpus Christi Project. *Am J Epidemiol*. 2004;160:376–383. doi: 10.1093/aje/kwh225
15. White H, Boden-Albala B, Wang C, Elkind MS, Rundek T, Wright CB, Sacco RL. Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. *Circulation*. 2005;111:1327–1331. doi: 10.1161/01.CIR.0000157736.19739.D0
16. Zhang Y, Galloway JM, Welty TK, Wiebers DO, Whisnant JP, Devereux RB, Kizer JR, Howard BV, Cowan LD, Yeh J, Howard WJ, Wang W, Best L, Lee ET. Incidence and risk factors for stroke in American Indians: the Strong Heart Study. *Circulation*. 2008;118:1577–1584. doi: 10.1161/CIRCULATIONAHA.108.772285
17. Howard G, Cushman M, Howard VJ, Kissela BM, Kleindorfer DO, Moy CS, Switzer J, Woo D. Risk factors for intracerebral hemorrhage: the REasons for Geographic and Racial Differences in Stroke (REGARDS) study [published correction appears in *Stroke*. 2013;44:e63]. *Stroke*. 2013;44:1282–1287. doi: 10.1161/STROKEAHA.111.000529
18. Kleindorfer DO, Khoury J, Moomaw CJ, Alwell K, Woo D, Flaherty ML, Khatri P, Adeoye O, Ferioli S, Broderick JP, Kissela BM. Stroke incidence is decreasing in whites but not in blacks: a population-based estimate of temporal trends in stroke incidence from the Greater Cincinnati/Northern Kentucky Stroke Study. *Stroke*. 2010;41:1326–1331. doi: 10.1161/STROKEAHA.109.575043
19. Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, Wolf PA. The lifetime risk of stroke: estimates from the Framingham Study. *Stroke*. 2006;37:345–350. doi: 10.1161/01.STR.0000199613.38911.b2
20. Hollander M, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A, Breteler MM. Incidence, risk, and case fatality of first ever stroke in the elderly population: the Rotterdam Study. *J Neurol Neurosurg Psychiatry*. 2003;74:317–321.
21. Lewsey JD, Gillies M, Jhund PS, Chalmers JW, Redpath A, Briggs A, Walters M, Langhorne P, Capewell S, McMurray JJ, Macintyre K. Sex differences in incidence, mortality, and survival in individuals with stroke in Scotland, 1986 to 2005. *Stroke*. 2009;40:1038–1043. doi: 10.1161/STROKEAHA.108.542787
22. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, Redgrave JN, Bull LM, Welch SJ, Cuthbertson FC, Binney LE, Gutnikov SA, Anslow P, Banning AP, Mant D, Mehta Z; Oxford Vascular Study. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *Lancet*. 2005;366:1773–1783. doi: 10.1016/S0140-6736(05)67702-1
23. Sealy-Jefferson S, Wing JJ, Sánchez BN, Brown DL, Meurer WJ, Smith MA, Morgenstern LB, Lisabeth LD. Age- and ethnic-specific sex differences in stroke risk. *Gend Med*. 2012;9:121–128. doi: 10.1016/j.genm.2012.02.002
24. Vega T, Zurriaga O, Ramos JM, Gil M, Alamo R, Lozano JE, López A, Miralles MT, Vaca P, Alvarez Mdel M; Group of Research for the RECENT Project. Stroke in Spain: epidemiologic incidence and patterns; a health sentinel network study. *J Stroke Cerebrovasc Dis*. 2009;18:11–16. doi: 10.1016/j.jstrokecerebrovasdis.2008.06.010
25. Madsen TE, Khoury J, Alwell K, Moomaw CJ, Rademacher E, Flaherty ML, Woo D, Mackey J, De Los Rios La Rosa F, Martini S, Ferioli S, Adeoye O, Khatri P, Broderick JP, Kissela BM, Kleindorfer D. Sex-specific stroke incidence over time in the Greater Cincinnati/Northern Kentucky Stroke Study. *Neurology*. 2017;89:990–996. doi: 10.1212/WNL.0000000000004325
26. Johnston SC, Fayad PB, Gorelick PB, Hanley DF, Shwayder P, van Husen D, Weiskopf T. Prevalence and knowledge of transient ischemic attack among US adults. *Neurology*. 2003;60:1429–1434.
27. Jiang B, Sun H, Ru X, Sun D, Chen Z, Liu H, Li Y, Zhang M, Wang L, Wang L, Wu S, Wang W. Prevalence, incidence, prognosis, early stroke risk, and stroke-related prognostic factors of definite or probable transient ischemic attacks in China, 2013. *Front Neurol*. 2017;8:309. doi: 10.3389/fneur.2017.00309
28. Béjot Y, Brenière C, Graber M, Garnier L, Durier J, Blanc-Labarre C, Delpont B, Giroud M. Contemporary epidemiology of transient ischemic attack in Dijon, France (2013-2015). *Neuroepidemiology*. 2017;49:135–141. doi: 10.1159/000484638
29. Kleindorfer D, Panagos P, Pancioli A, Khoury J, Kissela B, Woo D, Schneider A, Alwell K, Jauch E, Miller R, Moomaw C, Shukla R, Broderick JP. Incidence and short-term prognosis of transient ischemic attack in a population-based study. *Stroke*. 2005;36:720–723. doi: 10.1161/01.STR.0000158917.59233.b7
30. Hankey GJ. Impact of treatment of people with transient ischaemic attacks on stroke incidence and public health. *Cerebrovasc Dis*. 1996;6(suppl 1):26–33.
31. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA*. 2000;284:2901–2906.
32. Wu CM, McLaughlin K, Lorenzetti DL, Hill MD, Manns BJ, Ghali WA. Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. *Arch Intern Med*. 2007;167:2417–2422. doi: 10.1001/archinte.167.22.2417
33. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol*. 2007;6:1063–1072. doi: 10.1016/S1474-4422(07)70274-0
34. Clark TG, Murphy MF, Rothwell PM. Long term risks of stroke, myocardial infarction, and vascular death in “low risk” patients with a non-recent transient ischaemic attack. *J Neurol Neurosurg Psychiatry*. 2003;74:577–580.
35. Luengo-Fernandez R, Paul NL, Gray AM, Pendlebury ST, Bull LM, Welch SJ, Cuthbertson FC, Rothwell PM; on behalf of the Oxford Vascular Study. Population-based study of disability and institutionalization after transient

ischemic attack and stroke: 10-year results of the Oxford Vascular Study. *Stroke*. 2013;44:2854–2861. doi: 10.1161/STROKEAHA.113.001584
36. Brazzelli M, Chappell FM, Miranda H, Shuler K, Dennis M, Sandercock PA, Muir K, Wardlaw JM. Diffusion-weighted imaging and diagnosis of transient ischemic attack. *Ann Neurol*. 2014;75:67–76. doi: 10.1002/ana.24026
37. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, Hatsukami TS, Higashida RT, Johnston SC, Kidwell CS, Lutsep HL, Miller E, Sacco RL. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. *Stroke*. 2009;40:2276–2293. doi: 10.1161/STROKEAHA.108.192218
38. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:2064–2089. doi: 10.1161/STR.0b013e318296aeca
39. Callaly E, Ni Chroinin D, Hannon N, Marnane M, Akijian L, Sheehan O, Merwick A, Hayden D, Horgan G, Duggan J, Murphy S, O'Rourke K, Dolan E, Williams D, Kyne L, Kelly PJ. Rates, predictors, and outcomes of early and late recurrence after stroke: the North Dublin Population Stroke study. *Stroke*. 2016;47:244–246. doi: 10.1161/STROKEAHA.115.011248
40. Fullerton HJ, Wintermark M, Hills NK, Dowling MM, Tan M, Rafay MF, Elkind MS, Barkovich AJ, deVeber GA; and the VIPS Investigators. Risk of recurrent arterial ischemic stroke in childhood: a prospective international study. *Stroke*. 2016;47:53–59. doi: 10.1161/STROKEAHA.115.011173
41. Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. *Stroke*. 2011;42:1489–1494. doi: 10.1161/STROKEAHA.110.602615
42. Pennlert J, Eriksson M, Carlberg B, Wiklund PG. Long-term risk and predictors of recurrent stroke beyond the acute phase. *Stroke*. 2014;45:1839–1841. doi: 10.1161/STROKEAHA.114.005060
43. Howard G, Kissela BM, Kleindorfer DO, McClure LA, Soliman EZ, Judd SE, Rhodes JD, Cushman M, Moy CS, Sands KA, Howard VJ. Differences in the role of black race and stroke risk factors for first vs. recurrent stroke. *Neurology*. 2016;86:637–642. doi: 10.1212/WNL.0000000000002376
44. Jin P, Matos Diaz I, Stein L, Thaler A, Tuhrim S, Dhamoon MS. Intermediate risk of cardiac events and recurrent stroke after stroke admission in young adults. *Int J Stroke*. 2017;13:576–584. doi: 10.1177/1747493017733929
45. Boulanger M, Bejot Y, Rothwell PM, Touze E. Long-term risk of myocardial infarction compared to recurrent stroke after transient ischemic attack and ischemic stroke: systematic review and meta-analysis. *J Am Heart Assoc*. 2018;7:e007267. doi: 10.1161/JAHA.117.007267
46. Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, Howard G, Kissela BM, Kittner SJ, Lichtman JH, Lisabeth LD, Schwamm LH, Smith EE, Towfighi A; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; Council on Functional Genomics and Translational Biology. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:315–353. doi: 10.1161/01.str.0000437068.30550.cf
47. Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying cause of death, 1999-2016. CDC WONDER Online Database [database online]. Released January 2013. Atlanta, GA: Centers for Disease Control and Prevention. https://wonder.cdc.gov/ucd-icd10.html. Accessed March 13, 2018.
48. Kochanek KD, Murphy SL, Xu JQ, Arias E. Mortality in the United States, 2016. NCHS Data Brief No. 293. Hyattsville, MD: National Center for Health Statistics; December 2017.
49. Howard G, Evans GW, Pearce K, Howard VJ, Bell RA, Mayer EJ, Burke GL. Is the stroke belt disappearing? An analysis of racial, temporal, and age effects. *Stroke*. 1995;26:1153–1158.
50. Gilsanz P, Mayeda ER, Glymour MM, Quesenberry CP, Whitmer RA. Association between birth in a high stroke mortality state, race, and risk of dementia. *JAMA Neurol*. 2017;74:1056–1062. doi: 10.1001/jamaneurol.2017.1553
51. Lackland DT. Impact of birth place and geographic location on risk disparities in cerebrovascular disease: implications for future research. *JAMA Neurol*. 2017;74:1043–1045. doi: 10.1001/jamaneurol.2017.1560
52. Howard VJ, McClure LA, Glymour MM, Cunningham SA, Kleindorfer DO, Crowe M, Wadley VG, Peace F, Howard G, Lackland DT. Effect of duration and age at exposure to the Stroke Belt on incident stroke in adulthood. *Neurology*. 2013;80:1655–1661. doi: 10.1212/WNL.0b013e3182904d59
53. Gillum RF, Kwagyan J, Obisesan TO. Ethnic and geographic variation in stroke mortality trends. *Stroke*. 2011;42:3294–3296. doi: 10.1161/STROKEAHA.111.625343
54. Schieb LJ, Ayala C, Valderrama AL, Veazie MA. Trends and disparities in stroke mortality by region for American Indians and Alaska Natives. *Am J Public Health*. 2014;104 Suppl 3:S368–S376. doi: 10.2105/AJPH.2013.301698
55. Pearson-Stuttard J, Guzman-Castillo M, Penalvo JL, Rehm CD, Afshin A, Danaei G, Kypridemos C, Gaziano T, Mozaffarian D, Capewell S, O'Flaherty M. Modeling future cardiovascular disease mortality in the United States: national trends and racial and ethnic disparities. *Circulation*. 2016;133:967–978. doi: 10.1161/CIRCULATIONAHA.115.019904
56. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, Mensah GA, Norrving B, Shiue I, Ng M, Estep K, Cercy K, Murray CJL, Forouzanfar MH; Global Burden of Diseases, Injuries and Risk Factors Study 2013 and Stroke Experts Writing Group. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol*. 2016;15:913–924. doi: 10.1016/S1474-4422(16)30073-4
57. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:1269–1324. doi: 10.1161/HYP.0000000000000066
58. Reboussin DM, Allen NB, Griswold ME, Guallar E, Hong Y, Lackland DT, Miller EPR 3rd, Polonsky T, Thompson-Paul AM, Vupputuri S. Systematic review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:e116–e135. doi: 10.1161/HYP.0000000000000067
59. Weiss J, Freeman M, Low A, Fu R, Kerfoot A, Paynter R, Motu'apuaka M, Kondo K, Kansagara D. Benefits and harms of intensive blood pressure treatment in adults aged 60 years or older: a systematic review and meta-analysis. *Ann Intern Med*. 2017;166:419–429. doi: 10.7326/M16-1754
60. Lackland DT, Carey RM, Conforto AB, Rosendorff C, Whelton PK, Gorelick PB. Implications of recent clinical trials and hypertension guidelines on stroke and future cerebrovascular research. *Stroke*. 2018;49:772–779. doi: 10.1161/STROKEAHA.117.019379
61. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387:957–967. doi: 10.1016/S0140-6736(15)01225-8
62. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels - updated overview and meta-analyses of randomized trials. *J Hypertens*. 2016;34:613–622. doi: 10.1097/HJH.0000000000000881
63. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, Woodward M, MacMahon S, Turnbull F, Hillis GS, Chalmers J, Mant J, Salam A, Rahimi K, Perkovic V, Rodgers A. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet*. 2016;387:435–443. doi: 10.1016/S0140-6736(15)00805-3
64. Law M, Morris J, Wald N. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomized trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:b1665. doi: 10.1136/bmj.b1665

65. Verdecchia P, Angeli F, Gentile G, Reboldi G. More versus less intensive blood pressure-lowering strategy: cumulative evidence and trial sequential analysis. *Hypertension*. 2016;68:642–653. doi: 10.1161/HYPERTENSIONAHA.116.07608
66. Bangalore S, Toklu B, Gianos E, Schwartzbard A, Weintraub H, Ogedegbe G, Messerli FH. Optimal systolic blood pressure target after SPRINT: insights from a network meta-analysis of randomized trials. *Am J Med*. 2017;130:707–719.e8. doi: 10.1016/j.amjmed.2017.01.004
67. Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, He H, Chen J, Whelton PK, He J. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. *JAMA Cardiol*. 2017;2:775–781. doi: 10.1001/jamacardio.2017.1421
68. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PWF. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2014;129(suppl 2):S75–S75]. *Circulation*. 2014;129(suppl 2):S49–S73. doi: 10.1161/01.cir.0000437741.48606.98
69. Perkovic V, Rodgers A. Redefining blood-pressure targets: SPRINT starts the marathon. *N Engl J Med*. 2015;373:2175–2178. doi: 10.1056/NEJMe1513301
70. The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575–1585. doi: 10.1056/NEJMoa1001286
71. Lackland DT, Voeks JH, Boan AD. Hypertension and stroke: an appraisal of the evidence and implications for clinical management. *Expert Rev Cardiovasc Ther*. 2016;14:609–616. doi: 10.1586/14779072.2016.1143359
72. White CL, Pergola PE, Szychowski JM, Talbert R, Cervantes-Arriaga A, Clark HD, Del Brutto OH, Godoy IE, Hill MD, Pelegrí A, Sussman CR, Taylor AA, Valdivia J, Anderson DC, Conwit R, Benavente OR; for the SPS3 Investigators. Blood pressure after recent stroke: baseline findings from the Secondary Prevention of Small Subcortical Strokes trial. *Am J Hypertens*. 2013;26:1114–1122. doi: 10.1093/ajh/hpt076
73. Huang Y, Cai X, Li Y, Su L, Mai W, Wang S, Hu Y, Wu Y, Xu D. Prehypertension and the risk of stroke: a meta-analysis. *Neurology*. 2014;82:1153–1161. doi: 10.1212/WNL.0000000000000268
74. SPS3 Study Group. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial [published correction appears in Lancet. 2013;382:506]. *Lancet*. 2013;382:507–515. doi: 10.1016/S0140-6736(13)60852-1
75. Odden MC, McClure LA, Sawaya BP, White CL, Peralta CA, Field TS, Hart RG, Benavente OR, Pergola PE. Achieved blood pressure and outcomes in the Secondary Prevention of Small Subcortical Strokes trial. *Hypertension*. 2016;67:63–69. doi: 10.1161/HYPERTENSIONAHA.115.06480
76. Walsh KB, Woo D, Sekar P, Osborne J, Moomaw CJ, Langefeld CD, Adeoye O. Untreated hypertension: a powerful risk factor for lobar and nonlobar intracerebral hemorrhage in whites, blacks, and Hispanics. *Circulation*. 2016;134:1444–1452. doi: 10.1161/CIRCULATIONAHA.116.024073
77. Pergola PE, White CL, Szychowski JM, Talbert R, Brutto OD, Castellanos M, Graves JW, Matamala G, Pretell EJ, Yee J, Rebello R, Zhang Y, Benavente OR; SPS3 Investigators. Achieved blood pressures in the Secondary Prevention of Small Subcortical Strokes (SPS3) study: challenges and lessons learned. *Am J Hypertens*. 2014;27:1052–1060. doi: 10.1093/ajh/hpu027
78. Khoury JC, Kleindorfer D, Alwell K, Moomaw CJ, Woo D, Adeoye O, Flaherty ML, Khatri P, Ferioli S, Broderick JP, Kissela BM. Diabetes mellitus: a risk factor for ischemic stroke in a large biracial population. *Stroke*. 2013;44:1500–1504. doi: 10.1161/STROKEAHA.113.001318
79. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet*. 2014;383:1973–1980. doi: 10.1016/S0140-6736(14)60040-4
80. Lee M, Saver JL, Hong KS, Song S, Chang KH, Ovbiagele B. Effect of prediabetes on future risk of stroke: meta-analysis. *BMJ*. 2012;344:e3564. doi: 10.1136/bmj.e3564
81. Shou J, Zhou L, Zhu S, Zhang X. Diabetes is an independent risk factor for stroke recurrence in stroke patients: a meta-analysis. *J Stroke Cerebrovasc Dis*. 2015;24:1961–1968. doi: 10.1016/j.jstrokecerebrovasdis.2015.04.004
82. Eriksson M, Carlberg B, Eliasson M. The disparity in long-term survival after a first stroke in patients with and without diabetes persists: the Northern Sweden MONICA study. *Cerebrovasc Dis*. 2012;34:153-160. doi: 10.1159/000339763
83. Fang HJ, Zhou YH, Tian YJ, Du HY, Sun YX, Zhong LY. Effects of intensive glucose lowering in treatment of type 2 diabetes mellitus on cardiovascular outcomes: a meta-analysis of data from 58,160 patients in 13 randomized controlled trials. *Int J Cardiol*. 2016;218:50–58. doi: 10.1016/j.ijcard.2016.04.163
84. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2015;313:603–615. doi: 10.1001/jama.2014.18574
85. Xie XX, Liu P, Wan FY, Lin SG, Zhong WL, Yuan ZK, Zou JJ, Liu LB. Blood pressure lowering and stroke events in type 2 diabetes: a network meta-analysis of randomized controlled trials. *Int J Cardiol*. 2016;208:141–146. doi: 10.1016/j.ijcard.2016.01.197
86. Redon J, Mancia G, Sleight P, Schumacher H, Gao P, Pogue J, Fagard R, Verdecchia P, Weber M, Böhm M, Williams B, Yusoff K, Teo K, Yusuf S; ONTARGET Investigators. Safety and efficacy of low blood pressures among patients with diabetes: subgroup analyses from the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). *J Am Coll Cardiol*. 2012;59:74–83. doi: 10.1016/j.jacc.2011.09.040
87. Banerjee C, Moon YP, Paik MC, Rundek T, Mora-McLaughlin C, Vieira JR, Sacco RL, Elkind MS. Duration of diabetes and risk of ischemic stroke: the Northern Manhattan Study. *Stroke*. 2012;43:1212–1217. doi: 10.1161/STROKEAHA.111.641381
88. Ashburner JM, Go AS, Chang Y, Fang MC, Fredman L, Applebaum KM, Singer DE. Effect of diabetes and glycemic control on ischemic stroke risk in AF patients: ATRIA study. *J Am Coll Cardiol*. 2016;67:239–247. doi: 10.1016/j.jacc.2015.10.080
89. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA*. 2003;290:1049–1056. doi: 10.1001/jama.290.8.1049
90. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983–988.
91. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, Seshadri S, Wolf PA, Vasan RS, Benjamin EJ, Levy D. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386:154–162. doi: 10.1016/S0140-6736(14)61774-8
92. Chamberlain AM, Brown RD Jr, Alonso A, Gersh BJ, Killian JM, Weston SA, Roger VL. No decline in the risk of stroke following incident atrial fibrillation since 2000 in the community: a concerning trend. *J Am Heart Assoc*. 2016;5:e00348. doi: 10.1161/JAHA.116.003408
93. Page RL, Wilkinson WE, Clair WK, McCarthy EA, Pritchett EL. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. *Circulation*. 1994;89:224–227.
94. Strickberger SA, Ip J, Saksena S, Curry K, Bahnson TD, Ziegler PD. Relationship between atrial tachyarrhythmias and symptoms. *Heart Rhythm*. 2005;2:125–131. doi: 10.1016/j.hrthm.2004.10.042
95. Tayal AH, Tian M, Kelly KM, Jones SC, Wright DG, Singh D, Jarouse J, Brillman J, Murali S, Gupta R. Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke. *Neurology*. 2008;71:1696–1701. doi: 10.1212/01.wnl.0000325059.86313.31
96. Elijovich L, Josephson SA, Fung GL, Smith WS. Intermittent atrial fibrillation may account for a large proportion of otherwise cryptogenic stroke: a study of 30-day cardiac event monitors. *J Stroke Cerebrovasc Dis*. 2009;18:185–189. doi: 10.1016/j.jstrokecerebrovasdis.2008.09.005
97. Flint AC, Banki NM, Ren X, Rao VA, Go AS. Detection of paroxysmal atrial fibrillation by 30-day event monitoring in cryptogenic ischemic stroke: the Stroke and Monitoring for PAF in Real Time (SMART) Registry. *Stroke*. 2012;43:2788–2790. doi: 10.1161/STROKEAHA.112.665844
98. Brachmann J, Morillo CA, Sanna T, Di Lazzaro V, Diener HC, Bernstein RA, Rymer M, Ziegler PD, Liu S, Passman RS. Uncovering atrial fibrillation beyond short-term monitoring in cryptogenic stroke patients: three-year results from the Cryptogenic Stroke and Underlying Atrial Fibrillation trial. *Circ Arrhythm Electrophysiol*. 2016;9:e003333. doi: 10.1161/CIRCEP.115.003333
99. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH; ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke [published correction appears in *N Engl J Med*. 2016;374:998]. *N Engl J Med*. 2012;366:120–129. doi: 10.1056/NEJMoa1105575

100. Turakhia MP, Ziegler PD, Schmitt SK, Chang Y, Fan J, Than CT, Keung EK, Singer DE. Atrial fibrillation burden and short-term risk of stroke: case-crossover analysis of continuously recorded heart rhythm from cardiac electronic implanted devices. *Circ Arrhythm Electrophysiol*. 2015;8:1040–1047. doi: 10.1161/CIRCEP.114.003057
101. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870.
102. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest*. 2010;137:263–272. doi: 10.1378/chest.09-1584
103. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2011;342:d124. doi: 10.1136/bmj.d124
104. Piccini JP, Stevens SR, Chang Y, Singer DE, Lokhnygina Y, Go AS, Patel MR, Mahaffey KW, Halperin JL, Breithardt G, Hankey GJ, Hacke W, Becker RC, Nessel CC, Fox KA, Califf RM; for the ROCKET AF Steering Committee and Investigators. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation*. 2013;127:224–232. doi: 10.1161/CIRCULATIONAHA.112.107128
105. Oldgren J, Hijazi Z, Lindbäck J, Alexander JH, Connolly SJ, Eikelboom JW, Ezekowitz MD, Granger CB, Hylek EM, Lopes RD, Siegbahn A, Yusuf S, Wallentin L; on behalf of the RE-LY and ARISTOTLE Investigators. Performance and validation of a novel biomarker-based stroke risk score for atrial fibrillation. *Circulation*. 2016;134:1697–1707. doi: 10.1161/CIRCULATIONAHA.116.022802
106. Link MS, Giugliano RP, Ruff CT, Scirica BM, Huikuri H, Oto A, Crompton AE, Murphy SA, Lanz H, Mercuri MF, Antman EM, Braunwald E; on behalf of the ENGAGE AF-TIMI 48 Investigators. Stroke and mortality risk in patients with various patterns of atrial fibrillation: results from the ENGAGE AF-TIMI 48 trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48). *Circ Arrhythm Electrophysiol*. 2017;10:e004267. doi: 10.1161/CIRCEP.116.004267
107. Steinberg BA, Hellkamp AS, Lokhnygina Y, Patel MR, Breithardt G, Hankey GJ, Becker RC, Singer DE, Halperin JL, Hacke W, Nessel CC, Berkowitz SD, Mahaffey KW, Fox KA, Califf RM, Piccini JP; ROCKET-AF Steering Committee and Investigators. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. *Eur Heart J*. 2015;36:288–296. doi: 10.1093/eurheartj/ehu359
108. Proietti M, Guiducci E, Cheli P, Lip GY. Is there an obesity paradox for outcomes in atrial fibrillation? A systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant trials. *Stroke*. 2017;48:857–866. doi: 10.1161/STROKEAHA.116.015984
109. Pandey A, Gersh BJ, McGuire DK, Shrader P, Thomas L, Kowey PR, Mahaffey KW, Hylek E, Sun S, Burton P, Piccini J, Peterson E, Fonarow GC. Association of body mass index with care and outcomes in patients with atrial fibrillation: results from the ORBIT-AF registry. *JACC Clin Electrophysiol*. 2016;2:355–363. doi: 10.1016/j.jacep.2015.12.001
110. Kamel H, Elkind MS, Bhave PD, Navi BB, Okin PM, Iadecola C, Devereux RB, Fink ME. Paroxysmal supraventricular tachycardia and the risk of ischemic stroke. *Stroke*. 2013;44:1550–1554. doi: 10.1161/STROKEAHA.113.001118
111. Overvad TF, Nielsen PB, Larsen TB, Søgaard P. Left atrial size and risk of stroke in patients in sinus rhythm: a systematic review. *Thromb Haemost*. 2016;116:206–219. doi: 10.1160/TH15-12-0923
112. Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. *Lancet*. 1995;346:1647–1653.
113. Zhang Y, Tuomilehto J, Jousilahti P, Wang Y, Antikainen R, Hu G. Total and high-density lipoprotein cholesterol and stroke risk. *Stroke*. 2012;43:1768–1774. doi: 10.1161/STROKEAHA.111.646778
114. Horenstein RB, Smith DE, Mosca L. Cholesterol predicts stroke mortality in the Women's Pooling Project. *Stroke*. 2002;33:1863–1868.
115. Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths [published correction appears in *Lancet*. 2008;372:292]. *Lancet*. 2007;370:1829–1839.
116. Amarenco P, Labreuche J, Touboul PJ. High-density lipoprotein-cholesterol and risk of stroke and carotid atherosclerosis: a systematic review. *Atherosclerosis*. 2008;196:489–496. doi: 10.1016/j.atherosclerosis.2007.07.033
117. Kurth T, Everett BM, Buring JE, Kase CS, Ridker PM, Gaziano JM. Lipid levels and the risk of ischemic stroke in women. *Neurology*. 2007;68:556–562. doi: 10.1212/01.wnl.0000254472.41810.0d
118. Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Blood pressure, cholesterol, and stroke in eastern Asia. *Lancet*. 1998;352:1801–1807.
119. Tirschwell DL, Smith NL, Heckbert SR, Lemaitre RN, Longstreth WT Jr, Psaty BM. Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. *Neurology*. 2004;63:1868–1875.
120. Peters SA, Singhateh Y, Mackay D, Huxley RR, Woodward M. Total cholesterol as a risk factor for coronary heart disease and stroke in women compared with men: a systematic review and meta-analysis. *Atherosclerosis*. 2016;248:123–131. doi: 10.1016/j.atherosclerosis.2016.03.016
121. Wang X, Dong Y, Qi X, Huang C, Hou L. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. *Stroke*. 2013;44:1833–1839. doi: 10.1161/STROKEAHA.113.001326
122. Curb JD, Abbott RD, Rodriguez BL, Masaki KH, Chen R, Popper JS, Petrovitch H, Ross GW, Schatz IJ, Belleau GC, Yano K. High density lipoprotein cholesterol and the risk of stroke in elderly men: the Honolulu Heart Program. *Am J Epidemiol*. 2004;160:150–157. doi: 10.1093/aje/kwh177
123. Huxley RR, Barzi F, Lam TH, Czernichow S, Fang X, Welborn T, Shaw J, Ueshima H, Zimmet P, Jee SH, Patel JV, Caterson I, Perkovic V, Woodward M; for the Asia Pacific Cohort Studies Collaboration and the Obesity in Asia Collaboration. Isolated low levels of high-density lipoprotein cholesterol are associated with an increased risk of coronary heart disease: an individual participant data meta-analysis of 23 studies in the Asia-Pacific region. *Circulation*. 2011;124:2056–2064. doi: 10.1161/CIRCULATIONAHA.111.028373
124. Psaty BM, Anderson M, Kronmal RA, Tracy RP, Orchard T, Fried LP, Lumley T, Robbins J, Burke G, Newman AB, Furberg CD. The association between lipid levels and the risks of incident myocardial infarction, stroke, and total mortality: the Cardiovascular Health Study. *J Am Geriatr Soc*. 2004;52:1639–1647. doi: 10.1111/j.1532-5415.2004.52455.x
125. Lee JS, Chang PY, Zhang Y, Kizer JR, Best LG, Howard BV. Triglyceride and HDL-C dyslipidemia and risks of coronary heart disease and ischemic stroke by glycemic dysregulation status: the Strong Heart Study. *Diabetes Care*. 2017;40:529–537. doi: 10.2337/dc16-1958
126. Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, Neeland IJ, Yuhanna IS, Rader DR, de Lemos JA, Shaul PW. HDL cholesterol efflux capacity and incident cardiovascular events. *N Engl J Med*. 2014;371:2383–2393. doi: 10.1056/NEJMoa1409065
127. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J; Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302:1993–2000. doi: 10.1001/jama.2009.1619
128. Imamura T, Doi Y, Arima H, Yonemoto K, Hata J, Kubo M, Tanizaki Y, Ibayashi S, Iida M, Kiyohara Y. LDL cholesterol and the development of stroke subtypes and coronary heart disease in a general Japanese population: the Hisayama study. *Stroke*. 2009;40:382–388. doi: 10.1161/STROKEAHA.108.529537
129. Sturgeon JD, Folsom AR, Longstreth WT Jr, Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. *Stroke*. 2007;38:2718–2725. doi: 10.1161/STROKEAHA.107.487090
130. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA*. 2008;300:2142–2152. doi: 10.1001/jama.2008.621
131. Bowman TS, Sesso HD, Ma J, Kurth T, Kase CS, Stampfer MJ, Gaziano JM. Cholesterol and the risk of ischemic stroke. *Stroke*. 2003;34:2930–2934. doi: 10.1161/01.STR.0000102171.91292.DC
132. Shahar E, Chambless LE, Rosamond WD, Boland LL, Ballantyne CM, McGovern PG, Sharrett AR. Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2003;34:623–631. doi: 10.1161/01.STR.0000057812.51734.FF

133. Wieberdink RG, Poels MM, Vernooij MW, Koudstaal PJ, Hofman A, van der Lugt A, Breteler MM, Ikram MA. Serum lipid levels and the risk of intracerebral hemorrhage: the Rotterdam Study. *Arterioscler Thromb Vasc Biol*. 2011;31:2982–2989. doi: 10.1161/ATVBAHA.111.234948
134. Hindy G, Engström G, Larsson SC, Traylor M, Markus HS, Melander O, Orho-Melander M; on behalf of the Stroke Genetics Network (SiGN). Role of blood lipids in the development of ischemic stroke and its subtypes: a Mendelian randomization study. *Stroke*. 2018;49:820–827. doi: 10.1161/STROKEAHA.117.019653
135. Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke. *Expert Rev Cardiovasc Ther*. 2010;8:917–932. doi: 10.1586/erc.10.56
136. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, Goldstein LB, Greenberg SM, Horvath SE, Iadecola C, Jauch EC, Moore WS, Wilson JA; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:3754–3832. doi: 10.1161/STR.0000000000000046
137. Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, Creager MA, Culebras A, Eckel RH, Hart RG, Hinchey JA, Howard VJ, Jauch EC, Levine SR, Meschia JF, Moore WS, Nixon JV, Pearson TA; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Epidemiology and Prevention; Council for High Blood Pressure Research, Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in *Stroke*. 2011;42:e26]. *Stroke*. 2011;42:517–584. doi: 10.1161/STR.0b013e3181fcb238
138. Kissela BM, Sauerbeck L, Woo D, Khoury J, Carrozzella J, Pancioli A, Jauch E, Moomaw CJ, Shukla R, Gebel J, Fontaine R, Broderick J. Subarachnoid hemorrhage: a preventable disease with a heritable component. *Stroke*. 2002;33:1321–1326.
139. Albertsen IE, Rasmussen LH, Lane DA, Overvad TF, Skjøth F, Overvad K, Lip GY, Larsen TB. The impact of smoking on thromboembolism and mortality in patients with incident atrial fibrillation: insights from the Danish Diet, Cancer, and Health study. *Chest*. 2014;145:559–566. doi: 10.1378/chest.13-1740
140. Bhat VM, Cole JW, Sorkin JD, Wozniak MA, Malarcher AM, Giles WH, Stern BJ, Kittner SJ. Dose-response relationship between cigarette smoking and risk of ischemic stroke in young women. *Stroke*. 2008;39:2439–2443. doi: 10.1161/STROKEAHA.107.510073
141. Hackshaw A, Morris JK, Boniface S, Tang JL, Milenkovic D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports [published correction appears in *BMJ*. 2018;361:k1611]. *BMJ*. 2018;360:j5855. doi: 10.1136/bmj.j5855
142. Peters SA, Huxley RR, Woodward M. Smoking as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 81 cohorts, including 3,980,359 individuals and 42,401 strokes. *Stroke*. 2013;44:2821–2828. doi: 10.1161/STROKEAHA.113.002342
143. Nakamura K, Barzi F, Lam TH, Huxley R, Feigin VL, Ueshima H, Woo J, Gu D, Ohkubo T, Lawes CM, Suh I, Woodward M; for the Asia Pacific Cohort Studies Collaboration. Cigarette smoking, systolic blood pressure, and cardiovascular diseases in the Asia-Pacific region. *Stroke*. 2008;39:1694–1702. doi:
144. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet*. 1996;348:498–505.
145. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet*. 1996;348:505–510.
146. Lee PN, Forey BA. Environmental tobacco smoke exposure and risk of stroke in nonsmokers: a review with meta-analysis. *J Stroke Cerebrovasc Dis*. 2006;15:190–201. doi: 10.1016/j.jstrokecerebrovasdis.2006.05.002
147. Oono IP, Mackay DF, Pell JP. Meta-analysis of the association between secondhand smoke exposure and stroke. *J Public Health (Oxf)*. 2011;33:496–502. doi: 10.1093/pubmed/fdr025
148. Malek AM, Cushman M, Lackland DT, Howard G, McClure LA. Secondhand smoke exposure and stroke: the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Am J Prev Med*. 2015;49:e89–e97. doi: 10.1016/j.amepre.2015.04.014
149. Nishino Y, Tsuji I, Tanaka H, Nakayama T, Nakatsuka H, Ito H, Suzuki T, Katanoda K, Sobue T, Tominaga S; Three-Prefecture Cohort Study Group. Stroke mortality associated with environmental tobacco smoke among never-smoking Japanese women: a prospective cohort study. *Prev Med*. 2014;67:41–45. doi: 10.1016/j.ypmed.2014.06.029
150. Lin MP, Ovbiagele B, Markovic D, Towfighi A. Association of secondhand smoke with stroke outcomes. *Stroke*. 2016;47:2828–2835. doi: 10.1161/STROKEAHA.116.014099
151. Lindbohm JV, Kaprio J, Jousilahti P, Salomaa V, Korja M. Sex, smoking, and risk for subarachnoid hemorrhage. *Stroke*. 2016;47:1975–1981. doi: 10.1161/STROKEAHA.116.012957
152. Vidyasagaran AL, Siddiqi K, Kanaan M. Use of smokeless tobacco and risk of cardiovascular disease: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2016;23:1970–1981. doi: 10.1177/2047487316654026
153. Boffetta P, Straif K. Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis. *BMJ*. 2009;339:b3060. doi: 10.1136/bmj.b3060
154. Bell EJ, Lutsey PL, Windham BG, Folsom AR. Physical activity and cardiovascular disease in African Americans in Atherosclerosis Risk in Communities. *Med Sci Sports Exerc*. 2013;45:901–907. doi: 10.1249/MSS.0b013e31827d87ec
155. Willey JZ, Moon YP, Sacco RL, Greenlee H, Diaz KM, Wright CB, Elkind MS, Cheung YK. Physical inactivity is a strong risk factor for stroke in the oldest old: findings from a multi-ethnic population (the Northern Manhattan Study). *Int J Stroke*. 2017;12:197–200. doi: 10.1177/1747493016676614

155a. Soares-Miranda L, Siscovick DS, Psaty BM, Longstreth WT, Mozaffarian D. Physical activity and risk of coronary heart disease and stroke in older adults: the Cardiovascular Health Study. *Circulation*. 2016;133:147–155.

156. Pandey A, Patel MR, Willis B, Gao A, Leonard D, Das SR, Defina L, Berry JD. Association between midlife cardiorespiratory fitness and risk of stroke: the Cooper Center Longitudinal Study [published correction appears in *Stroke*. 2016;47:e203]. *Stroke*. 2016;47:1720–1726. doi: 10.1161/STROKEAHA.115.011532
157. Åberg ND, Kuhn HG, Nyberg J, Waern M, Friberg P, Svensson J, Torén K, Rosengren A, Åberg MA, Nilsson M. Influence of cardiovascular fitness and muscle strength in early adulthood on long-term risk of stroke in Swedish men. *Stroke*. 2015;46:1769–1776. doi: 10.1161/STROKEAHA.115.009008
158. Armstrong ME, Green J, Reeves GK, Beral V, Cairns BJ; on behalf of the Million Women Study Collaborators. Frequent physical activity may not reduce vascular disease risk as much as moderate activity: large prospective study of women in the United Kingdom. *Circulation*. 2015;131:721–729. doi: 10.1161/CIRCULATIONAHA.114.010296
159. Blomstrand A, Blomstrand C, Ariai N, Bengtsson C, Björkelund C. Stroke incidence and association with risk factors in women: a 32-year follow-up of the Prospective Population Study of Women in Gothenburg. *BMJ Open*. 2014;4:e005173. doi: 10.1136/bmjopen-2014-005173
160. Tikk K, Sookthai D, Monni S, Gross ML, Lichy C, Kloss M, Kaaks R. Primary preventive potential for stroke by avoidance of major lifestyle risk factors: the European Prospective Investigation into Cancer and Nutrition-Heidelberg cohort. *Stroke*. 2014;45:2041–2046. doi: 10.1161/STROKEAHA.114.005025
161. Jefferis BJ, Whincup PH, Papacosta O, Wannamethee SG. Protective effect of time spent walking on risk of stroke in older men. *Stroke*. 2014;45:194–199. doi: 10.1161/STROKEAHA.113.002246
162. Chomistek AK, Manson JE, Stefanick ML, Lu B, Sands-Lincoln M, Going SB, Garcia L, Allison MA, Sims ST, LaMonte MJ, Johnson KC, Eaton CB. Relationship of sedentary behavior and physical activity to incident cardiovascular disease: results from the Women's Health Initiative. *J Am Coll Cardiol*. 2013;61:2346–2354. doi: 10.1016/j.jacc.2013.03.031
163. Pandey A, Salahuddin U, Garg S, Ayers C, Kulinski J, Anand V, Mayo H, Kumbhani DJ, de Lemos J, Berry JD. Continuous dose-response association between sedentary time and risk for cardiovascular disease: a meta-analysis. *JAMA Cardiol*. 2016;1:575–583. doi: 10.1001/jamacardio.2016.1567
164. McDonnell MN, Hillier SL, Judd SE, Yuan Y, Hooker SP, Howard VJ. Association between television viewing time and risk of incident stroke in a general population: results from the REGARDS study. *Prev Med*. 2016;87:1–5. doi: 10.1016/j.ypmed.2016.02.013

165. Kubota Y, Iso H, Yamagishi K, Sawada N, Tsugane S; on behalf of the JPHC Study Group. Daily total physical activity and incident stroke: the Japan Public Health Center-Based Prospective Study. *Stroke*. 2017;48:1730–1736. doi: 10.1161/STROKEAHA.117.017560

165a. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Fitó M, Gea A, Hernán MA, Martínez-González MA, for the PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. 2018;378:e34. doi: 10.1056/NEJMoa1800389

166. Bernstein AM, de Koning L, Flint AJ, Rexrode KM, Willett WC. Soda consumption and the risk of stroke in men and women. *Am J Clin Nutr*. 2012;95:1190–1199. doi: 10.3945/ajcn.111.030205

167. Chowdhury R, Stevens S, Gorman D, Pan A, Warnakula S, Chowdhury S, Ward H, Johnson L, Crowe F, Hu FB, Franco OH. Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: systematic review and meta-analysis. *BMJ*. 2012;345:e6698. doi: 10.1136/bmj.e6698

168. Larsson SC, Virtamo J, Wolk A. Total and specific fruit and vegetable consumption and risk of stroke: a prospective study. *Atherosclerosis*. 2013;227:147–152. doi: 10.1016/j.atherosclerosis.2012.12.022

169. Larsson SC, Wallin A, Wolk A. Dietary approaches to stop hypertension diet and incidence of stroke: results from 2 prospective cohorts. *Stroke*. 2016;47:986–990. doi: 10.1161/STROKEAHA.116.012675

170. Hansen CP, Overvad K, Kyrø C, Olsen A, Tjønneland A, Johnsen SP, Jakobsen MU, Dahm CC. Adherence to a healthy Nordic diet and risk of stroke: a Danish cohort study. *Stroke*. 2017;48:259–264. doi: 10.1161/STROKEAHA.116.015019

171. Martínez-González MA, Dominguez LJ, Delgado-Rodríguez M. Olive oil consumption and risk of CHD and/or stroke: a meta-analysis of case-control, cohort and intervention studies. *Br J Nutr*. 2014;112:248–259. doi: 10.1017/S0007114514000713

172. Cheng P, Wang J, Shao W. Monounsaturated fatty acid intake and stroke risk: a meta-analysis of prospective cohort studies. *J Stroke Cerebrovasc Dis*. 2016;25:1326–1334. doi: 10.1016/j.jstrokecerebrovasdis.2016.02.017

173. Alexander DD, Bylsma LC, Vargas AJ, Cohen SS, Doucette A, Mohamed M, Irvin SR, Miller PE, Watson H, Fryzek JP. Dairy consumption and CVD: a systematic review and meta-analysis [published correction appears in *Br J Nutr*. 2016;115:2268]. *Br J Nutr*. 2016;115:737–750. doi: 10.1017/S0007114515005000

174. Mayhew AJ, de Souza RJ, Meyre D, Anand SS, Mente A. A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality. *Br J Nutr*. 2016;115:212–225. doi: 10.1017/S0007114515004316

175. Wu D, Guan Y, Lv S, Wang H, Li J. No evidence of increased risk of stroke with consumption of refined grains: a meta-analysis of prospective cohort studies. *J Stroke Cerebrovasc Dis*. 2015;24:2738–2746. doi: 10.1016/j.jstrokecerebrovasdis.2015.08.004

176. Wu P, Haththotuwa R, Kwok CS, Babu A, Kotronias RA, Rushton C, Zaman A, Fryer AA, Kadam U, Chew-Graham CA, Mamas MA. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003497. doi: 10.1161/CIRCOUTCOMES.116.003497

177. Ford JA, MacLennan GS, Avenell A, Bolland M, Grey A, Witham M; RECORD Trial Group. Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis. *Am J Clin Nutr*. 2014;100:746–755. doi: 10.3945/ajcn.113.082602

178. D'Elia L, Iannotta C, Sabino P, Ippolito R. Potassium-rich diet and risk of stroke: updated meta-analysis. *Nutr Metab Cardiovasc Dis*. 2014;24:585–587. doi: 10.1016/j.numecd.2014.03.001

179. Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ*. 2009;339:b4567. doi: 10.1136/bmj.b4567

180. Wang ZM, Zhao D, Nie ZL, Zhao H, Zhou B, Gao W, Wang LS, Yang ZJ. Flavonol intake and stroke risk: a meta-analysis of cohort studies. *Nutrition*. 2014;30:518–523. doi: 10.1016/j.nut.2013.10.009

181. Huo Y, Li J, Qin X, Huang Y, Wang X, Gottesman RF, Tang G, Wang B, Chen D, He M, Fu J, Cai Y, Shi X, Zhang Y, Cui Y, Sun N, Li X, Cheng X, Wang J, Yang X, Yang T, Xiao C, Zhao G, Dong Q, Zhu D, Wang X, Ge J, Zhao L, Hu D, Liu L, Hou FF; CSPPT Investigators. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *JAMA*. 2015;313:1325–1335. doi: 10.1001/jama.2015.2274

182. Pase MP, Himali JJ, Beiser AS, Aparicio HJ, Satizabal CL, Vasan RS, Seshadri S, Jacques PF. Sugar- and artificially sweetened beverages and the risks of incident stroke and dementia: a prospective cohort study. *Stroke*. 2017;48:1139–1146. doi: 10.1161/STROKEAHA.116.016027

183. Fox CS, Polak JF, Chazaro I, Cupples A, Wolf PA, D'Agostino RA, O'Donnell CJ. Genetic and environmental contributions to atherosclerosis phenotypes in men and women: heritability of carotid intima-media thickness in the Framingham Heart Study. *Stroke*. 2003;34:397–401.

184. Liao D, Myers R, Hunt S, Shahar E, Paton C, Burke G, Province M, Heiss G. Familial history of stroke and stroke risk: the Family Heart Study. *Stroke*. 1997;28:1908–1912.

185. Schulz UG, Flossmann E, Rothwell PM. Heritability of ischemic stroke in relation to age, vascular risk factors, and subtypes of incident stroke in population-based studies. *Stroke*. 2004;35:819–824. doi: 10.1161/01.STR.0000121646.23955.0f

186. Markus HS, Bevan S. Mechanisms and treatment of ischaemic stroke–insights from genetic associations. *Nat Rev Neurol*. 2014;10:723–730. doi: 10.1038/nrneurol.2014.196

187. Gretarsdottir S, Thorleifsson G, Manolescu A, Styrkarsdottir U, Helgadottir A, Gschwendtner A, Kostulas K, Kuhlenbäumer G, Bevan S, Jonsdottir T, Bjarnason H, Saemundsdottir J, Palsson S, Arnar DO, Holm H, Thorgeirsson G, Valdimarsson EM, Sveinbjörnsdottir S, Gieger C, Berger K, Wichmann HE, Hillert J, Markus H, Gulcher JR, Ringelstein EB, Kong A, Dichgans M, Gudbjartsson DF, Thorsteinsdottir U, Stefansson K. Risk variants for atrial fibrillation on chromosome 4q25 associate with ischemic stroke. *Ann Neurol*. 2008;64:402–409. doi: 10.1002/ana.21480

188. Anderson CD, Biffi A, Rost NS, Cortellini L, Furie KL, Rosand J. Chromosome 9p21 in ischemic stroke: population structure and meta-analysis. *Stroke*. 2010;41:1123–1131. doi: 10.1161/STROKEAHA.110.580589

189. Dichgans M, Malik R, König IR, Rosand J, Clarke R, Gretarsdottir S, Thorleifsson G, Mitchell BD, Assimes TL, Levi C, O'Donnell CJ, Fornage M, Thorsteinsdottir U, Psaty BM, Hengstenberg C, Seshadri S, Erdmann J, Bis JC, Peters A, Boncoraglio GB, März W, Meschia JF, Kathiresan S, Ikram MA, McPherson R, Stefansson K, Sudlow C, Reilly MP, Thompson JR, Sharma P, Hopewell JC, Chambers JC, Watkins H, Rothwell PM, Roberts R, Markus HS, Samani NJ, Farrall M, Schunkert H; and the METASTROKE Consortium; CARDIoGRAM Consortium; C4D Consortium; International Stroke Genetics Consortium. Shared genetic susceptibility to ischemic stroke and coronary artery disease: a genome-wide analysis of common variants. *Stroke*. 2014;45:24–36. doi: 10.1161/STROKEAHA.113.002707

190. Malik R, Chauhan G, Traylor M, Sargurupremraj M, Okada Y, Mishra A, Rutten-Jacobs L, Giese AK, van der Laan SW, Gretarsdottir S, Anderson CD, Chong M, Adams HHH, Ago T, Almgren P, Amouyel P, Ay H, Bartz TM, Benavente OR, Bevan S, Boncoraglio GB, Brown RD Jr, Butterworth AS, Carrera C, Carty CL, Chasman DI, Chen WM, Cole JW, Correa A, Cotlarciuc I, Cruchaga C, Danesh J, de Bakker PIW, DeStefano AL, den Hoed M, Duan Q, Engelter ST, Falcone GJ, Gottesman RF, Grewal RP, Gudnason V, Gustafsson S, Haessler J, Harris TB, Hassan A, Havulinna AS, Heckbert SR, Holliday EG, Howard G, Hsu FC, Hyacinth HI, Ikram MA, Ingelsson E, Irvin MR, Jian X, Jiménez-Conde J, Johnson JA, Jukema JW, Kanai M, Keene KL, Kissela BM, Kleindorfer DO, Kooperberg C, Kubo M, Lange LA, Langefeld CD, Langenberg C, Launer LJ, Lee JM, Lemmens R, Leys D, Lewis CM, Lin WY, Lindgren AG, Lorentzen E, Magnusson PK, Maguire J, Manichaikul A, McArdle PF, Meschia JF, Mitchell BD, Mosley TH, Nalls MA, Ninomiya T, O'Donnell MJ, Psaty BM, Pulit SL, Rannikmäe K, Reiner AP, Rexrode KM, Rice K, Rich SS, Ridker PM, Rost NS, Rothwell PM, Rotter JI, Rundek T, Sacco RL, Sakaue S, Sale MM, Salomaa V, Sapkota BR, Schmidt R, Schmidt CO, Schminke U, Sharma P, Slowik A, Sudlow CLM, Tanislav C, Tatlisumak T, Taylor KD, Thijs VNS, Thorleifsson G, Thorsteinsdottir U, Tiedt S, Trompet S, Tzourio C, van Duijn CM, Walters M, Wareham NJ, Wassertheil-Smoller S, Wilson JG, Wiggins KL, Yang Q, Yusuf S, Bis JC, Pastinen T, Ruusalepp A, Schadt EE, Koplev S, Björkegren JLM, Codoni V, Civelek M, Smith NL, Trégouët DA, Christophersen IE, Roselli C, Lubitz SA, Ellinor PT, Tai ES, Kooner JS, Kato N, He J, van der Harst P, Elliott P, Chambers JC, Takeuchi F, Johnson AD, Sanghera DK, Melander O, Jern C, Strbian D, Fernandez-Cadenas I, Longstreth WT Jr, Rolfs A, Hata J, Woo D, Rosand J, Pare G, Hopewell JC, Saleheen D, Stefansson K, Worrall BB, Kittner SJ, Seshadri S, Fornage M, Markus HS, Howson JMM, Kamatani Y, Debette S, Dichgans M, Malik R, Chauhan G, Traylor M, Sargurupremraj M, Okada Y, Mishra A, Rutten-Jacobs L, Giese AK, van der Laan SW, Gretarsdottir S, Anderson CD, Chong M, Adams HHH, Ago T, Almgren P, Amouyel P, Ay H, Bartz TM, Benavente OR, Bevan S, Boncoraglio GB, Brown RD Jr, Butterworth AS, Carrera C, Carty CL, Chasman DI, Chen WM, Cole JW, Correa A,

Cotlarciuc I, Cruchaga C, Danesh J, de Bakker PIW, DeStefano AL, Hoed MD, Duan Q, Engelter ST, Falcone GJ, Gottesman RF, Grewal RP, Gudnason V, Gustafsson S, Haessler J, Harris TB, Hassan A, Havulinna AS, Heckbert SR, Holliday EG, Howard G, Hsu FC, Hyacinth HI, Ikram MA, Ingelsson E, Irvin MR, Jian X, Jiménez-Conde J, Johnson JA, Jukema JW, Kanai M, Keene KL, Kissela BM, Kleindorfer DO, Kooperberg C, Kubo M, Lange LA, Langefeld CD, Langenberg C, Launer LJ, Lee JM, Lemmens R, Leys D, Lewis CM, Lin WY, Lindgren AG, Lorentzen E, Magnusson PK, Maguire J, Manichaikul A, McArdle PF, Meschia JF, Mitchell BD, Mosley TH, Nalls MA, Ninomiya T, O'Donnell MJ, Psaty BM, Pulit SL, Rannikmäe K, Reiner AP, Rexrode KM, Rice K, Rich SS, Ridker PM, Rost NS, Rothwell PM, Rotter JI, Rundek T, Sacco RL, Sakaue S, Sale MM, Salomaa V, Sapkota BR, Schmidt R, Schmidt CO, Schminke U, Sharma P, Slowik A, Sudlow CLM, Tanislav C, Tatlisumak T, Taylor KD, Thijs VNS, Thorleifsson G, Thorsteinsdottir U, Tiedt S, Trompet S, Tzourio C, van Duijn CM, Walters M, Wareham NJ, Wassertheil-Smoller S, Wilson JG, Wiggins KL, Yang Q, Yusuf S, Amin N, Aparicio HS, Arnett DK, Attia J, Beiser AS, Berr C, Buring JE, Bustamante M, Caso V, Cheng YC, Choi SH, Chowhan A, Cullell N, Dartigues JF, Delavaran H, Delgado P, Dörr M, Engström G, Ford I, Gurpreet WS, Hamsten A, Heitsch L, Hozawa A, Ibanez L, Ilinca A, Ingelsson M, Iwasaki M, Jackson RD, Jood K, Jousilahti P, Kaffashian S, Kalra L, Kamouchi M, Kitazono T, Kjartansson O, Kloss M, Koudstaal PJ, Krupinski J, Labovitz DL, Laurie CC, Levi CR, Li L, Lind L, Lindgren CM, Lioutas V, Liu YM, Lopez OL, Makoto H, Martinez-Majander N, Matsuda K, Minegishi N, Montaner J, Morris AP, Muiño E, Müller-Nurasyid M, Norrving B, Ogishima S, Parati EA, Peddareddygari LR, Pedersen NL, Pera J, Perola M, Pezzini A, Pileggi S, Rabionet R, Riba-Llena I, Ribasés M, Romero JR, Roquer J, Rudd AG, Sarin AP, Sarju R, Sarnowski C, Sasaki M, Satizabal CL, Satoh M, Sattar N, Sawada N, Sibolt G, Sigurdsson Á, Smith A, Sobue K, Soriano-Tárraga C, Stanne T, Stine OC, Stott DJ, Strauch K, Takai T, Tanaka H, Tanno K, Teumer A, Tomppo L, Torres-Aguila NP, Touze E, Tsugane S, Uitterlinden AG, Valdimarsson EM, van der Lee SJ, Völzke H, Wakai K, Weir D, Williams SR, Wolfe CDA, Wong Q, Xu H, Yamaji T, Sanghera DK, Melander O, Jern C, Strbian D, Fernandez-Cadenas I, Longstreth WT Jr, Rolfs A, Hata J, Woo D, Rosand J, Pare G, Hopewell JC, Saleheen D, Stefansson K, Worrall BB, Kittner SJ, Seshadri S, Fornage M, Markus HS, Howson JMM, Kamatani Y, Debette S, Dichgans M; AFGen Consortium; Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium; International Genomics of Blood Pressure (iGEN-BP) Consortium; INVENT Consortium; STARNET; BioBank Japan Cooperative Hospital Group; COMPASS Consortium; EPIC-CVD Consortium; EPIC-InterAct Consortium; International Stroke Genetics Consortium (ISGC); METASTROKE Consortium; Neurology Working Group of the CHARGE Consortium; NINDS Stroke Genetics Network (SiGN); UK Young Lacunar DNA Study; MEGASTROKE Consortium; MEGASTROKE Consortium:. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. *Nat Genet*. 2018;50:524–537. doi: 10.1038/s41588-018-0058-3

191. Traylor M, Malik R, Nalls MA, Cotlarciuc I, Radmanesh F, Thorleifsson G, Hanscombe KB, Langefeld C, Saleheen D, Rost NS, Yet I, Spector TD, Bell JT, Hannon E, Mill J, Chauhan G, Debette S, Bis JC, Longstreth WT Jr, Ikram MA, Launer LJ, Seshadri S, Hamilton-Bruce MA, Jimenez-Conde J, Cole JW, Schmidt R, Słowik A, Lemmens R, Lindgren A, Melander O, Grewal RP, Sacco RL, Rundek T, Rexrode K, Arnett DK, Johnson JA, Benavente OR, Wasssertheil-Smoller S, Lee JM, Pulit SL, Wong Q, Rich SS, de Bakker PI, McArdle PF, Woo D, Anderson CD, Xu H, Heitsch L, Fornage M, Jern C, Stefansson K, Thorsteinsdottir U, Gretarsdottir S, Lewis CM, Sharma P, Sudlow CL, Rothwell PM, Boncoraglio GB, Thijs V, Levi C, Meschia JF, Rosand J, Kittner SJ, Mitchell BD, Dichgans M, Worrall BB, Markus HS; METASTROKE, UK Young Lacunar DNA Study, NINDS Stroke Genetics Network, Neurology Working Group of the CHARGE Consortium; International Stroke Genetics Consortium. Genetic variation at 16q24.2 is associated with small vessel stroke. *Ann Neurol*. 2017;81:383–394. doi: 10.1002/ana.24840
192. Shendre A, Wiener H, Irvin MR, Zhi D, Limdi NA, Overton ET, Wassel CL, Divers J, Rotter JI, Post WS, Shrestha S. Admixture mapping of subclinical atherosclerosis and subsequent clinical events among African Americans in 2 large cohort studies. *Circ Cardiovasc Genet*. 2017;10:e001569. doi: 10.1161/CIRCGENETICS.116.001569
193. Malik R, Traylor M, Pulit SL, Bevan S, Hopewell JC, Holliday EG, Zhao W, Abrantes P, Amouyel P, Attia JR, Battey TW, Berger K, Boncoraglio GB, Chauhan G, Cheng YC, Chen WM, Clarke R, Cotlarciuc I, Debette S, Falcone GJ, Ferro JM, Gamble DM, Ilinca A, Kittner SJ, Kourkoulis CE, Lemmens R, Levi CR, Lichtner P, Lindgren A, Liu J, Meschia JF, Mitchell BD, Oliveira SA, Pera J, Reiner AP, Rothwell PM, Sharma P, Slowik A, Sudlow CL, Tatlisumak T, Thijs V, Vicente AM, Woo D, Seshadri S, Saleheen D, Rosand J, Markus HS, Worrall BB, Dichgans M; ISGC Analysis Group; METASTROKE collaboration; Wellcome Trust Case Control Consortium 2 (WTCCC2); NINDS Stroke Genetics Network (SiGN). Low-frequency and common genetic variation in ischemic stroke: the METASTROKE collaboration [published correction appears in *Neurology*. 2016;87:1306]. *Neurology*. 2016;86:1217–1226. doi: 10.1212/WNL.0000000000002528
194. Erdmann J, Stark K, Esslinger UB, Rumpf PM, Koesling D, de Wit C, Kaiser FJ, Braunholz D, Medack A, Fischer M, Zimmermann ME, Tennstedt S, Graf E, Eck S, Aherrahrou Z, Nahrstaedt J, Willenborg C, Bruse P, Brænne I, Nöthen MM, Hofmann P, Braund PS, Mergia E, Reinhard W, Burgdorf C, Schreiber S, Balmforth AJ, Hall AS, Bertram L, Steinhagen-Thiessen E, Li SC, März W, Reilly M, Kathiresan S, McPherson R, Walter U, Ott J, Samani NJ, Strom TM, Meitinger T, Hengstenberg C, Schunkert H; CARDIoGRAM. Dysfunctional nitric oxide signalling increases risk of myocardial infarction. *Nature*. 2013;504:432–436. doi: 10.1038/nature12722
195. Dichgans M. Genetics of ischaemic stroke. *Lancet Neurol*. 2007;6:149–161. doi: 10.1016/S1474-4422(07)70028-5
196. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, Alamowitch S, Domenga V, Cécillion M, Marechal E, Maciazek J, Vayssiere C, Cruaud C, Cabanis EA, Ruchoux MM, Weissenbach J, Bach JF, Bousser MG, Tournier-Lasserve E. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature*. 1996;383:707–710. doi: 10.1038/383707a0
197. Devan WJ, Falcone GJ, Anderson CD, Jagiella JM, Schmidt H, Hansen BM, Jimenez-Conde J, Giralt-Steinhauer E, Cuadrado-Godia E, Soriano C, Ayres AM, Schwab K, Kassis SB, Valant V, Pera J, Urbanik A, Viswanathan A, Rost NS, Goldstein JN, Freudenberger P, Stögerer EM, Norrving B, Tirschwell DL, Selim M, Brown DL, Silliman SL, Worrall BB, Meschia JF, Kidwell CS, Montaner J, Fernandez-Cadenas I, Delgado P, Greenberg SM, Roquer J, Lindgren A, Slowik A, Schmidt R, Woo D, Rosand J, Biffi A; on behalf of the International Stroke Genetics Consortium. Heritability estimates identify a substantial genetic contribution to risk and outcome of intracerebral hemorrhage. *Stroke*. 2013;44:1578–1583. doi: 10.1161/STROKEAHA.111.000089
198. Carpenter AM, Singh IP, Gandhi CD, Prestigiacomo CJ. Genetic risk factors for spontaneous intracerebral haemorrhage. *Nat Rev Neurol*. 2016;12:40–49. doi: 10.1038/nrneurol.2015.226
199. Woo D, Falcone GJ, Devan WJ, Brown WM, Biffi A, Howard TD, Anderson CD, Brouwers HB, Valant V, Battey TW, Radmanesh F, Raffeld MR, Baedorf-Kassis S, Deka R, Woo JG, Martin LJ, Haverbusch M, Moomaw CJ, Sun G, Broderick JP, Flaherty ML, Martini SR, Kleindorfer DO, Kissela B, Comeau ME, Jagiella JM, Schmidt H, Freudenberger P, Pichler A, Enzinger C, Hansen BM, Norrving B, Jimenez-Conde J, Giralt-Steinhauer E, Elosua R, Cuadrado-Godia E, Soriano C, Roquer J, Kraft P, Ayres AM, Schwab K, McCauley JL, Pera J, Urbanik A, Rost NS, Goldstein JN, Viswanathan A, Stögerer EM, Tirschwell DL, Selim M, Brown DL, Silliman SL, Worrall BB, Meschia JF, Kidwell CS, Montaner J, Fernandez-Cadenas I, Delgado P, Malik R, Dichgans M, Greenberg SM, Rothwell PM, Lindgren A, Slowik A, Schmidt R, Langefeld CD, Rosand J; International Stroke Genetics Consortium. Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage. *Am J Hum Genet*. 2014;94:511–521. doi: 10.1016/j.ajhg.2014.02.012
200. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Low glomerular filtration rate and risk of stroke: meta-analysis. *BMJ*. 2010;341:c4249. doi: 10.1136/bmj.c4249
201. Lee M, Saver JL, Chang KH, Ovbiagele B. Level of albuminuria and risk of stroke: systematic review and meta-analysis. *Cerebrovasc Dis*. 2010;30:464–469. doi: 10.1159/000317069
202. Masson P, Webster AC, Hong M, Turner R, Lindley RI, Craig JC. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2015;30:1162–1169. doi: 10.1093/ndt/gfv009
203. Mahmoodi BK, Yatsuya H, Matsushita K, Sang Y, Gottesman RF, Astor BC, Woodward M, Longstreth WT Jr, Psaty BM, Shlipak MG, Folsom AR, Gansevoort RT, Coresh J. Association of kidney disease measures with ischemic versus hemorrhagic strokes: pooled analyses of 4 prospective community-based cohorts. *Stroke*. 2014;45:1925–1931. doi: 10.1161/STROKEAHA.114.004900

204. Sandsmark DK, Messé SR, Zhang X, Roy J, Nessel L, Lee Hamm L, He J, Horwitz EJ, Jaar BG, Kallem RR, Kusek JW, Mohler ER 3rd, Porter A, Seliger SL, Sozio SM, Townsend RR, Feldman HI, Kasner SE; CRIC Study Investigators. Proteinuria, but not eGFR, predicts stroke risk in chronic kidney disease: Chronic Renal Insufficiency Cohort study. *Stroke*. 2015;46:2075–2080. doi: 10.1161/STROKEAHA.115.009861
205. El Husseini N, Fonarow GC, Smith EE, Ju C, Schwamm LH, Hernandez AF, Schulte PJ, Xian Y, Goldstein LB. Renal dysfunction is associated with poststroke discharge disposition and in-hospital mortality: findings from Get With The Guidelines-Stroke. *Stroke*. 2017;48:327–334. doi: 10.1161/STROKEAHA.116.014601
206. Wang X, Wang Y, Patel UD, Barnhart HX, Li Z, Li H, Wang C, Zhao X, Liu L, Wang Y, Laskowitz DT. Comparison of associations of reduced estimated glomerular filtration rate with stroke outcomes between hypertension and no hypertension. *Stroke*. 2017;48:1691–1694. doi: 10.1161/STROKEAHA.117.016864
207. Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, Howard VJ, Lichtman JH, Lisabeth LD, Piña IL, Reeves MJ, Rexrode KM, Saposnik G, Singh V, Towfighi A, Vaccarino V, Walters MR; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council for High Blood Pressure Research. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association [published corrections appear in *Stroke*. 2014;45:e95 and *Stroke*. 2014;45:e214]. *Stroke*. 2014;45:1545–1588. doi: 10.1161/01.str.0000442009.06663.48
208. Kissela BM, Khoury JC, Alwell K, Moomaw CJ, Woo D, Adeoye O, Flaherty ML, Khatri P, Ferioli S, De Los Rios La Rosa F, Broderick JP, Kleindorfer DO. Age at stroke: temporal trends in stroke incidence in a large, biracial population. *Neurology*. 2012;79:1781–1787. doi: 10.1212/WNL.0b013e318270401d
209. Friberg J, Scharling H, Gadsbøll N, Truelsen T, Jensen GB; Copenhagen City Heart Study. Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (the Copenhagen City Heart Study). *Am J Cardiol*. 2004;94:889–894. doi: 10.1016/j.amjcard.2004.06.023
210. Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, Go AS. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation*. 2005;112:1687–1691. doi: 10.1161/CIRCULATIONAHA.105.553438
211. Dagres N, Nieuwlaat R, Vardas PE, Andresen D, Lévy S, Cobbe S, Kremastinos DT, Breithardt G, Cokkinos DV, Crijns HJ. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. *J Am Coll Cardiol*. 2007;49:572–577. doi: 10.1016/j.jacc.2006.10.047
212. Poli D, Antonucci E, Grifoni E, Abbate R, Gensini GF, Prisco D. Gender differences in stroke risk of atrial fibrillation patients on oral anticoagulant treatment. *Thromb Haemost*. 2009;101:938–942.
213. Avgil Tsadok M, Jackevicius CA, Rahme E, Humphries KH, Behlouli H, Pilote L. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. *JAMA*. 2012;307:1952–1958. doi: 10.1001/jama.2012.3490
214. Canoy D, Beral V, Balkwill A, Wright FL, Kroll ME, Reeves GK, Green J, Cairns BJ; for the Million Women Study Collaborators. Age at menarche and risks of coronary heart and other vascular diseases in a large UK cohort. *Circulation*. 2015;131:237–244. doi: 10.1161/CIRCULATIONAHA.114.010070
215. Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, Kavousi M, Franco OH. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiol*. 2016;1:767–776. doi: 10.1001/jamacardio.2016.2415
216. Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, Kooperberg C, Baird A, Kotchen T, Curb JD, Black H, Rossouw JE, Aragaki A, Safford M, Stein E, Laowattana S, Mysiw WJ; WHI Investigators. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA*. 2003;289:2673–2684. doi: 10.1001/jama.289.20.2673
217. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321–333.
218. Hendrix SL, Wassertheil-Smoller S, Johnson KC, Howard BV, Kooperberg C, Rossouw JE, Trevisan M, Aragaki A, Baird AE, Bray PF, Buring JE, Criqui MH, Herrington D, Lynch JK, Rapp SR, Torner J; for the WHI Investigators. Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation*. 2006;113:2425–2434. doi: 10.1161/CIRCULATIONAHA.105.594077
219. Simon JA, Hsia J, Cauley JA, Richards C, Harris F, Fong J, Barrett-Connor E, Hulley SB. Postmenopausal hormone therapy and risk of stroke: the Heart and Estrogen-progestin Replacement Study (HERS). *Circulation*. 2001;103:638–642.
220. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med*. 2001;345:1243–1249. doi: 10.1056/NEJMoa010534
221. Renoux C, Dell'aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ*. 2010;340:c2519. doi: 10.1136/bmj.c2519
222. MacClellan LR, Giles W, Cole J, Wozniak M, Stern B, Mitchell BD, Kittner SJ. Probable migraine with visual aura and risk of ischemic stroke: the Stroke Prevention in Young Women study. *Stroke*. 2007;38:2438–2445. doi: 10.1161/STROKEAHA.107.488395
223. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2009;339:b3914. doi: 10.1136/bmj.b3914
224. Demel SL, Kittner S, Ley SH, McDermott M, Rexrode KM. Stroke risk factors unique to women. *Stroke*. 2018;49:518–523. doi: 10.1161/STROKEAHA.117.018415
225. Kittner SJ, Stern BJ, Feeser BR, Hebel R, Nagey DA, Buchholz DW, Earley CJ, Johnson CJ, Macko RF, Sloan MA, Wityk RJ, Wozniak MA. Pregnancy and the risk of stroke. *N Engl J Med*. 1996;335:768–774. doi: 10.1056/NEJM199609123351102
226. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension*. 2009;53:944–951. doi: 10.1161/HYPERTENSIONAHA.109.130765
227. Miller EC, Gatollari HJ, Too G, Boehme AK, Leffert L, Marshall RS, Elkind MSV, Willey JZ. Risk factors for pregnancy-associated stroke in women with preeclampsia. *Stroke*. 2017;48:1752–1759. doi: 10.1161/STROKEAHA.117.017374
228. Chow FC, Wilson MR, Wu K, Ellis RJ, Bosch RJ, Linas BP. Stroke incidence is highest in women and non-Hispanic blacks living with HIV in the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials cohort. *AIDS*. 2018;32:1125–1135. doi: 10.1097/QAD.0000000000001799
229. Chow FC, Regan S, Zanni MV, Looby SE, Bushnell CD, Meigs JB, Grinspoon SK, Feske SK, Triant VA. Elevated ischemic stroke risk among women living with HIV infection. *AIDS*. 2018;32:59–67. doi: 10.1097/QAD.0000000000001650
230. Xie C, Zhu R, Tian Y, Wang K. Association of obstructive sleep apnoea with the risk of vascular outcomes and all-cause mortality: a meta-analysis. *BMJ Open*. 2017;7:e013983. doi: 10.1136/bmjopen-2016-013983
231. Lisabeth LD, Sánchez BN, Chervin RD, Morgenstern LB, Zahuranec DB, Tower SD, Brown DL. High prevalence of poststroke sleep-disordered breathing in Mexican Americans. *Sleep Med*. 2017;33:97–102. doi: 10.1016/j.sleep.2016.01.010
232. Broadley SA, Jørgensen L, Cheek A, Salonikis S, Taylor J, Thompson PD, Antic R. Early investigation and treatment of obstructive sleep apnoea after acute stroke. *J Clin Neurosci*. 2007;14:328–333. doi: 10.1016/j.jocn.2006.01.017
233. Wu Z, Chen F, Yu F, Wang Y, Guo Z. A meta-analysis of obstructive sleep apnea in patients with cerebrovascular disease. *Sleep Breath*. 2017;22:729–742. doi: 10.1007/s11325-017-1604-4
234. Nicholson JS, McDermott MJ, Huang Q, Zhang H, Tyc VL. Full and home smoking ban adoption after a randomized controlled trial targeting secondhand smoke exposure reduction. *Nicotine Tob Res*. 2015;17:612–616. doi: 10.1093/ntr/ntu201
235. Brown DL, Mowla A, McDermott M, Morgenstern LB, Hegeman G 3rd, Smith MA, Garcia NM, Chervin RD, Lisabeth LD. Ischemic stroke subtype and presence of sleep-disordered breathing: the BASIC sleep apnea study. *J Stroke Cerebrovasc Dis*. 2015;24:388–393. doi: 10.1016/j.jstrokecerebrovasdis.2014.09.007

236. Martínez-García MA, Soler-Cataluña JJ, Ejarque-Martínez L, Soriano Y, Román-Sánchez P, Illa FB, Canal JM, Durán-Cantolla J. Continuous positive airway pressure treatment reduces mortality in patients with ischemic stroke and obstructive sleep apnea: a 5-year follow-up study. *Am J Respir Crit Care Med*. 2009;180:36–41. doi: 10.1164/rccm.200808-1341OC
237. Parra O, Arboix A, Montserrat JM, Quintó L, Bechich S, García-Eroles L. Sleep-related breathing disorders: impact on mortality of cerebrovascular disease. *Eur Respir J*. 2004;24:267–272.
238. Sahlin C, Sandberg O, Gustafson Y, Bucht G, Carlberg B, Stenlund H, Franklin KA. Obstructive sleep apnea is a risk factor for death in patients with stroke: a 10-year follow-up. *Arch Intern Med*. 2008;168:297–301. doi: 10.1001/archinternmed.2007.70
239. Turkington PM, Bamford J, Wanklyn P, Elliott MW. Prevalence and predictors of upper airway obstruction in the first 24 hours after acute stroke. *Stroke*. 2002;33:2037–2042.
240. Leng Y, Cappuccio FP, Wainwright NW, Surtees PG, Luben R, Brayne C, Khaw KT. Sleep duration and risk of fatal and nonfatal stroke: a prospective study and meta-analysis. *Neurology*. 2015;84:1072–1079. doi: 10.1212/WNL.0000000000001371
241. Yin J, Jin X, Shan Z, Li S, Huang H, Li P, Peng X, Peng Z, Yu K, Bao W, Yang W, Chen X, Liu L. Relationship of sleep duration with all-cause mortality and cardiovascular events: a systematic review and dose-response meta-analysis of prospective cohort studies. *J Am Heart Assoc*. 2017;6:e005947. doi: 10.1161/JAHA.117.005947
242. Li W, Wang D, Cao S, Yin X, Gong Y, Gan Y, Zhou Y, Lu Z. Sleep duration and risk of stroke events and stroke mortality: a systematic review and meta-analysis of prospective cohort studies. *Int J Cardiol*. 2016;223:870–876. doi: 10.1016/j.ijcard.2016.08.302
243. Jackson CA, Mishra GD. Depression and risk of stroke in midaged women: a prospective longitudinal study. *Stroke*. 2013;44:1555–1560. doi: 10.1161/STROKEAHA.113.001147
244. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review [published correction appears in *JAMA*. 2011;306:2565]. *JAMA*. 2011;306:1241–1249. doi: 10.1001/jama.2011.1282
245. Booth J, Connelly L, Lawrence M, Chalmers C, Joice S, Becker C, Dougall N. Evidence of perceived psychosocial stress as a risk factor for stroke in adults: a meta-analysis. *BMC Neurol*. 2015;15:233. doi: 10.1186/s12883-015-0456-4
246. Lightbody CE, Clegg A, Patel K, Lucas JC, Storey H, Hackett ML, Watkins DCL. Systematic review and meta-analysis of psychosocial risk factors for stroke. *Semin Neurol*. 2017;37:294–306. doi: 10.1055/s-0037-1603758
247. Wassertheil-Smoller S, Qi Q, Dave T, Mitchell BD, Jackson RD, Liu S, Park K, Salinas J, Dunn EC, Leira EC, Xu H, Ryan K, Smoller JW. Polygenic risk for depression increases risk of ischemic stroke: from the Stroke Genetics Network Study. *Stroke*. 2018;49:543–548. doi: 10.1161/STROKEAHA.117.018857
248. Simmons C, Noble JM, Leighton-Herrmann E, Hecht MF, Williams O. Community-level measures of stroke knowledge among children: findings from Hip Hop Stroke. *J Stroke Cerebrovasc Dis*. 2017;26:139–142. doi: 10.1016/j.jstrokecerebrovasdis.2016.08.045
249. Mochari-Greenberger H, Towfighi A, Mosca L. National women's knowledge of stroke warning signs, overall and by race/ethnic group. *Stroke*. 2014;45:1180–1182. doi: 10.1161/STROKEAHA.113.004242
250. Martinez M, Prabhakar N, Drake K, Coull B, Chong J, Ritter L, Kidwell C. Identification of barriers to stroke awareness and risk factor management unique to Hispanics. *Int J Environ Res Public Health*. 2015;13:ijerph13010023. doi: 10.3390/ijerph13010023
251. Madsen TE, Baird KA, Silver B, Gjelsvik A. Analysis of gender differences in knowledge of stroke warning signs. *J Stroke Cerebrovasc Dis*. 2015;24:1540–1547. doi: 10.1016/j.jstrokecerebrovasdis.2015.03.017
252. Frankel DS, Parker SE, Rosenfeld LE, Gorelick PB. HRS/NSA 2014 Survey of Atrial Fibrillation and Stroke: gaps in knowledge and perspective, opportunities for improvement. *J Stroke Cerebrovasc Dis*. 2015;24:1691–1700. doi: 10.1016/j.jstrokecerebrovasdis.2015.06.026
253. Kleindorfer D, Lindsell CJ, Moomaw CJ, Alwell K, Woo D, Flaherty ML, Adeoye O, Zakaria T, Broderick JP, Kissela BM. Which stroke symptoms prompt a 911 call? A population-based study. *Am J Emerg Med*. 2010;28:607–612. doi: 10.1016/j.ajem.2009.02.016
254. Centers for Disease Control and Prevention (CDC). Prevalence and most common causes of disability among adults: United States, 2005. *MMWR Morb Mortal Wkly Rep*. 2009;58:421–426.
255. Singh T, Peters SR, Tirschwell DL, Creutzfeldt CJ. Palliative care for hospitalized patients with stroke: results from the 2010 to 2012 National Inpatient Sample. *Stroke*. 2017;48:2534–2540. doi: 10.1161/STROKEAHA.117.016893
256. US Burden of Disease Collaborators. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA*. 2013;310:591–608. doi: 10.1001/jama.2013.13805
257. Janus-Laszuk B, Mirowska-Guzel D, Sarzynska-Dlugosz I, Czlonkowska A. Effect of medical complications on the after-stroke rehabilitation outcome. *NeuroRehabilitation*. 2017;40:223–232. doi: 10.3233/NRE-161407
258. Sherman DG, Albers GW, Bladin C, Fieschi C, Gabbai AA, Kase CS, O'Riordan W, Pineo GF; PREVAIL Investigators. The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison. *Lancet*. 2007;369:1347–1355. doi: 10.1016/S0140-6736(07)60633-3
259. Chan L, Hu CJ, Fan YC, Li FY, Hu HH, Hong CT, Bai CH. Incidence of poststroke seizures: a meta-analysis. *J Clin Neurosci*. 2018;47:347–351. doi: 10.1016/j.jocn.2017.10.088
260. O'Donnell MJ, Diener HC, Sacco RL, Panju AA, Vinisko R, Yusuf S; PRoFESS Investigators. Chronic pain syndromes after ischemic stroke: PRoFESS trial. *Stroke*. 2013;44:1238–1243. doi: 10.1161/STROKEAHA.111.671008
261. Kapral MK, Fang J, Alibhai SM, Cram P, Cheung AM, Casaubon LK, Prager M, Stamplecoski M, Rashkovan B, Austin PC. Risk of fractures after stroke: results from the Ontario Stroke Registry. *Neurology*. 2017;88:57–64. doi: 10.1212/WNL.0000000000003457
262. Glozier N, Moullaali TJ, Sivertsen B, Kim D, Mead G, Jan S, Li Q, Hackett ML. The course and impact of poststroke insomnia in stroke survivors aged 18 to 65 years: results from the Psychosocial Outcomes In StrokE (POISE) Study. *Cerebrovasc Dis Extra*. 2017;7:9–20. doi: 10.1159/000455751
263. Li J, Yuan M, Liu Y, Zhao Y, Wang J, Guo W. Incidence of constipation in stroke patients: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2017;96:e7225. doi: 10.1097/MD.0000000000007225
264. Ryan AS, Ivey FM, Serra MC, Hartstein J, Hafer-Macko CE. Sarcopenia and physical function in middle-aged and older stroke survivors. *Arch Phys Med Rehabil*. 2017;98:495–499. doi: 10.1016/j.apmr.2016.07.015
265. Towfighi A, Ovbiagele B, El Husseini N, Hackett ML, Jorge RE, Kissela BM, Mitchell PH, Skolarus LE, Whooley MA, Williams LS; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes Research. Poststroke depression: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2017;48:e30–e43. doi: 10.1161/STR.0000000000000113
266. Harnod T, Lin CL, Kao CH. Risk of suicide attempt in poststroke patients: a population-based cohort study. *J Am Heart Assoc*. 2018;7:e007830. doi: 10.1161/JAHA.117.007830
267. Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. *Int J Stroke*. 2014;9:1017–1025. doi: 10.1111/ijs.12357
268. Bartoli F, Lillia N, Lax A, Crocamo C, Mantero V, Carrà G, Agostoni E, Clerici M. Depression after stroke and risk of mortality: a systematic review and meta-analysis. *Stroke Res Treat*. 2013;2013:862978. doi: 10.1155/2013/862978
269. Samuelsson M, Lindell D, Norrving B. Presumed pathogenetic mechanisms of re-current stroke after lacunar infarction. *Cerebrovasc Dis*. 1996;6:6:128–136.
270. Miyao S, Takano A, Teramoto J, Takahashi A. Leukoaraiosis in relation to prognosis for patients with lacunar infarction. *Stroke*. 1992;23:1434–1438.
271. Hackett ML, Anderson CS, House A, Xia J. Interventions for treating depression after stroke. *Cochrane Database Syst Rev*. 2008;(4):CD003437. doi: 10.1002/14651858.CD003437.pub3
272. Alexopoulos GS, Wilkins VM, Marino P, Kanellopoulos D, Reding M, Sirey JA, Raue PJ, Ghosh S, O'Dell MW, Kiosses DN. Ecosystem focused therapy in poststroke depression: a preliminary study. *Int J Geriatr Psychiatry*. 2012;27:1053–1060. doi: 10.1002/gps.2822
273. Kirkness CJ, Becker KJ, Cain KC, Kohen R, Tirschwell DL, Teri L, Veith RR,Mitchell PH. Abstract W P125: Telephone versus in-person psychosocial behavioral treatment in post-stroke depression. *Stroke*. 2015;46(suppl 1):AWP125.
274. Mitchell PH, Veith RC, Becker KJ, Buzaitis A, Cain KC, Fruin M, Tirschwell D, Teri L. Brief psychosocial-behavioral intervention with antidepressant reduces poststroke depression significantly more than usual care with

antidepressant: living well with stroke: randomized, controlled trial. *Stroke*. 2009;40:3073–3078. doi: 10.1161/STROKEAHA.109.549808
275. Thomas SA, Walker MF, Macniven JA, Haworth H, Lincoln NB. Communication and Low Mood (CALM): a randomized controlled trial of behavioural therapy for stroke patients with aphasia. *Clin Rehabil*. 2013;27:398–408. doi: 10.1177/0269215512462227
276. Salter KL, Foley NC, Zhu L, Jutai JW, Teasell RW. Prevention of post-stroke depression: does prophylactic pharmacotherapy work? *J Stroke Cerebrovasc Dis*. 2013;22:1243–1251. doi: 10.1016/j.jstrokecerebrovasdis.2012.03.013
277. Robinson RG, Jorge RE, Moser DJ, Acion L, Solodkin A, Small SL, Fonzetti P, Hegel M, Arndt S. Escitalopram and problem-solving therapy for prevention of poststroke depression: a randomized controlled trial [published correction appears in *JAMA*. 2009;301:1024]. *JAMA*. 2008;299:2391–2400. doi: 10.1001/jama.299.20.2391
278. Delavaran H, Jönsson AC, Lövkvist H, Iwarsson S, Elmståhl S, Norrving B, Lindgren A. Cognitive function in stroke survivors: a 10-year follow-up study. *Acta Neurol Scand*. 2017;136:187–194. doi: 10.1111/ane.12709
279. Dhamoon MS, Moon YP, Paik MC, Boden-Albala B, Rundek T, Sacco RL, Elkind MS. Long-term functional recovery after first ischemic stroke: the Northern Manhattan Study. *Stroke*. 2009;40:2805–2811. doi: 10.1161/STROKEAHA.109.549576
280. Dhamoon MS, Moon YP, Paik MC, Boden-Albala B, Rundek T, Sacco RL, Elkind MS. Quality of life declines after first ischemic stroke: the Northern Manhattan Study. *Neurology*. 2010;75:328–334. doi: 10.1212/WNL.0b013e3181ea9f03
281. Dhamoon MS, Moon YP, Paik MC, Sacco RL, Elkind MS. Trajectory of functional decline before and after ischemic stroke: the Northern Manhattan Study. *Stroke*. 2012;43:2180–2184. doi: 10.1161/STROKEAHA.112.658922
282. Levine DA, Galecki AT, Langa KM, Unverzagt FW, Kabeto MU, Giordani B, Wadley VG. Trajectory of cognitive decline after incident stroke. *JAMA*. 2015;314:41–51. doi: 10.1001/jama.2015.6968
283. Tang EY, Amiesimaka O, Harrison SL, Green E, Price C, Robinson L, Siervo M, Stephan BC. Longitudinal effect of stroke on cognition: a systematic review. *J Am Heart Assoc*. 2018;7:e006443. doi: 10.1161/JAHA.117.006443
284. Dhamoon MS, Longstreth WT Jr, Bartz TM, Kaplan RC, Elkind MSV. Disability trajectories before and after stroke and myocardial infarction: the Cardiovascular Health Study. *JAMA Neurol*. 2017;74:1439–1445. doi: 10.1001/jamaneurol.2017.2802
285. El Husseini N, Goldstein LB, Peterson ED, Zhao X, Olson DM, Williams JW Jr, Bushnell C, Laskowitz DT. Depression status is associated with functional decline over 1-year following acute stroke. *J Stroke Cerebrovasc Dis*. 2017;26:1393–1399. doi: 10.1016/j.jstrokecerebrovasdis.2017.03.026
286. Winovich DT, Longstreth WT Jr, Arnold AM, Varadhan R, Zeki Al Hazzouri A, Cushman M, Newman AB, Odden MC. Factors associated with ischemic stroke survival and recovery in older adults. *Stroke*. 2017;48:1818–1826. doi: 10.1161/STROKEAHA.117.016726
287. Medicare Payment Advisory Commission (MedPAC). Report to the Congress: Medicare payment policy. Washington, DC: Medicare Payment Advisory Commission; 2013. http://medpac.gov/docs/default-source/reports/mar13_entirereport.pdf. Accessed August 23, 2016.
288. Lichtman JH, Leifheit-Limson EC, Jones SB, Wang Y, Goldstein LB. Preventable readmissions within 30 days of ischemic stroke among Medicare beneficiaries. *Stroke*. 2013;44:3429–3435. doi: 10.1161/STROKEAHA.113.003165
289. Ottenbacher KJ, Karmarkar A, Graham JE, Kuo YF, Deutsch A, Reistetter TA, Al Snih S, Granger CV. Thirty-day hospital readmission following discharge from postacute rehabilitation in fee-for-service Medicare patients. *JAMA*. 2014;311:604–614. doi: 10.1001/jama.2014.8
290. Whitson HE, Landerman LR, Newman AB, Fried LP, Pieper CF, Cohen HJ. Chronic medical conditions and the sex-based disparity in disability: the Cardiovascular Health Study. *J Gerontol A Biol Sci Med Sci*. 2010;65:1325–1331. doi: 10.1093/gerona/glq139
291. Gall SL, Tran PL, Martin K, Blizzard L, Srikanth V. Sex differences in long-term outcomes after stroke: functional outcomes, handicap, and quality of life. *Stroke*. 2012;43:1982–1987. doi: 10.1161/STROKEAHA.111.632547
292. Ottenbacher KJ, Campbell J, Kuo YF, Deutsch A, Ostir GV, Granger CV. Racial and ethnic differences in postacute rehabilitation outcomes after stroke in the United States. *Stroke*. 2008;39:1514–1519. doi: 10.1161/STROKEAHA.107.501254
293. Ellis C, Boan AD, Turan TN, Ozark S, Bachman D, Lackland DT. Racial differences in poststroke rehabilitation utilization and functional outcomes. *Arch Phys Med Rehabil*. 2015;96:84–90. doi: 10.1016/j.apmr.2014.08.018
294. Lisabeth LD, Sánchez BN, Baek J, Skolarus LE, Smith MA, Garcia N, Brown DL, Morgenstern LB. Neurological, functional, and cognitive stroke outcomes in Mexican Americans. *Stroke*. 2014;45:1096–1101. doi: 10.1161/STROKEAHA.113.003912
295. Bettger JP, Thomas L, Liang L, Xian Y, Bushnell CD, Saver JL, Fonarow GC, Peterson ED. Hospital variation in functional recovery after stroke. *Circ Cardiovasc Qual Outcomes*. 2017;10:e002391. doi: 10.1161/CIRCOUTCOMES.115.002391
296. Olaiya MT, Cadilhac DA, Kim J, Nelson MR, Srikanth VK, Andrew NE, Bladin CF, Gerraty RP, Fitzgerald SM, Phan T, Frayne J, Thrift AG; STANDFIRM (Shared Team Approach Between Nurses and Doctors for Improved Risk Factor Management) Investigators. Long-term unmet needs and associated factors in stroke or TIA survivors: an observational study. *Neurology*. 2017;89:68–75. doi: 10.1212/WNL.0000000000004063
297. Loh AZ, Tan JS, Zhang MW, Ho RC. The global prevalence of anxiety and depressive symptoms among caregivers of stroke survivors. *J Am Med Dir Assoc*. 2017;18:111–116. doi: 10.1016/j.jamda.2016.08.014
298. Agrawal N, Johnston SC, Wu YW, Sidney S, Fullerton HJ. Imaging data reveal a higher pediatric stroke incidence than prior US estimates. *Stroke*. 2009;40:3415–3421. doi: 10.1161/STROKEAHA.109.564633
299. Kirton A, Armstrong-Wells J, Chang T, Deveber G, Rivkin MJ, Hernandez M, Carpenter J, Yager JY, Lynch JK, Ferriero DM; International Pediatric Stroke Study Investigators. Symptomatic neonatal arterial ischemic stroke: the International Pediatric Stroke Study. *Pediatrics*. 2011;128:e1402–e1410. doi: 10.1542/peds.2011-1148
300. Mallick AA, Ganesan V, Kirkham FJ, Fallon P, Hedderly T, McShane T, Parker AP, Wassmer E, Wraige E, Amin S, Edwards HB, O'Callaghan FJ. Diagnostic delays in paediatric stroke. *J Neurol Neurosurg Psychiatry*. 2015;86:917–921. doi: 10.1136/jnnp-2014-309188
301. Mackay MT, Wiznitzer M, Benedict SL, Lee KJ, Deveber GA, Ganesan V; International Pediatric Stroke Study Group. Arterial ischemic stroke risk factors: the International Pediatric Stroke Study. *Ann Neurol*. 2011;69:130–140. doi: 10.1002/ana.22224
302. Ganesan V, Prengler M, McShane MA, Wade AM, Kirkham FJ. Investigation of risk factors in children with arterial ischemic stroke. *Ann Neurol*. 2003;53:167–173. doi: 10.1002/ana.10423
303. Wintermark M, Hills NK, deVeber GA, Barkovich AJ, Elkind MS, Sear K, Zhu G, Leiva-Salinas C, Hou Q, Dowling MM, Bernard TJ, Friedman NR, Ichord RN, Fullerton HJ; VIPS Investigators. Arteriopathy diagnosis in childhood arterial ischemic stroke: results of the Vascular Effects of Infection in Pediatric Stroke study. *Stroke*. 2014;45:3597–3605. doi: 10.1161/STROKEAHA.114.007404
304. Fox CK, Sidney S, Fullerton HJ. Community-based case-control study of childhood stroke risk associated with congenital heart disease. *Stroke*. 2015;46:336–340. doi: 10.1161/STROKEAHA.114.007218
305. Asakai H, Cardamone M, Hutchinson D, Stojanovski B, Galati JC, Cheung MM, Mackay MT. Arterial ischemic stroke in children with cardiac disease. *Neurology*. 2015;85:2053–2059. doi: 10.1212/WNL.0000000000002036
306. Gelfand AA, Fullerton HJ, Jacobson A, Sidney S, Goadsby PJ, Kurth T, Pressman A. Is migraine a risk factor for pediatric stroke? *Cephalalgia*. 2015;35:1252–1260. doi: 10.1177/0333102415576222
307. Hills NK, Johnston SC, Sidney S, Zielinski BA, Fullerton HJ. Recent trauma and acute infection as risk factors for childhood arterial ischemic stroke. *Ann Neurol*. 2012;72:850–858. doi: 10.1002/ana.23688
308. Hills NK, Sidney S, Fullerton HJ. Timing and number of minor infections as risk factors for childhood arterial ischemic stroke. *Neurology*. 2014;83:890–897. doi: 10.1212/WNL.0000000000000752
309. Elkind MS, Hills NK, Glaser CA, Lo WD, Amlie-Lefond C, Dlamini N, Kneen R, Hod EA, Wintermark M, deVeber GA, Fullerton HJ; and the VIPS Investigators. Herpesvirus infections and childhood arterial ischemic stroke: results of the VIPS study. *Circulation*. 2016;133:732–741. doi: 10.1161/CIRCULATIONAHA.115.018595
310. Kenet G, Lütkhoff LK, Albisetti M, Bernard T, Bonduel M, Brandao L, Chabrier S, Chan A, deVeber G, Fiedler B, Fullerton HJ, Goldenberg NA, Grabowski E, Günther G, Heller C, Holzhauer S, Iorio A, Journeycake J, Junker R, Kirkham FJ, Kurnik K, Lynch JK, Male C, Manco-Johnson M, Mesters R, Monagle P, van Ommen CH, Raffini L, Rostásy K, Simioni P, Sträter RD, Young G, Nowak-Göttl U. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and

meta-analysis of observational studies. *Circulation*. 2010;121:1838–1847. doi: 10.1161/CIRCULATIONAHA.109.913673
311. Curtis C, Mineyko A, Massicotte P, Leaker M, Jiang XY, Floer A, Kirton A. Thrombophilia risk is not increased in children after perinatal stroke [published correction appears in *Blood*. 2017;130:382]. *Blood*. 2017;129:2793–2800. doi: 10.1182/blood-2016-11-750893
312. Bigi S, Fischer U, Wehrli E, Mattle HP, Boltshauser E, Bürki S, Jeannet PY, Fluss J, Weber P, Nedeltchev K, El-Koussy M, Steinlin M, Arnold M. Acute ischemic stroke in children versus young adults. *Ann Neurol*. 2011;70:245–254. doi: 10.1002/ana.22427
313. George MG, Tong X, Kuklina EV, Labarthe DR. Trends in stroke hospitalizations and associated risk factors among children and young adults, 1995-2008. *Ann Neurol*. 2011;70:713–721. doi: 10.1002/ana.22539
314. Mallick AA, Ganesan V, Kirkham FJ, Fallon P, Hedderly T, McShane T, Parker AP, Wassmer E, Wraige E, Amin S, Edwards HB, Tilling K, O'Callaghan FJ. Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: a prospective population-based study. *Lancet Neurol*. 2014;13:35–43. doi: 10.1016/S1474-4422(13)70290-4
315. Fullerton HJ, Wu YW, Zhao S, Johnston SC. Risk of stroke in children: ethnic and gender disparities. *Neurology*. 2003;61:189–194.
316. Lehman LL, Fullerton HJ. Changing ethnic disparity in ischemic stroke mortality in US children after the STOP trial. *JAMA Pediatr*. 2013;167:754–758. doi: 10.1001/jamapediatrics.2013.89
317. Elbers J, deVeber G, Pontigon AM, Moharir M. Long-term outcomes of pediatric ischemic stroke in adulthood. *J Child Neurol*. 2014;29:782–788. doi: 10.1177/0883073813484358
318. Boardman JP, Ganesan V, Rutherford MA, Saunders DE, Mercuri E, Cowan F. Magnetic resonance image correlates of hemiparesis after neonatal and childhood middle cerebral artery stroke. *Pediatrics*. 2005;115:321–326. doi: 10.1542/peds.2004-0427
319. Hajek CA, Yeates KO, Anderson V, Mackay M, Greenham M, Gomes A, Lo W. Cognitive outcomes following arterial ischemic stroke in infants and children. *J Child Neurol*. 2014;29:887–894. doi: 10.1177/0883073813491828
320. Studer M, Boltshauser E, Capone Mori A, Datta A, Fluss J, Mercati D, Hackenberg A, Keller E, Maier O, Marcoz JP, Ramelli GP, Poloni C, Schmid R, Schmitt-Mechelke T, Wehrli E, Heinks T, Steinlin M. Factors affecting cognitive outcome in early pediatric stroke. *Neurology*. 2014;82:784–792. doi: 10.1212/WNL.0000000000000162
321. Lo W, Gordon A, Hajek C, Gomes A, Greenham M, Perkins E, Zumberge N, Anderson V, Yeates KO, Mackay MT. Social competence following neonatal and childhood stroke. *Int J Stroke*. 2014;9:1037–1044. doi: 10.1111/ijs.12222
322. Bemister TB, Brooks BL, Dyck RH, Kirton A. Parent and family impact of raising a child with perinatal stroke. *BMC Pediatr*. 2014;14:182. doi: 10.1186/1471-2431-14-182
323. Danchaivijitr N, Cox TC, Saunders DE, Ganesan V. Evolution of cerebral arteriopathies in childhood arterial ischemic stroke. *Ann Neurol*. 2006;59:620–626. doi: 10.1002/ana.20800
324. Tuppin P, Samson S, Woimant F, Chabrier S. Management and 2-year follow-up of children aged 29 days to 17 years hospitalized for a first stroke in France (2009-2010). *Arch Pediatr*. 2014;21:1305–1315. doi: 10.1016/j.arcped.2014.08.023
325. Fullerton HJ, Wu YW, Sidney S, Johnston SC. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. *Pediatrics*. 2007;119:495–501. doi: 10.1542/peds.2006-2791
326. Koroknay-Pál P, Niemelä M, Lehto H, Kivisaari R, Numminen J, Laakso A, Hernesniemi J. De novo and recurrent aneurysms in pediatric patients with cerebral aneurysms. *Stroke*. 2013;44:1436–1439. doi: 10.1161/STROKEAHA.111.676601
327. Wusthoff CJ, Kessler SK, Vossough A, Ichord R, Zelonis S, Halperin A, Gordon D, Vargas G, Licht DJ, Smith SE. Risk of later seizure after perinatal arterial ischemic stroke: a prospective cohort study. *Pediatrics*. 2011;127:e1550–e1557. doi: 10.1542/peds.2010-1577
328. Fox CK, Glass HC, Sidney S, Lowenstein DH, Fullerton HJ. Acute seizures predict epilepsy after childhood stroke. *Ann Neurol*. 2013;74:249–256. doi: 10.1002/ana.23916
329. Hsu CJ, Weng WC, Peng SS, Lee WT. Early-onset seizures are correlated with late-onset seizures in children with arterial ischemic stroke. *Stroke*. 2014;45:1161–1163. doi: 10.1161/STROKEAHA.113.004015
330. Beslow LA, Abend NS, Gindville MC, Bastian RA, Licht DJ, Smith SE, Hillis AE, Ichord RN, Jordan LC. Pediatric intracerebral hemorrhage: acute symptomatic seizures and epilepsy. *JAMA Neurol*. 2013;70:448–454. doi: 10.1001/jamaneurol.2013.1033
331. Bernard TJ, Rivkin MJ, Scholz K, deVeber G, Kirton A, Gill JC, Chan AK, Hovinga CA, Ichord RN, Grotta JC, Jordan LC, Benedict S, Friedman NR, Dowling MM, Elbers J, Torres M, Sultan S, Cummings DD, Grabowski EF, McMillan HJ, Beslow LA, Amlie-Lefond C; on behalf of the Thrombolysis in Pediatric Stroke Study. Emergence of the primary pediatric stroke center: impact of the thrombolysis in pediatric stroke trial. *Stroke*. 2014;45:2018–2023. doi: 10.1161/STROKEAHA.114.004919
332. Ladner TR, Mahdi J, Gindville MC, Gordon A, Harris ZL, Crossman K, Pruthi S, Abramo TJ, Jordan LC. Pediatric acute stroke protocol activation in a children's hospital emergency department. *Stroke*. 2015;46:2328–2331. doi: 10.1161/STROKEAHA.115.009961
333. DeLaroche AM, Sivaswamy L, Farooqi A, Kannikeswaran N. Pediatric stroke clinical pathway improves the time to diagnosis in an emergency department. *Pediatr Neurol*. 2016;65:39–44. doi: 10.1016/j.pediatrneurol.2016.09.005
334. Hamilton W, Huang H, Seiber E, Lo W. Cost and outcome in pediatric ischemic stroke. *J Child Neurol*. 2015;30:1483–1488. doi: 10.1177/0883073815570673
335. Plumb P, Seiber E, Dowling MM, Lee J, Bernard TJ, deVeber G, Ichord RN, Bastian R, Lo WD. Out-of-pocket costs for childhood stroke: the impact of chronic illness on parents' pocketbooks. *Pediatr Neurol*. 2015;52:73–6.e2. doi: 10.1016/j.pediatrneurol.2014.09.010
336. Nedeltchev K, der Maur TA, Georgiadis D, Arnold M, Caso V, Mattle HP, Schroth G, Remonda L, Sturzenegger M, Fischer U, Baumgartner RW. Ischaemic stroke in young adults: predictors of outcome and recurrence. *J Neurol Neurosurg Psychiatry*. 2005;76:191–195. doi: 10.1136/jnnp.2004.040543
337. Swerdel JN, Rhoads GG, Cheng JQ, Cosgrove NM, Moreyra AE, Kostis JB, Kostis WJ; Myocardial Infarction Data Acquisition System (MIDAS 29) Study Group. Ischemic stroke rate increases in young adults: evidence for a generational effect? *J Am Heart Assoc*. 2016;5:e004245.
338. Rutten-Jacobs LC, Arntz RM, Maaijwee NA, Schoonderwaldt HC, Dorresteijn LD, van Dijk EJ, de Leeuw FE. Long-term mortality after stroke among adults aged 18 to 50 years. *JAMA*. 2013;309:1136–1144. doi: 10.1001/jama.2013.842
339. Synhaeve NE, Arntz RM, van Alebeek ME, van Pamelen J, Maaijwee NA, Rutten-Jacobs LC, Schoonderwaldt HC, de Kort PL, van Dijk EJ, de Leeuw FE. Women have a poorer very long-term functional outcome after stroke among adults aged 18-50 years: the FUTURE study. *J Neurol*. 2016;263:1099–1105. doi: 10.1007/s00415-016-8042-2
340. Dehlendorff C, Andersen KK, Olsen TS. Sex disparities in stroke: women have more severe strokes but better survival than men. *J Am Heart Assoc*. 2015;4:e001967. doi: 10.1161/JAHA.115.001967
341. Russo T, Felzani G, Marini C. Stroke in the very old: a systematic review of studies on incidence, outcome, and resource use. *J Aging Res*. 2011;2011:108785. doi: 10.4061/2011/108785
342. Ay H, Arsava EM, Andsberg G, Benner T, Brown RD Jr, Chapman SN, Cole JW, Delavaran H, Dichgans M, Engström G, Giralt-Steinhauer E, Grewal RP, Gwinn K, Jern C, Jimenez-Conde J, Jood K, Katsnelson M, Kissela B, Kittner SJ, Kleindorfer DO, Labovitz DL, Lanfranconi S, Lee JM, Lehm M, Lemmens R, Levi C, Li L, Lindgren A, Markus HS, McArdle PF, Melander O, Norrving B, Peddareddygari LR, Pedersén A, Pera J, Rannikmäe K, Rexrode KM, Rhodes D, Rich SS, Roquer J, Rosand J, Rothwell PM, Rundek T, Sacco RL, Schmidt R, Schürks M, Seiler S, Sharma P, Slowik A, Sudlow C, Thijs V, Woodfield R, Worrall BB, Meschia JF. Pathogenic ischemic stroke phenotypes in the NINDS-Stroke Genetics Network [published correction appears in *Stroke*. 2015;46:e17]. *Stroke*. 2014;45:3589–3596. doi: 10.1161/STROKEAHA.114.007362
343. Forti P, Maioli F, Procaccianti G, Nativio V, Lega MV, Coveri M, Zoli M, Sacquegna T. Independent predictors of ischemic stroke in the elderly: prospective data from a stroke unit [published correction appears in *Neurology*. 2013;81:1882]. *Neurology*. 2013;80:29–38. doi: 10.1212/WNL.0b013e31827b1a41
344. Saposnik G, Black S; Stroke Outcome Research Canada (SORCan) Working Group. Stroke in the very elderly: hospital care, case fatality and disposition. *Cerebrovasc Dis*. 2009;27:537–543. doi: 10.1159/000214216
345. Kammersgaard LP, Jørgensen HS, Reith J, Nakayama H, Pedersen PM, Olsen TS; Copenhagen Stroke Study. Short- and long-term prognosis for very old stroke patients: the Copenhagen Stroke Study. *Age Ageing*. 2004;33:149–154. doi: 10.1093/ageing/afh052
346. Ovbiagele B, Markovic D, Towfighi A. Recent age- and gender-specific trends in mortality during stroke hospitalization in the United States. *Int J Stroke*. 2011;6:379–387. doi: 10.1111/j.1747-4949.2011.00590.x

347. Howard G, Goff DC. Population shifts and the future of stroke: forecasts of the future burden of stroke. *Ann N Y Acad Sci*. 2012;1268:14–20. doi: 10.1111/j.1749-6632.2012.06665.x
348. Olsen TS, Andersen KK. Stroke in centenarians. *Geriatr Gerontol Int*. 2014;14:84–88. doi: 10.1111/ggi.12058
349. McKinney JS, Cheng JQ, Rybinnik I, Kostis JB. Comprehensive stroke centers may be associated with improved survival in hemorrhagic stroke. *J Am Heart Assoc*. 2015;4:e001448. doi: 10.1161/JAHA.114.001448
350. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev*. 2013;9:CD000197. doi: 10.1002/14651858.CD000197.pub3
351. Man S, Cox M, Patel P, Smith EE, Reeves MJ, Saver JL, Bhatt DL, Xian Y, Schwamm LH, Fonarow GC. Differences in acute ischemic stroke quality of care and outcomes by primary stroke center certification organization. *Stroke*. 2017;48:412–419. doi: 10.1161/STROKEAHA.116.014426
352. Man S, Schold JD, Uchino K. Impact of stroke center certification on mortality after ischemic stroke: the Medicare cohort from 2009 to 2013. *Stroke*. 2017;48:2527–2533. doi: 10.1161/STROKEAHA.116.016473
353. Fonarow GC, Zhao X, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Xian Y, Hernandez AF, Peterson ED, Schwamm LH. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. *JAMA*. 2014;311:1632–1640. doi: 10.1001/jama.2014.3203
354. Ramirez L, Kim-Tenser MA, Sanossian N, Cen S, Wen G, He S, Mack WJ, Towfighi A. Trends in acute ischemic stroke hospitalizations in the United States. *J Am Heart Assoc*. 2016;5:e003233. doi: 10.1161/JAHA.116.003233
355. Kumar N, Khera R, Pandey A, Garg N. Racial differences in outcomes after acute ischemic stroke hospitalization in the United States. *J Stroke Cerebrovasc Dis*. 2016;25:1970–1977. doi: 10.1016/j.jstrokecerebrovasdis.2016.03.049
356. Wang FW, Esterbrooks D, Kuo YF, Mooss A, Mohiuddin SM, Uretsky BF. Outcomes after carotid artery stenting and endarterectomy in the Medicare population. *Stroke*. 2011;42:2019–2025. doi: 10.1161/STROKEAHA.110.608992
357. Jalbert JJ, Nguyen LL, Gerhard-Herman MD, Kumamaru H, Chen CY, Williams LA, Liu J, Rothman AT, Jaff MR, Seeger JD, Benenati JF, Schneider PA, Aronow HD, Johnston JA, Brott TG, Tsai TT, White CJ, Setoguchi S. Comparative effectiveness of carotid artery stenting versus carotid endarterectomy among Medicare beneficiaries. *Circ Cardiovasc Qual Outcomes*. 2016;9:275–285. doi: 10.1161/CIRCOUTCOMES.115.002336
358. Kim LK, Yang DC, Swaminathan RV, Minutello RM, Okin PM, Lee MK, Sun X, Wong SC, McCormick DJ, Bergman G, Allareddy V, Singh H, Feldman DN. Comparison of trends and outcomes of carotid artery stenting and endarterectomy in the United States, 2001 to 2010. *Circ Cardiovasc Interv*. 2014;7:692–700. doi: 10.1161/CIRCINTERVENTIONS.113.001338
359. Al-Damluji MS, Dharmarajan K, Zhang W, Geary LL, Stilp E, Dardik A, Mena-Hurtado C, Curtis JP. Readmissions after carotid artery revascularization in the Medicare population. *J Am Coll Cardiol*. 2015;65:1398–1408. doi: 10.1016/j.jacc.2015.01.048
360. Bangalore S, Bhatt DL, Röther J, Alberts MJ, Thornton J, Wolski K, Goto S, Hirsch AT, Smith SC, Aichner FT, Topakian R, Cannon CP, Steg PG; for the REACH Registry Investigators. Late outcomes after carotid artery stenting versus carotid endarterectomy: insights from a propensity-matched analysis of the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Circulation*. 2010;122:1091–1100. doi: 10.1161/CIRCULATIONAHA.109.933341
361. Obeid T, Alshaikh H, Nejim B, Arhuidese I, Locham S, Malas M. Fixed and variable cost of carotid endarterectomy and stenting in the United States: a comparative study. *J Vasc Surg*. 2017;65:1398–1406.e1. doi: 10.1016/j.jvs.2016.11.062
362. McDonald RJ, Kallmes DF, Cloft HJ. Comparison of hospitalization costs and Medicare payments for carotid endarterectomy and carotid stenting in asymptomatic patients. *AJNR Am J Neuroradiol*. 2012;33:420–425. doi: 10.3174/ajnr.A2791
363. Sternbergh WC 3rd, Crenshaw GD, Bazan HA, Smith TA. Carotid endarterectomy is more cost-effective than carotid artery stenting. *J Vasc Surg*. 2012;55:1623–1628. doi: 10.1016/j.jvs.2011.12.045
364. Vilain KR, Magnuson EA, Li H, Clark WM, Begg RJ, Sam AD 2nd, Sternbergh WC 3rd, Weaver FA, Gray WA, Voeks JH, Brott TG, Cohen DJ; on behalf of the CREST Investigators. Costs and cost-effectiveness of carotid stenting versus endarterectomy for patients at standard surgical risk: results from the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). *Stroke*. 2012;43:2408–2416. doi: 10.1161/STROKEAHA.112.661355
365. Witt AH, Johnsen SP, Jensen LP, Hansen AK, Hundborg HH, Andersen G. Reducing delay of carotid endarterectomy in acute ischemic stroke patients: a nationwide initiative. *Stroke*. 2013;44:686–690. doi: 10.1161/STROKEAHA.111.678565
366. Mokin M, Rojas H, Levy EI. Randomized trials of endovascular therapy for stroke: impact on stroke care. *Nat Rev Neurol*. 2016;12:86–94. doi: 10.1038/nrneurol.2015.240
367. Rebello LC, Haussen DC, Grossberg JA, Belagaje S, Lima A, Anderson A, Frankel MR, Nogueira RG. Early endovascular treatment in intravenous tissue plasminogen activator-ineligible patients. *Stroke*. 2016;47:1131–1134. doi: 10.1161/STROKEAHA.115.012586
368. Regenhardt RW, Mecca AP, Flavin SA, Boulouis G, Lauer A, Zachrison KS, Boomhower J, Patel AB, Hirsch JA, Schwamm LH, Leslie-Mazwi TM. Delays in the air or ground transfer of patients for endovascular thrombectomy. *Stroke*. 2018;49:1419–1425. doi: 10.1161/STROKEAHA.118.020618
369. Agency for Healthcare Research and Quality. Total expenditures in millions by condition, United States, 1996–2015: Medical Expenditure Panel Survey. https://meps.ahrq.gov/mepstrends/hc_cond/. Accessed March 13, 2018.
370. Agency for Healthcare Research and Quality. Mean expenditure per person with care by condition, United States, 1996–2015: Medical Expenditure Panel Survey. https://meps.ahrq.gov/mepstrends/hc_cond/. Accessed March 13, 2018.
371. RTI International. Projections of Cardiovascular Disease Prevalence and Costs: 2015–2035: Technical Report [report prepared for the American Heart Association]. Research Triangle Park, NC: RTI International; November 2016. RTI project number 021480.003.001.001. https://healthmetrics.heart.org/wp-content/uploads/2017/10/Projections-of-Cardiovascular-Disease.pdf. Accessed November 14, 2018.
372. Godwin KM, Wasserman J, Ostwald SK. Cost associated with stroke: outpatient rehabilitative services and medication. *Top Stroke Rehabil*. 2011;18(suppl 1):676–684. doi: 10.1310/tsr18s01-676
373. Ellis C, Simpson AN, Bonilha H, Mauldin PD, Simpson KN. The one-year attributable cost of poststroke aphasia. *Stroke*. 2012;43:1429–1431. doi: 10.1161/STROKEAHA.111.647339
374. Eshak ES, Honjo K, Iso H, Ikeda A, Inoue M, Sawada N, Tsugane S. Changes in the employment status and risk of stroke and stroke types. *Stroke*. 2017;48:1176–1182. doi: 10.1161/STROKEAHA.117.016967
374a. Kivimäki M, Jokela M, Nyberg ST, Singh-Manoux A, Fransson EI, Alfredsson L, Bjorner JB, Borritz M, Burr H, Casini A, Clays E, De Bacquer D, Dragano N, Erbel R, Geuskens GA, Hamer M, Hooftman WE, Houtman IL, Jöckel KH, Kittel F, Knutsson A, Koskenvuo M, Lunau T, Madsen IE, Nielsen ML, Nordin M, Oksanen T, Pejtersen JH, Pentti J, Rugulies R, Salo P, Shipley MJ, Siegrist J, Steptoe A, Suominen SB, Theorell T, Vahtera J, Westerholm PJ, Westerlund H, O'Reilly D, Kumari M, Batty GD, Ferrie JE, Virtanen M; for the IPD-Work Consortium. Long working hours and risk of coronary heart disease and stroke: a systematic review and meta-analysis of published and unpublished data for 603.838 individuals. *Lancet*. 2015;386:1739–1746. doi: 10.1016/S0140-6736(15)60295-1
375. Nagayoshi M, Everson-Rose SA, Iso H, Mosley TH Jr, Rose KM, Lutsey PL. Social network, social support, and risk of incident stroke: Atherosclerosis Risk in Communities study. *Stroke*. 2014;45:2868–2873. doi: 10.1161/STROKEAHA.114.005815
376. Everson-Rose SA, Roetker NS, Lutsey PL, Kershaw KN, Longstreth WT Jr, Sacco RL, Diez Roux AV, Alonso A. Chronic stress, depressive symptoms, anger, hostility, and risk of stroke and transient ischemic attack in the Multi-Ethnic Study of Atherosclerosis. *Stroke*. 2014;45:2318–2323. doi: 10.1161/STROKEAHA.114.004815
377. Global Burden of Disease Study 2016. Global Burden of Disease Study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed May 1, 2018.
378. Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, Moran AE, Sacco RL, Anderson LM, Truelsen T, O'Donnell M, Venketasubramanian N, Barker-Collo S, Lawes CM, Wang W, Shinohara Y, Witt E, Ezzati M, Naghavi M, Murray C; Global Burden of Diseases, Injuries, Risk Factors Study 2010 (GBD 2010); GBD Stroke Experts Group. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet Glob Health*. 2013;1:e259–e281. doi: 10.1016/S2214-109X(13)70089-5

379. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA 3rd, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De León FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010 [published correction appears in *Lancet*. 2013;381:628]. *Lancet*. 2012;380:2095–2128. doi: 10.1016/S0140-6736(12)61728-0

380. Kissela BM, Khoury J, Kleindorfer D, Woo D, Schneider A, Alwell K, Miller R, Ewing I, Moomaw CJ, Szaflarski JP, Gebel J, Shukla R, Broderick JP. Epidemiology of ischemic stroke in patients with diabetes: the Greater Cincinnati/Northern Kentucky Stroke Study. *Diabetes Care*. 2005;28:355–359.

15. CONGENITAL CARDIOVASCULAR DEFECTS AND KAWASAKI DISEASE

***ICD-9* 745 to 747; *ICD-10* Q20 to Q28. See Tables 15-1 through 15-4 and Charts 15-1 through 15-7**

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CCDs arise from abnormal formation of the heart or major blood vessels. CCDs range in severity from very minor abnormalities that will never require medical therapy or intervention to complex malformations, including absent or atretic portions of the heart, that could require multiple surgeries and interventions, or even cardiac transplantation. Thus, there is significant variability in their presentation and requirements for care that can have a significant impact on morbidity, mortality, and healthcare costs in children and adults.[1] Some types of CCDs are associated with diminished quality of life,[2] on par with what is seen in other chronic pediatric health conditions,[3] as well as deficits in cognitive functioning[4] and neurodevelopmental outcomes.[5] Health outcomes generally continue to improve for CCDs, including survival, which has led to a population shift into adulthood. There is a growing population of adults with both congenital heart defects and the more usual adult medical diagnoses,[6] which adds to the management complexity of this group of patients[7,8] and emphasizes the importance of specialty care by adult congenital HD specialists.[9]

Abbreviations Used in Chapter 15

ACS	acute coronary syndrome
AHA	American Heart Association
AMI	acute myocardial infarction
ASD	atrial septal defect
AV	atrioventricular
CABG	coronary artery bypass graft
CCD	congenital cardiovascular defect
CDC	Centers for Disease Control and Prevention
CI	confidence interval
DM	diabetes mellitus
GBD	Global Burden of Disease
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HLHS	hypoplastic left heart syndrome
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
ICU	intensive care unit
IHD	ischemic heart disease
IQR	interquartile range
IVIG	intravenous immunoglobulin
KD	Kawasaki disease
NH	non-Hispanic
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
OR	odds ratio
RR	relative risk
RV	right ventricle
STS	Society of Thoracic Surgeons
TGA	transposition of the great arteries
TOF	tetralogy of Fallot
UI	uncertainty interval
VSD	ventricular septal defect

Overall Lifespan Prevalence (See Tables 15-1 through 15-3)

The 32nd Bethesda Conference estimated that the total number of adults living with CCDs in the United States in 2000 was 800 000.[1,10] In 2002, the estimated prevalence of CCDs was 650 000 to 1.3 million in all age groups.[10] The annual birth prevalence of CCDs ranged from 2.4 to 13.7 per 1000 live births (Table 15-2). In the United States, 1 in 150 adults is expected to have some form of congenital heart defect, including mild lesions such as a well-functioning bicuspid aortic valve and more severe disease such as HLHS.[7] The estimated prevalence of CCDs ranges from 2.5% for hypoplastic right heart syndrome to 20.1% for VSD in children and from 1.8% for TGA to 20.1% for VSD in adults (Table 15-3). In population data from Canada, the measured prevalence of CCDs in the general population was 13.11 per 1000 children and 6.12 per 1000 adults in the year 2010.[11] The expected growth rates of the congenital heart defects population vary from 1% to 5% per year depending on age and the distribution of lesions.[12]

Estimates of the distribution of lesions in the CCD population using available data vary based on proposed assumptions. If all those born with CCDs between 1940 and 2002 were treated, there would be ≈750 000 survivors with simple lesions, 400 000 with moderate lesions, and 180 000 with complex lesions; in addition, there would be 3.0 million people alive with bicuspid aortic valves.[12] Without treatment, the number of survivors in each group would be 400 000, 220 000, and 30 000, respectively. The actual numbers surviving were projected to be between these 2 sets of estimates as of more than a decade ago.[12] The most common types of defects in children are VSD, 620 000 people; ASD, 235 000 people; valvar pulmonary stenosis, 185 000 people; and patent ductus arteriosus, 173 000 people.[12] The most common lesions seen in adults are ASD and TOF.[10]

Birth Prevalence

The incidence of disorders present before birth, such as CCDs, is generally described as the *birth prevalence*. The birth prevalence of CCDs is reported as 6.9 per 1000 live births in North America, 8.2 per 1000 live births in Europe, and 9.3 per 1000 live births in Asia.[15] The

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overall birth prevalence of CCDs at the Bhabha Atomic Research Centre Hospital in Mumbai, India, from 2006 through 2011 was 13.28 per 1000 live births.[16]

Variations in birth prevalence rates may be related to the age at detection; major defects can be identified in the prenatal or neonatal period, but minor defects might not be detected until later in childhood or, in fact, adulthood, which makes it challenging to estimate birth prevalence and population prevalence. To distinguish more serious defects, some studies report the number of new cases of sufficient severity to result in death or an invasive procedure within the first year of life (in addition to the overall birth prevalence). Birth prevalence rates are likely to increase over time because of improved technological advancements in diagnosis and screening, particularly fetal cardiac ultrasound,[17] pulse oximetry,[18] and echocardiography during infancy.

Overall Birth Prevalence (See Table 15-2)

- According to population-based data from the Metropolitan Atlanta Congenital Defects Program (Atlanta, GA), a CCD occurred in 1 of every 111 to 125 births (live, still, or >20 weeks' gestation) from 1995 to 1997 and from 1998 to 2005. Some defects showed variations by sex and racial distribution.[19]
- According to population-based data from Alberta, Canada, there was a total birth prevalence of 12.42 per 1000 total births (live, still, or >20 weeks' gestation).[20]
- An estimated minimum of 40 000 infants are expected to be affected by CCDs each year in the United States. Of these, ≈25%, or 2.4 per 1000 live births, require invasive treatment in the first year of life (Table 15-2).

Birth Prevalence of Specific Defects

- The National Birth Defects Prevention Network showed the average birth prevalence of 21 selected major birth defects for 13 states in the United States from 2004 to 2006. These data indicated that there are >6100 estimated annual cases of 5 CCDs: truncus arteriosus (0.07 per 1000 births), TGA (0.3 per 1000 births), TOF (0.4 per 1000 births), AV septal defect (0.47 per 1000 births), and HLHS (0.23 per 1000 births).[21,22]
- Metropolitan Atlanta Congenital Defects Program data for specific defects at birth showed the following: VSD, 4.2 per 1000 births; ASD, 1.3 per 1000 births; valvar pulmonic stenosis, 0.6 per 1000 births; TOF, 0.5 per 1000 births; aortic coarctation, 0.4 per 1000 births; AV septal defect, 0.4 per 1000 births; and TGA (0.2 per 1000 births).[19]
- Bicuspid aortic valve occurs in 13.7 of every 1000 people; these defects might not require treatment in infancy or childhood but could require care later in adulthood.[23]

Mortality (See Tables 15-1 and 15-4 and Charts 15-1 through 15-5)

Overall mortality attributable to CCDs:

- In 2016 (NHLBI tabulation):
  - Mortality related to CCDs was 3063 deaths (Table 15-1), a 13.3% decrease from 2006.
  - CCDs (*ICD-10* Q20–Q28) were the most common cause of infant deaths resulting from birth defects (*ICD-10* Q00–Q99); 22.0% of infants who died of a birth defect had a heart defect (*ICD-10* Q20-Q24).
  - The age-adjusted death rate (deaths per 100 000 people) attributable to CCDs was 1.0, a 16.7% decrease from 2006.
- According to a review of Norwegian national mortality data in live-born children with CCDs from 1994 to 2009, the all-cause mortality rate was 17.4% for children with severe congenital heart defects and 3.0% for children with milder forms of CCDs, with declining mortality rates over the analysis period related to declining operative mortality and more frequent pregnancy terminations.[24]
- Death rates attributed to CCDs decrease as gestational age advances toward 40 weeks.[25] In-hospital mortality of infants with major CCDs is independently associated with late-preterm birth (OR, 2.70 [95% CI, 1.69–4.33]) compared with delivery at later gestational ages.[26,27]
- Similarly, postoperative mortality of infants with CCDs born near term (37 weeks) is 1.34 (95% CI, 1.05–1.71; P=0.02) higher than for those born full term,[28,29] with higher complication rates and longer lengths of stay. The presence of CCDs substantially increases mortality of very low-birth-weight infants; in a study of very low-birth-weight infants, the mortality rate with serious congenital heart defects was 44% compared with 12.7% in very low-birth-weight infants without serious CCDs.[30]
- Analysis of the STS Congenital Heart Surgery Database, a voluntary registry with self-reported data for a 3-year cycle (2013–2016) from 116 centers performing CCD surgery (112 based in 40 US states, 3 in Canada, and 1 in Turkey),[31] showed that of 122 193 total patients who underwent an operation with analyzable data, the aggregate hospital discharge mortality rate was 3.0% (95% CI, 2.9%–3.1%).[32] The mortality rate was 8.6%

(95% CI, 8.2%–9.1%) for neonates,[32] 2.8% (95% CI, 2.6%–3.0%) for infants, 1.0% (95% CI, 0.9%–1.1%) for children (>1 year to 18 years of age),[32] and 1.5% (95% CI, 1.3%–1.8%) for adults (>18 years of age).[32]

- Another recent analysis of mortality after CCD surgery, culled from the Pediatric Cardiac Care Consortium's US-based multicenter data registry, demonstrated that although standardized mortality ratios continue to decrease, there remains increased mortality in CCD patients compared with the general population. The data included 35 998 patients with median follow-up of 18 years and an overall standardized mortality ratio of 8.3% (95% CI, 8.0%–8.7%).[33]
- The Japan Congenital Cardiovascular Surgery Database reported similar surgical outcomes for congenital HD from 28 810 patients operated on between 2008 and 2012, with 2.3% and 3.5% mortality at 30 and 90 days, respectively.[34]
- In population-based data from Canada, 8123 deaths occurred among 71 686 patients with CCDs followed up for nearly 1 million patient-years.[7]
- Among 12 644 adults with CCDs followed up at a single Canadian center from 1980 to 2009, 308 patients in the study cohorts (19%) died.[35]
- Trends in age-adjusted death rates attributable to CCD mortality showed a decline from 1999 to 2016 (Chart 15-1); this varied by race/ethnicity and sex (Charts 15-2 and 15-3).
- From 1999 to 2016, there was a decline in the age-adjusted death rates attributable to CCDs in black, white, and Hispanic people (Chart 15-2), in both males and females (Chart 15-3), and in age groups 1 to 4 years, 5 to 14 years, 15 to 24 years, and ≥25 years (Chart 15-4) in the United States.
- CCD-related mortality varies substantially by age, with infants showing the highest mortality rates from 1999 to 2016 (Chart 15-4).
- The US 2016 age-adjusted death rate (deaths per 100 000 people) attributable to CCDs was 1.0 for NH white males, 1.3 for NH black males, 1.0 for Hispanic males, 0.8 for NH white females, 1.1 for NH black females, and 0.8 for Hispanic females. Infant (<1 year of age) mortality rates were 28.9 for NH white infants, 42.0 for NH black infants, and 31.0 for Hispanic infants (Chart 15-5).[36]
- Mortality after congenital heart surgery also differs between races/ethnicities, even after adjustment for access to care. The risk of in-hospital mortality for minority patients compared with white patients is 1.22 (95% CI, 1.05–1.41) for Hispanics, 1.27 (95% CI, 1.09–1.47) for NH blacks, and 1.56 (95% CI, 1.37–1.78) for other NH people.[37] Similarly, another study found that a higher risk of in-hospital mortality was associated with nonwhite race (OR, 1.36 [95% CI, 1.19–1.54]) and Medicaid insurance (OR, 1.26 [95% CI, 1.09–1.46]).[38] One center's experience suggested race was independently associated with neonatal surgical outcomes only in patients with less complex CCDs.[39] Another center found that a home monitoring program can reduce mortality even in this vulnerable population.[40]
- The population-weighted mortality rate for surgery for congenital heart defects is slightly higher in males (5.1%) than females (4.6%) <20 years old (Table 15-4).
- Data from the HCUP's Kids' Inpatient Database from 2000, 2003, and 2006 show male children had more CCD surgeries in infancy, more high-risk surgeries, and more procedures to correct multiple cardiac defects. Female infants with high-risk CCDs had a 39% higher adjusted mortality than males.[40,41] According to CDC multiple-cause death data from 1999 to 2006, sex differences in mortality over time varied with age. Between the ages of 18 and 34 years, mortality over time decreased significantly in females but not in males.[42]
- In studies that examined trends since 1979, age-adjusted death rates declined 22% for critical CCDs[43] and 39% for all CCDs,[44] and deaths tended to occur at progressively older ages. CDC mortality data from 1979 to 2005 showed all-age death rates had declined by 60% for VSD and 40% for TOF.[45] Population-based data from Canada showed overall mortality decreased by 31% and the median age of death increased from 2 to 23 years between 1987 and 2005.[7]
- Further analysis of the Kids' Inpatient Database from 2000 to 2009 showed a decrease in HLHS stage 3 mortality by 14% and a decrease in stage 1 mortality by 6%.[46] Surgical interventions are the primary treatment for reducing mortality. A Pediatric Heart Network study of 15 North American centers revealed that even in lesions associated with the highest mortality, such as HLHS, aggressive palliation can lead to an increase in the 12-month survival rate, from 64% to 74%.[47]
- Surgical interventions are common in adults with CCDs. Mortality rates for 12 CCD procedures were examined with data from 1988 to 2003 reported in the NIS. A total of 30 250 operations were identified, which yielded a national estimate of 152 277±7875 operations. Of these, 27% were performed in patients ≥18 years of age. The overall in-hospital mortality rate for adult patients with CCDs was 4.71% (95% CI, 4.19%–5.23%),

with a significant reduction in mortality observed when surgery was performed on such adult patients by pediatric versus nonpediatric heart surgeons (1.87% versus 4.84%; $P<0.0001$).[48] For adults with CCDs, specialist care is a key determinant of mortality and morbidity. In a single-center report of 4461 adult patients with CCDs with 48 828 patient-years of follow-up, missed appointments and delay in care were predictors of mortality.[49]

Hospitalizations (See Table 15-1)

- In 2014, the total number of hospital discharges for CCDs for all ages was 39 000 (Table 15-1).
- Hospitalization of infants with CCDs is common; one-third of patients with congenital heart defects require hospitalization during infancy,[45,50] often in an ICU.
- Although the most common CCD lesions were shunts, including patent ductus arteriosus, VSDs, and ASDs, TOF accounted for a higher proportion of in-hospital death than any other birth defect.

Cost

- Using HCUP 2013 NIS data, one study noted that hospitalization costs for individuals of all ages with CCDs exceeded $6.1 billion in 2013, which represents 27% of all birth defect–associated hospital costs.[51]
- Among pediatric hospitalizations (age 0–20 years) in the HCUP 2012 Kids' Inpatient Database[52]:
  - Pediatric hospitalizations with CCDs (4.4% of total pediatric hospitalizations) accounted for $6.6 billion in hospitalization spending (23% of total pediatric hospitalization costs).
  - 26.7% of all CCD costs were attributed to critical CCDs, with the highest costs attributable to HLHS, coarctation of the aorta, and TOF.
  - Median (IQR) hospital cost was $51 302 ($32 088–$100 058) in children who underwent cardiac surgery, $21 920 ($13 068–$51 609) in children who underwent cardiac catheterization, $4134 ($1771–$10 253) in children who underwent noncardiac surgery, and $23 062 ($5529–$71 887) in children admitted for medical treatments.
  - The mean cost of CCDs was higher in infancy ($36 601) than in older ages and in those with critical congenital heart defects ($52 899).
- Other studies confirm the high cost of HLHS. An analysis of 1941 neonates with HLHS showed a median cost of $99 070 for stage 1 palliation (Norwood or Sano procedure), $35 674 for stage 2 palliation (Glenn procedure), $36 928 for stage 3 palliation (Fontan procedure), and $289 292 for transplantation.[53]
- Other CCD lesions are less costly. In 2124 patients undergoing congenital heart operations between 2001 and 2007, total costs for the other surgeries were $12 761 (ASD repair), $18 834 (VSD repair), $28 223 (TOF repair), and $55 430 (arterial switch operation).[54]
- A recent Canadian study demonstrated increasing hospitalization costs for children and adults with CCDs, particularly those with complex lesions, which appears independent from inflation or length of stay.[55]

Risk Factors

- Numerous intrinsic and extrinsic nongenetic risk factors are thought to contribute to CCDs.[56,57]
- Intrinsic risk factors for CCDs include various genetic syndromes. Twins are at higher risk for CCDs[58]; one report from Kaiser Permanente data showed monochorionic twins were at particular risk (RR, 11.6 [95% CI, 9.2–14.5]).[59] Known risks generally focus on maternal exposures, but a study of paternal occupational exposure documented a higher incidence of CCDs with paternal exposure to phthalates.[60]
- Other paternal exposures that increase risk for CCDs include paternal anesthesia, which has been implicated in TOF (3.6%); sympathomimetic medication and coarctation of the aorta (5.8%); pesticides and VSDs (5.5%); and solvents and HLHS (4.6%).[61]
- Known maternal risks include smoking[62,63] during the first trimester of pregnancy, which has also been associated with a ≥30% increased risk of the following lesions in the fetus: ASD, pulmonary valvar stenosis, truncus arteriosus, TGA,[64] and septal defects (particularly for heavy smokers [≥25 cigarettes daily]).[65] Maternal smoking might account for 1.4% of all congenital heart defects.
- Exposure to secondhand smoke has also been implicated as a risk factor.[66]
- Air pollutants can also increase the risk of CCDs. In a retrospective review of singleton infants born in Florida from 2000 to 2009, maternal exposure during pregnancy to the air pollutant benzene was associated with an increased risk in the fetus

of critical and noncritical CCDs (1.33 [95% CI, 1.07–1.65]).[67]

- Maternal binge drinking[68] is also associated with an increased risk of CCDs, and the combination of binge drinking and smoking can be particularly deleterious: Mothers who smoke and report any binge drinking in the 3 months before pregnancy are at an increased risk of giving birth to a child with a CCD (adjusted OR, 12.65).[68]
- Maternal obesity is also associated with CCDs. A meta-analysis of 14 studies of females without gestational DM showed infants born to mothers who were moderately and severely obese, respectively, had 1.1 and 1.4 times greater risk of CCDs than infants born to normal-weight mothers.[69–71] The risk of TOF was 1.9 times higher among infants born to mothers with severe obesity than among infants born to normal-weight mothers.[70]
- Maternal DM, including gestational DM, has also been associated with CCDs, both isolated (CCD[s] as the only major congenital anomaly) and multiple (CCD[s] plus ≥1 noncardiac major congenital anomalies).[72,73] Pregestational DM is also associated with CCDs, specifically TOF.[74]
- Preeclampsia is considered a risk factor for CCDs, although not critical defects.[75]
- Folate deficiency is a well-documented risk for congenital malformations, including CCDs, and folic acid supplementation is routinely recommended during pregnancy.[56] An observational study of folic acid supplementation in Hungarian females showed a decrease in the incidence of CCDs, including VSD (OR, 0.57 [95% CI, 0.45–0.73]), TOF (OR, 0.53 [95% CI, 0.17–0.94]), dextro-TGA (OR, 0.47 [95% CI, 0.26–0.86]), and ASD secundum (OR, 0.63 [95% CI, 0.40–0.98]).[75] A US population-based case-control study showed an inverse relationship between folic acid use and the risk of TGA (Baltimore-Washington Infant Study, 1981–1989).[76]
- An observational study from Quebec, Canada, of 1.3 million births from 1990 to 2005 found a 6% per year reduction in severe congenital heart defects using a time-trend analysis before and after public health measures were instituted that mandated folic acid fortification of grain and flour products in Canada.[77]
- Maternal infections, including rubella and chlamydia, have been associated with congenital heart defects.[78,79]
- High altitude has also been described as a risk factor for CCDs. Tibetan children living at 4200 to 4900 m had a higher prevalence of congenital heart defects (12.09 per 1000) than those living at lower altitudes of 3500 to 4100 m; patent ductus arteriosus and ASD contributed to the increased prevalence.[80]

Screening

Pulse oximetry screening for CCDs was recommended by the US Department of Health and Human Services in 2010.[81] It was incorporated as part of the US recommended uniform screening panel for newborns in 2011 and has been endorsed by the AHA and the American Academy of Pediatrics.[82] At present, all 50 states and the District of Columbia have laws or regulations mandating newborn screening for identification of previously unidentified (by fetal cardiac ultrasound) newborn CCDs,[83] and several studies have demonstrated the benefit of such screening.[84–86]

- Several key factors contribute to effective screening, including probe placement (postductal), oximetry cutoff (<95%), timing (>24 hours of life), and altitude (<2643 ft, 806 m).
- If fully implemented, screening would predict identification of 1189 additional infants with critical congenital heart defects and yield 1975 false-positive results.[87]
- A simulation model estimates that screening the entire United States for critical CCDs with pulse oximetry would uncover 875 infants (95% UI, 705–1060) who truly have nonsyndromic CCDs versus 880 (95% UI, 700–1080) false-negative screenings (no CCDs).[88]
- It has been estimated that 29.5% (95% CI, 28.1%–31.0%) of nonsyndromic children with critical CCDs are diagnosed after 3 days and thus might benefit from pulse oximetry screening.[89]
- A meta-analysis of 13 studies that included 229421 newborns found pulse oximetry had a sensitivity of 76.5% (95% CI, 67.7%–83.5%) for detection of critical CCDs and a specificity of 99.9% (95% CI, 99.7%–99.9%), with a false-positive rate of 0.14% (95% CI, 0.06%–0.33%).[90]
- A recent observational study demonstrated that statewide implementation of mandatory policies for newborn screening for critical CCDs was associated with a significant decrease (33.4% [95% CI, 10.6%–50.3%]) in infant cardiac deaths between 2007 and 2013 compared with states without such policies.[91]
- The cost of identifying a newborn with a critical CCD has been estimated at $20862 per newborn detected and $40385 per life-year gained (2011 US dollars).[88]
- Reports outside of the United States have shown similar performance of pulse oximetry screening in identifying critical CCDs,[92] with a sensitivity and specificity of pulse oximetry screening for critical congenital heart defects of 100% and 99.7%, respectively.

Genetics and Family History

- CCDs have a heritable component. There is a greater concordance of CCDs in monozygotic than dizygotic twins.[93] Among parents with ASD or VSD, 2.6% and 3.7%, respectively, have children who are similarly affected, 21 times the estimated population frequency.[94] However, a large fraction of CCDs occur in families with no other history of CCDs, which suggests the possibility of de novo genetic events.
- Large chromosomal abnormalities are associated with some CCDs. For example, aneuploidies such as trisomy 13, 18, and 21 account for 9% to 18% of CCDs.[89] The specific genes responsible for CCDs that are disrupted by these abnormalities are difficult to identify. There are studies that suggest that *DSCAM* and *COL6A* contribute to Down syndrome–associated CCDs.[95]
- Copy number variants also contribute to CCDs and have been shown to be overrepresented in larger cohorts of patients with specific forms of CCDs.[96] The most common copy number variant is del22q11, which encompasses the T-box transcription factor (*TBX1*) gene and presents as DiGeorge syndrome and velocardiofacial syndrome. Others include del17q11, which causes William syndrome.[97]
- Single point mutations are also a cause of CCDs and include mutations in a core group of cardiac transcription factors (*NKX2.5*, *TBX1*, *TBX5*, and *MEF2*),[97] *ZIC3*, and the *NOTCH1* gene (dominantly inherited and found in ≈5% of cases of bicuspid aortic valve) and related NOTCH signaling genes.[98]
- Recent advances in whole-exome sequencing have suggested that 10% of sporadic severe cases of CCDs are caused by de novo mutations,[99] particularly in chromatin-regulating genes.
- Rare monogenic CCDs also exist, including monogenic forms of ASD, heterotaxy, severe mitral valve prolapse, and bicuspid aortic valve.[97]
- There is no exact consensus currently on the role, type, and utility of clinical genetic testing in people with CCDs,[97] but it should be offered to patients with multiple congenital abnormalities or congenital syndromes (including CCD lesions associated with a high prevalence of 22q11 deletion or DiGeorge syndrome), and it can be considered in patients with a family history, in those with developmental delay, and in patients with left-sided obstructive lesions.[1]
- A Pediatric Cardiac Genomics Consortium has been developed to provide and better understand phenotype and genotype data from large cohorts of patients with CCDs.[100]

Global Burden of CCDs (See Charts 15-6 and 15-7)

- In 2016[101]:
  - Prevalence of congenital heart anomalies was an estimated 15.4 million people.
  - There were 200 000 deaths attributed to congenital heart anomalies worldwide.
- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories.[101]
  - Age-standardized mortality rates of CCDs are lowest in high-income countries (Chart 15-6).
  - The prevalence of congenital heart anomalies is highest in Northern and Central Europe (Chart 15-7).

Kawasaki Disease
ICD-9 446.1; *ICD-10* M30.3.

2016 Mortality: Underlying Mortality—5, All-Cause Mortality—7 (NHLBI tabulation).

KD is an acute inflammatory illness characterized by fever, rash, nonexudative limbal-sparing conjunctivitis, extremity changes, red lips and strawberry tongue, and a swollen lymph node. In areas where bacille Calmette-Guerin vaccination is common, the site can reactivate in KD.[102] The most feared consequence of this vasculitis is coronary artery aneurysms, which can result in coronary ischemic events and other cardiovascular outcomes in the acute period or years later.[103] The cause of KD is unknown, but it could be an immune response to an acute infectious illness based in part on genetic susceptibilities.[104,105] This is supported by the occurrence of epidemics and variation in incidence by age, geography, and season, but also by race/ethnicity, sex, and family history.[105,106] The Nationwide Longitudinal Survey in Japan has shown that breastfeeding is protective against developing KD.[107]

Prevalence

- KD is the most common cause of acquired HD in children in the US and other developed countries.[106]

Incidence

- The incidence was 20.8 per 100 000 US children aged <5 years in 2006.[108] This is the most recent national estimate available and is limited by reliance on weighted hospitalization data from 38 states.
- Boys have a 1.5-fold higher incidence of KD than girls.[108]

- Although KD can occur into adolescence (and rarely beyond), 76.8% of US children with KD are <5 years of age.[108]
- Race-specific incidence rates indicate that KD is most common among Americans of Asian and Pacific Island descent (30.3 per 100 000 children <5 years old), occurs with intermediate frequency in NH blacks (17.5 per 100 000 children <5 years old) and Hispanics (15.7 per 100 000 children <5 years old), and is least common in whites (12.0 per 100 000 children <5 years old).[108]
- There is also geographic variation in KD incidence within the United States. States with higher Asian American populations have higher rates of KD; for example, rates are 2.5-fold higher in Hawaii (50.4 per 100 000 children <5 years old) than in the continental United States.[109] Within Hawaii, the race-specific rates of KD per 100 000 children <5 years old in 1996 to 2006 were 210.5 for Japanese, 86.9 for Native Hawaiian, 83.2 for Chinese, 64.5 for Filipino, and 13.7 for white children.[109]
- There are seasonal variations in KD; KD is more common during the winter and early spring months, except in Hawaii, where no clear seasonal trend is seen.[108,109]
- KD can recur. Recurrence rates are not available for US children, but incidence of first recurrence among children with a history of KD has been reported as 6.5 per 1000 person-years in Japan (2007–2010) and 2.6 per 1000 person-years in Canada (2004–2014).[110,111] Recurrences constitute 2% to 4% of total KD cases in both the United States and Japan.[112]

Hospital Discharges

- In 2014, there were 6000 all-listed diagnoses discharges for KD, with 4000 males and 2000 females (HCUP, unpublished NHLBI tabulation).

Secular Trends

- Although the incidence of KD is rising worldwide, there is no clear secular trend in the United States. US hospitalizations for KD were 17.5 and 20.8 per 100 000 children aged <5 years in 1997 and 2006, respectively, but the test for linear trend was not significant.[108]

Complications of KD

- In the acute phase (up to ≈6 weeks from fever onset), several important cardiovascular complications can occur.
  - KD shock syndrome, with variable contributions from myocardial dysfunction and decreased peripheral resistance, occurs in 5% to 7% of KD cases and is associated with higher risk of coronary arterial dilation, resistance to IVIG treatment, and rarely, long-term myocardial dysfunction or death.[106,113]
  - It is estimated that even with current therapy (high-dose IVIG within the first 10 days of illness), 20% of children develop transient coronary artery dilation (*Z* score >2), 5% develop coronary artery aneurysms (*Z* score ≥2.5), and 1% develop giant aneurysms (*Z* score ≥10 or >8 mm).[107] Estimates are complicated by variability in ascertainment method (administrative codes or research measurement), size criteria, timing (because the majority of dilated segments and approximately half of aneurysms reduce to normal dimensions over time), and therapeutic regimens in the underlying studies. In the most recent US data from 2 centers in 2004 to 2008, maximal coronary artery dimensions reached *Z* scores ≥2.5 in 30% of KD cases up to 12 weeks from fever onset, including medium (*Z* score ≥5 to <10) and giant aneurysms in ≈6% and ≈3% of KD cases, respectively.[114] Risk factors for coronary artery abnormalities include younger age, male sex, late treatment, and failure to respond to initial IVIG with defervescence.[114–117]
  - Peak KD-associated mortality occurs during the acute phase but is rare, estimated at 0 to 0.17% in older US data and 0.03% in recent data from Japan.[118–120] Mortality is related to thrombosis or rupture of rapidly expanding aneurysms, or less commonly, shock or macrophage activation syndrome with multiorgan failure.[118,119,121]
- Long term, IHD and death are related to coronary artery stenosis or thrombosis.
  - Prognosis is predicted largely by coronary artery size 1 month from illness onset. In a Taiwanese study of 1073 KD cases from 1980 to 2012, coronary artery aneurysms were present in 18.3% beyond 1 month, including 11.6% with small, 4.1% with medium, and 2.5% with giant aneurysms. Among those with persistent aneurysms beyond 1 month, IHD death occurred in 2%, nonfatal AMI occurred in another 2%, and myocardial ischemia occurred in another 3%, for a total 7% ischemic event rate during 1 to 46 years of follow-up. Nearly all events occurred in those with giant aneurysms, for whom the ischemia event–free survival rates were 0.63 and 0.36 at 10 and 20 years, respectively, after KD onset.[122] Findings were similar in a Canadian study of 1356 KD patients diagnosed in 1990 to 2007 and followed for up to 15 years, and in a Japanese study

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of 76 patients with giant aneurysms diagnosed since 1972 and followed up through 2011.[123,124]

- A recent Japanese multicenter cohort study of 1006 individuals identified risk factors for 10-year incidence of coronary events (thrombosis, stenosis, obstruction, acute ischemic events, or coronary intervention).[125] Significant risk factors included giant-sized aneurysm (HR, 8.9 [95% CI, 5.1–15.4]), male sex (HR, 2.8 [95% CI, 1.7–4.8]), and resistance to IVIG therapy (HR, 2.2 [95% CI, 1.4–3.6]).
- Among 261 adults <40 years old with ACS who underwent coronary angiography in San Diego, CA, from 2005 to 2009, 5% had aneurysms consistent with late sequelae of KD.[126]

Treatment and Control

- Treatment of acute KD rests on diminishing the inflammatory response with IVIG, which clearly reduces the incidence of coronary artery aneurysms. Aspirin is routinely used for its anti-inflammatory and antiplatelet effects, but it does not reduce the incidence of coronary artery aneurysms.[106] On the basis of a Cochrane review, addition of prednisolone to the standard IVIG regimen could further reduce the incidence of coronary artery abnormalities (RR, 0.29 [95% CI, 0.18–0.46]), but the applicability of these data to non-Asian and less severe KD cases is not certain.[127] Other anti-inflammatory treatments have also been used, based on limited data.[106]
- Management of established coronary artery aneurysms in the short- and long-term is centered on thromboprophylaxis. Successful coronary intervention for late coronary stenosis or thrombosis has been accomplished percutaneously and surgically (eg, CABG).[124,128]

Global Burden of KD

- The annual incidence of KD is highest in Japan, at 308.0 per 100 000 children <5 years of age in 2014, followed by South Korea at 194.7 per 100 000 children <5 years of age in 2014 and Taiwan at 55.9 per 100 000 in children <5 years of age for the period 2000 to 2014.[120,129,130] National incidence data are lacking for China, but the most recent estimates for Shanghai are 71.9 per 100 000 children <5 years of age in 2012.[131]
- In Japan, the cumulative incidence of KD at age 10 years has been calculated with national survey data as >1%, at 1.5 per 100 boys and 1.2 per 100 girls for 2007 to 2010.[132] Using different methodology with complete capture of cases through the national health insurance program, Taiwan recorded a cumulative incidence of 2.78% by age 5 years in 2014.[130]
- The incidence of KD is lower in Canada, at 19.6 per 100 000 children <5 years of age for the period 2004 to 2014, and in European countries, such as Italy with 14.7 per 100 000 children <5 years of age in 2008 to 2013, Spain with 8 per 100 000 children <5 years of age in 2004 to 2014, and Germany with 7.2 per 100 000 children <5 years of age in 2011 to 2012.[111,133–136]
- The incidence of KD is rising worldwide, with potential contributions from improved recognition, diagnosis of incomplete KD more often, and true increasing incidence.[120,130,135]

Table 15-1. Congenital Cardiovascular Defects

Population Group	Estimated Prevalence, 2002, All Ages	Mortality, 2016, All Ages*	Hospital Discharges, 2014, All Ages
Both sexes	2.4 million[137]	3063	39 000
Males	…	1670 (54.5%)†	21 000
Females	…	1393 (45.5%)†	18 000
NH white males	…	973	…
NH white females	…	821	…
NH black males	…	284	…
NH black females	…	248	…
Hispanic males	…	322	…
Hispanic females	…	245	…
NH Asian or Pacific Islander males	…	66	…
NH Asian or Pacific Islander females	…	54	…
NH American Indian or Alaska Native	…	38	…

Ellipses (…) indicate data not available; and NH, non-Hispanic.

*Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total congenital cardiovascular mortality that is for males vs females.

Sources: Mortality: Centers for Disease Control and Prevention/National Center for Health Statistics, 2016 Mortality Multiple Cause-of-Death—United States. These data represent underlying cause of death only. Hospital discharges: Healthcare Cost and Utilization Project, National (Nationwide) Inpatient Sample, 2014, Agency for Healthcare Research and Quality; data include those inpatients discharged alive, dead, or status unknown.

Table 15-2. Annual Birth Prevalence of CCDs in the United States[15,21]

Type of Presentation	Rate per 1000 Live Births	Estimated Number (Variable With Yearly Birth Rate)
Fetal loss	Unknown	Unknown
Invasive procedure during the first year	2.4	9200
Detected during first year*	8	36 000
Bicuspid aortic valve	13.7	54 800

CCD indicates congenital cardiovascular defect.

*Includes stillbirths and pregnancy termination at <20 weeks' gestation; includes some defects that resolve spontaneously or do not require treatment.

Table 15-3. Estimated Prevalence of CCDs and Percent Distribution by Type, United States, 2002* (in Thousands)

Type	Prevalence, N			Percent of Total		
	Total	Children	Adults	Total	Children	Adults
Total	994	463	526	100	100	100
VSD†	199	93	106	20.1	20.1	20.1
ASD	187	78	109	18.8	16.8	20.6
Patent ductus arteriosus	144	58	86	14.2	12.4	16.3
Valvular pulmonic stenosis	134	58	76	13.5	12.6	14.4
Coarctation of aorta	76	31	44	7.6	6.8	8.4
Valvular aortic stenosis	54	25	28	5.4	5.5	5.2
TOF	61	32	28	6.1	7	5.4
AV septal defect	31	18	13	3.1	3.9	2.5
TGA	26	17	9	2.6	3.6	1.8
Hypoplastic right heart syndrome	22	12	10	2.2	2.5	1.9
Double-outlet RV	9	9	0	0.9	1.9	0.1
Single ventricle	8	6	2	0.8	1.4	0.3
Anomalous pulmonary venous connection	9	5	3	0.9	1.2	0.6
Truncus arteriosus	9	6	2	0.7	1.3	0.5
HLHS	3	3	0	0.3	0.7	0
Other	22	12	10	2.1	2.6	1.9

ASD indicates atrial septal defect; AV, atrioventricular; CCD, congenital cardiovascular defect; HLHS, hypoplastic left heart syndrome; RV, right ventricle; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; and VSD, ventricular septal defect.

*Excludes an estimated 3 million bicuspid aortic valve prevalence (2 million in adults and 1 million in children).

†Small VSD, 117 000 (65 000 adults and 52 000 children); large VSD, 82 000 (41 000 adults and 41 000 children).

Source: Data derived from Hoffman et al.[12]

Table 15-4. Surgery for Congenital Heart Disease

	Sample	Population, Weighted
Surgery for congenital heart disease, n	14 888	25 831
Deaths, n	736	1253
Mortality rate, %	4.9	4.8
By sex (81 missing in sample)		
Male, n	8127	14 109
Deaths, n	420	714
Mortality rate, %	5.2	5.1
Female, n	6680	11 592
Deaths, n	315	539
Mortality rate, %	4.7	4.6
By type of surgery		
ASD secundum surgery, n	834	1448
Deaths, n	3	6
Mortality rate, %	0.4	0.4
Norwood procedure for HLHS, n	161	286
Deaths, n	42	72
Mortality rate, %	26.1	25.2

In 2003, 25 000 cardiovascular operations for congenital cardiovascular defects were performed on children <20 years of age. Inpatient mortality rate after all types of cardiac surgery was 4.8%. Nevertheless, mortality risk varies substantially for different defect types, from 0.4% for ASD repair to 25.2% for first-stage palliation for HLHS. Fifty-five percent of operations were performed in males. In unadjusted analysis, mortality after cardiac surgery was somewhat higher for males than for females (5.1% vs 4.6%). ASD indicates atrial septal defect; and HLHS, hypoplastic left heart syndrome.

Source: Data derived from Ma et al.[138]

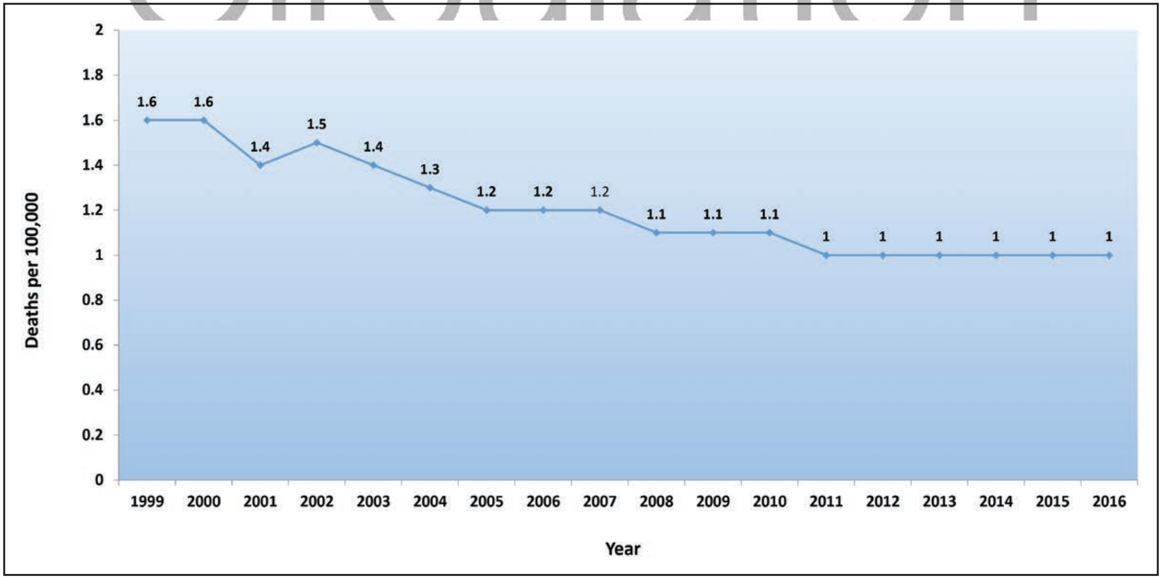

Chart 15-1. Trends in age-adjusted death rates attributable to congenital cardiovascular defects, 1999 to 2016.
Source: National Center for Health Statistics, National Vital Statistics System.

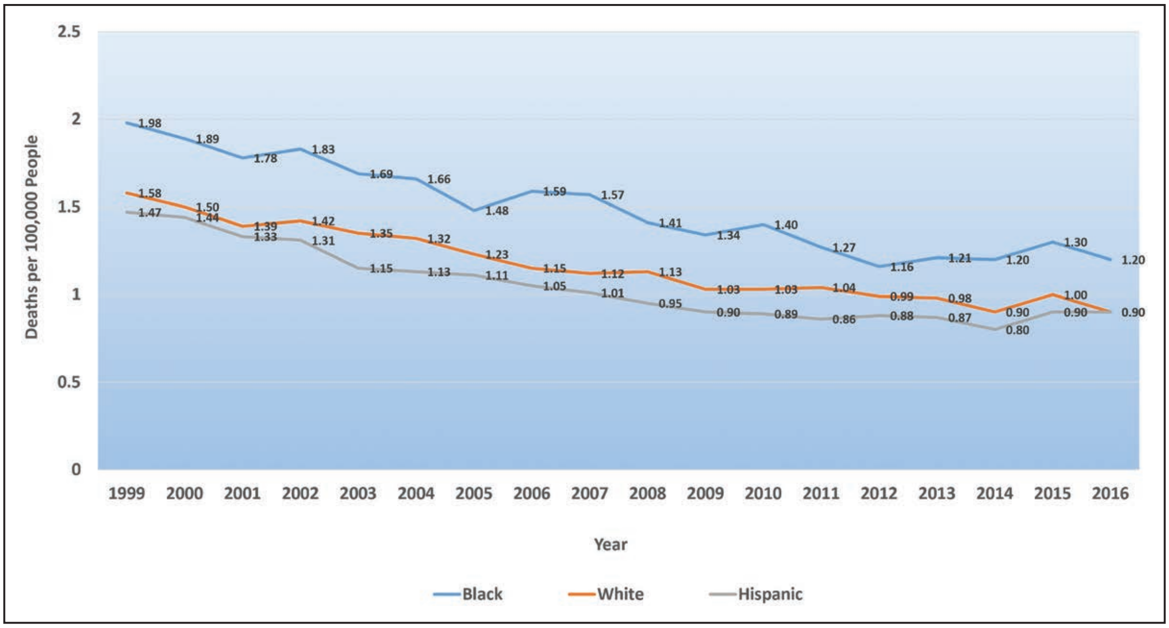

Chart 15-2. Trends in age-adjusted death rates attributable to congenital cardiovascular defects by race/ethnicity, 1999 to 2016.
Source: National Center for Health Statistics, National Vital Statistics System.

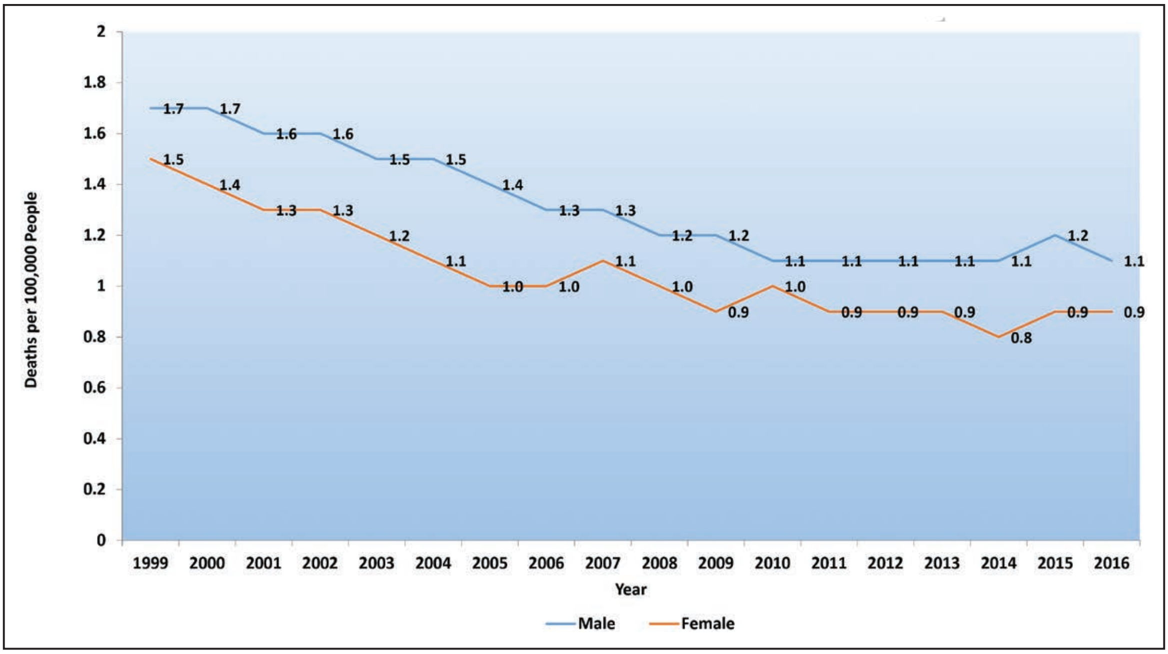

Chart 15-3. Trends in age-adjusted death rates attributable to congenital cardiovascular defects by sex, 1999 to 2016.
Source: National Center for Health Statistics, National Vital Statistics System.

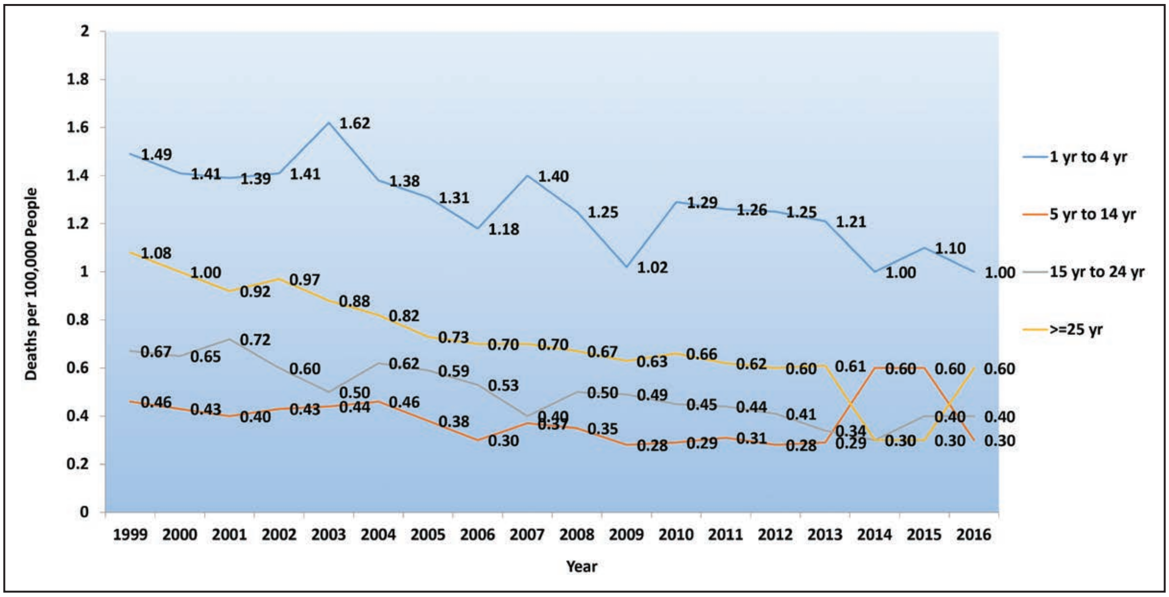

Chart 15-4. Trends in age-specific death rates attributable to congenital cardiovascular defects by age at death, 1999 to 2016.
Source: National Center for Health Statistics, National Vital Statistics System.

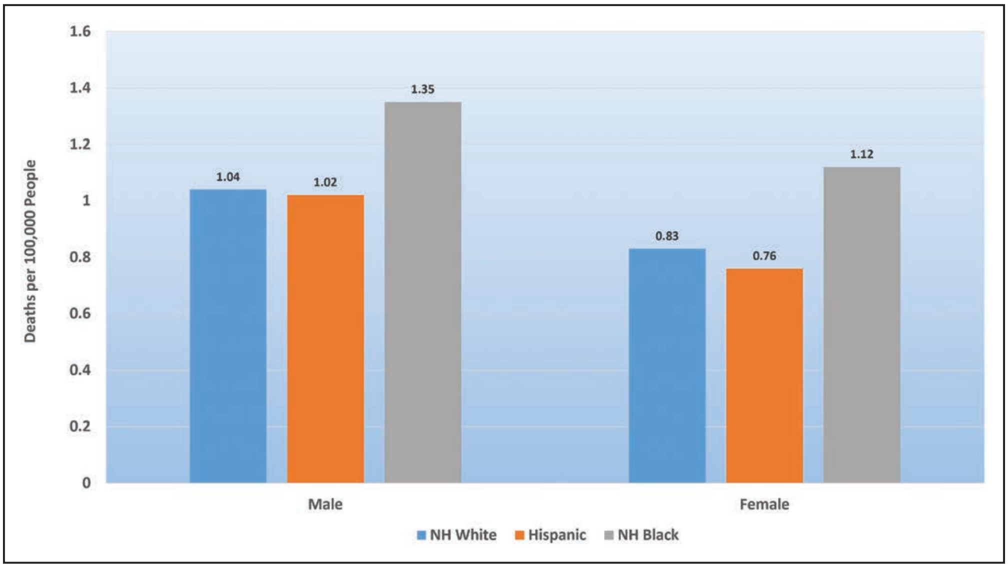

Chart 15-5. Age-adjusted death rates attributable to congenital cardiovascular defects, by sex and race/ethnicity, 2016.
NH indicates non-Hispanic.
Source: National Center for Health Statistics, National Vital Statistics System.

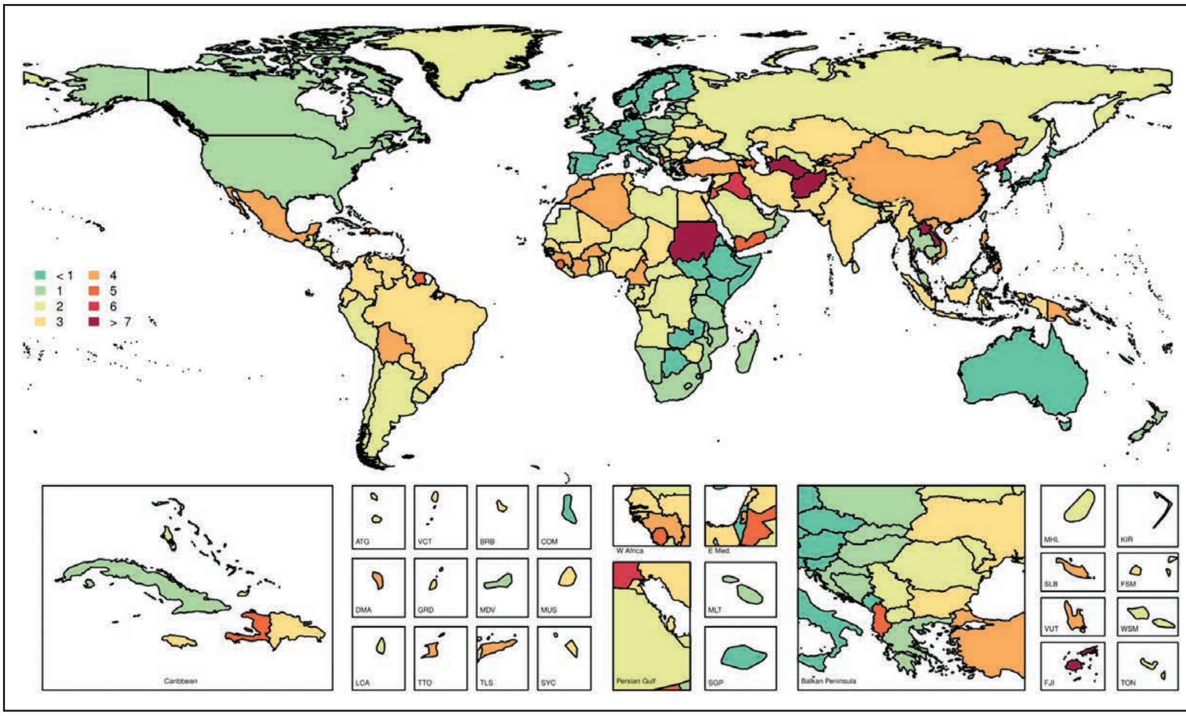

Chart 15-6. Age-standardized global mortality rates of congenital heart anomalies per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[101] Printed with permission. Copyright © 2017, University of Washington

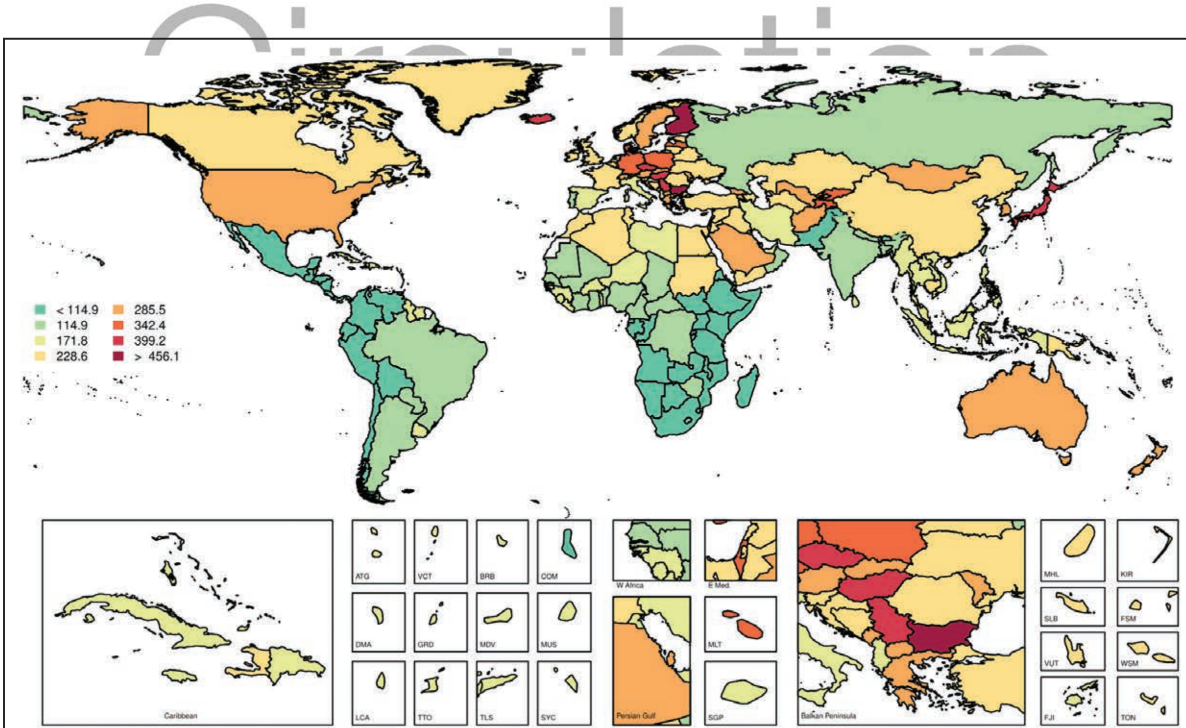

Chart 15-7. Age-standardized global prevalence rates of congenital heart anomalies per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[101] Printed with permission. Copyright © 2017, University of Washington.

REFERENCES

1. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). *Circulation*. 2008;118:e714–e833. doi: 10.1161/CIRCULATIONAHA.108.190690
2. Fteropoulli T, Stygall J, Cullen S, Deanfield J, Newman SP. Quality of life of adult congenital heart disease patients: a systematic review of the literature. *Cardiol Young*. 2013;23:473–485. doi: 10.1017/S1047951112002351
3. Mellion K, Uzark K, Cassedy A, Drotar D, Wernovsky G, Newburger JW, Mahony L, Mussatto K, Cohen M, Limbers C, Marino BS; Pediatric Cardiac Quality of Life Inventory Testing Study Consortium. Health-related quality of life outcomes in children and adolescents with congenital heart disease. *J Pediatr*. 2014;164:781–788.e1. doi: 10.1016/j.jpeds.2013.11.066
4. Karsdorp PA, Everaerd W, Kindt M, Mulder BJ. Psychological and cognitive functioning in children and adolescents with congenital heart disease: a meta-analysis. *J Pediatr Psychol*. 2007;32:527–541. doi: 10.1093/jpepsy/jsl047
5. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, Mussatto KA, Uzark K, Goldberg CS, Johnson WH Jr, Li J, Smith SE, Bellinger DC, Mahle WT; on behalf of the American Heart Association Congenital Heart Defects Committee, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. *Circulation*. 2012;126:1143–1172. doi: 10.1161/CIR.0b013e318265ee8a
6. Roche SL, Silversides CK. Hypertension, obesity, and coronary artery disease in the survivors of congenital heart disease. *Can J Cardiol*. 2013;29:841–848. doi: 10.1016/j.cjca.2013.03.021
7. Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing mortality in congenital heart disease. *J Am Coll Cardiol*. 2010;56:1149–1157. doi: 10.1016/j.jacc.2010.03.085
8. Sable C, Foster E, Uzark K, Bjornsen K, Canobbio MM, Connolly HM, Graham TP, Gurvitz MZ, Kovacs A, Meadows AK, Reid GJ, Reiss JG, Rosenbaum KN, Sagerman PJ, Saidi A, Schonberg R, Shah S, Tong E, Williams RG; on behalf of the American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Best practices in managing transition to adulthood for adolescents with congenital heart disease: the transition process and medical and psychosocial issues: a scientific statement from the American Heart Association. *Circulation*. 2011;123:1454–1485. doi: 10.1161/CIR.0b013e3182107c56
9. Gurvitz M, Valente AM, Broberg C, Cook S, Stout K, Kay J, Ting J, Kuehl K, Earing M, Webb G, Houser L, Opotowsky A, Harmon A, Graham D, Khairy P, Gianola A, Verstappen A, Landzberg M; Alliance for Adult Research in Congenital Cardiology (AARCC) and Adult Congenital Heart Association. Prevalence and predictors of gaps in care among adult congenital heart disease patients: HEART-ACHD (The Health, Education, and Access Research Trial). *J Am Coll Cardiol*. 2013;61:2180–2184. doi: 10.1016/j.jacc.2013.02.048
10. Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JI, Somerville J, Williams RG, Webb GD. Task force 1: the changing profile of congenital heart disease in adult life. *J Am Coll Cardiol*. 2001;37:1170–1175.
11. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. *Circulation*. 2014;130:749–756. doi: 10.1161/CIRCULATIONAHA.113.008396
12. Hoffman JI, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. *Am Heart J*. 2004;147:425–439. doi: 10.1016/j.ahj.2003.05.003
13. Deleted in proof.
14. Deleted in proof.
15. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2011;58:2241–2247. doi: 10.1016/j.jacc.2011.08.025
16. Sawant SP, Amin AS, Bhat M. Prevalence, pattern and outcome of congenital heart disease in Bhabha Atomic Research Centre Hospital, Mumbai. *Indian J Pediatr*. 2013;80:286–291. doi: 10.1007/s12098-012-0910-x
17. Botto LD, Correa A, Erickson JD. Racial and temporal variations in the prevalence of heart defects. *Pediatrics*. 2001;107:E32.
18. Koppel RI, Druschel CM, Carter T, Goldberg BE, Mehta PN, Talwar R, Bierman FZ. Effectiveness of pulse oximetry screening for congenital heart disease in asymptomatic newborns. *Pediatrics*. 2003;111:451–455.
19. Reller MD, Strickland MJ, Riehle-Colarusso T, Mahle WT, Correa A. Prevalence of congenital heart defects in metropolitan Atlanta, 1998-2005. *J Pediatr*. 2008;153:807–813. doi: 10.1016/j.jpeds.2008.05.059
20. Bedard T, Lowry RB, Sibbald B, Harder JR, Trevenen C, Horobec V, Dyck JD. Congenital heart defect case ascertainment by the Alberta Congenital Anomalies Surveillance System. *Birth Defects Res A Clin Mol Teratol*. 2012;94:449–458. doi: 10.1002/bdra.23007
21. Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, Anderson P, Mason CA, Collins JS, Kirby RS, Correa A; National Birth Defects Prevention Network. Updated national birth prevalence estimates for selected birth defects in the United States, 2004-2006. *Birth Defects Res A Clin Mol Teratol*. 2010;88:1008–1016. doi: 10.1002/bdra.20735
22. Mai CT, Riehle-Colarusso T, O'Halloran A, Cragan JD, Olney RS, Lin A, Feldkamp M, Botto LD, Rickard R, Anderka M, Ethen M, Stanton C, Ehrhardt J, Canfield M; National Birth Defects Prevention Network. Selected birth defects data from population-based birth defects surveillance programs in the United States, 2005–2009: featuring critical congenital heart defects targeted for pulse oximetry screening. *Birth Defects Res A Clin Mol Teratol*. 2012;94:970–983.
23. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002;39:1890–1900.
24. Jortveit J, Øyen N, Leirgul E, Fomina T, Tell GS, Vollset SE, Eskedal L, Døhlen G, Birkeland S, Holmstrøm H. Trends in mortality of congenital heart defects. *Congenit Heart Dis*. 2016;11:160–168. doi: 10.1111/chd.12307
25. Cnota JF, Gupta R, Michelfelder EC, Ittenbach RF. Congenital heart disease infant death rates decrease as gestational age advances from 34 to 40 weeks. *J Pediatr*. 2011;159:761–765. doi: 10.1016/j.jpeds.2011.04.020
26. Swenson AW, Dechert RE, Schumacher RE, Attar MA. The effect of late preterm birth on mortality of infants with major congenital heart defects. *J Perinatol*. 2012;32:51–54. doi: 10.1038/jp.2011.50
27. Best KE, Tennant PWG, Rankin J. Survival, by birth weight and gestational age, in individuals with congenital heart disease: a population-based study. *J Am Heart Assoc*. 2017;6:e005213. doi: 10.1161/JAHA.116.005213
28. Costello JM, Polito A, Brown DW, McElrath TF, Graham DA, Thiagarajan RR, Bacha EA, Allan CK, Cohen JN, Laussen PC. Birth before 39 weeks' gestation is associated with worse outcomes in neonates with heart disease. *Pediatrics*. 2010;126:277–284. doi: 10.1542/peds.2009-3640
29. Costello JM, Pasquali SK, Jacobs JP, He X, Hill KD, Cooper DS, Backer CL, Jacobs ML. Gestational age at birth and outcomes after neonatal cardiac surgery: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. *Circulation*. 2014;129:2511–2517. doi: 10.1161/CIRCULATIONAHA.113.005864
30. Archer JM, Yeager SB, Kenny MJ, Soll RF, Horbar JD. Distribution of and mortality from serious congenital heart disease in very low birth weight infants. *Pediatrics*. 2011;127:293–299. doi: 10.1542/peds.2010-0418
31. Shahian DM, Jacobs JP, Edwards FH, Brennan JM, Dokholyan RS, Prager RL, Wright CD, Peterson ED, McDonald DE, Grover FL. The Society of Thoracic Surgeons national database. *Heart*. 2013;99:1494–1501. doi: 10.1136/heartjnl-2012-303456
32. The Society of Thoracic Surgeons (STS) National Database: Congenital Heart Surgery Database participants, Spring 2017 Harvest. Society of Thoracic Surgeons website. https://www.sts.org/sites/default/files/documents/CHSD_ExecutiveSummary_AllPatients_Spring2017.pdf. Accessed November 5, 2017.
33. Jacobs ML, Jacobs JP, Hill KD, Hornik C, O'Brien SM, Pasquali SK, Vener D, Kumar SR, Habib RH, Shahian DM, Edwards FH, Fernandez FG. The Society of Thoracic Surgeons Congenital Heart Surgery Database: 2017 update on research. *Ann Thorac Surg*. 2017;104:731–741. doi: 10.1016/j.athoracsur.2017.07.001
34. Spector LG, Menk JS, Knight JH, McCracken C, Thomas AS, Vinocur JM, Oster ME, St Louis JD, Moller JH, Kochilas L. Trends in long-term mortality after congenital heart surgery. *J Am Coll Cardiol*. 2018;71:2434–2446. doi: 10.1016/j.jacc.2018.03.491

35. Hoashi T, Miyata H, Murakami A, Hirata Y, Hirose K, Matsumura G, Ichikawa H, Sawa Y, Takamoto S. The current trends of mortality following congenital heart surgery: the Japan Congenital Cardiovascular Surgery Database. *Interact Cardiovasc Thorac Surg*. 2015;21:151–156. doi: 10.1093/icvts/ivv109
36. Greutmann M, Tobler D, Kovacs AH, Greutmann-Yantiri M, Haile SR, Held L, Ivanov J, Williams WG, Oechslin EN, Silversides CK, Colman JM. Increasing mortality burden among adults with complex congenital heart disease. *Congenit Heart Dis*. 2015;10:117–127. doi: 10.1111/chd.12201
37. National Center for Health Statistics. Centers for Disease Control and Prevention website. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2016. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed May 21, 2018.
38. Oster ME, Strickland MJ, Mahle WT. Racial and ethnic disparities in post-operative mortality following congenital heart surgery. *J Pediatr*. 2011;159:222–226. doi: 10.1016/j.jpeds.2011.01.060
39. Chan T, Pinto NM, Bratton SL. Racial and insurance disparities in hospital mortality for children undergoing congenital heart surgery. *Pediatr Cardiol*. 2012;33:1026–1039. doi: 10.1007/s00246-012-0221-z
40. Lasa JJ, Cohen MS, Wernovsky G, Pinto NM. Is race associated with morbidity and mortality after hospital discharge among neonates undergoing heart surgery? *Pediatr Cardiol*. 2013;34:415–423. doi: 10.1007/s00246-012-0475-5
41. Castellanos DA, Herrington C, Adler S, Haas K, Ram Kumar S, Kung GC. Home monitoring program reduces mortality in high-risk sociodemographic single-ventricle patients [published correction appears in *Pediatr Cardiol*. 2017;38:206]. *Pediatr Cardiol*. 2016;37:1575–1580. doi: 10.1007/s00246-016-1472-x
42. Gilboa SM, Salemi JL, Nembhard WN, Fixler DE, Correa A. Mortality resulting from congenital heart disease among children and adults in the United States, 1999 to 2006. *Circulation*. 2010;122:2254–2263. doi: 10.1161/CIRCULATIONAHA.110.947002
43. Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. *Pediatrics*. 2013;131:e1502–e1508. doi: 10.1542/peds.2012-3435
44. Boneva RS, Botto LD, Moore CA, Yang Q, Correa A, Erickson JD. Mortality associated with congenital heart defects in the United States: trends and racial disparities, 1979-1997. *Circulation*. 2001;103:2376–2381.
45. Marino BS, Bird GL, Wernovsky G. Diagnosis and management of the newborn with suspected congenital heart disease. *Clin Perinatol*. 2001;28:91–136.
46. Czosek RJ, Anderson JB, Heaton PC, Cassedy A, Schnell B, Cnota JF. Staged palliation of hypoplastic left heart syndrome: trends in mortality, cost, and length of stay using a national database from 2000 through 2009. *Am J Cardiol*. 2013;111:1792–1799. doi: 10.1016/j.amjcard.2013.02.039
47. Ohye RG, Sleeper LA, Mahony L, Newburger JW, Pearson GD, Lu M, Goldberg CS, Tabbutt S, Frommelt PC, Ghanayem NS, Laussen PC, Rhodes JF, Lewis AB, Mital S, Ravishankar C, Williams IA, Dunbar-Masterson C, Atz AM, Colan S, Minich LL, Pizarro C, Kanter KR, Jaggers J, Jacobs JP, Krawczeski CD, Pike N, McCrindle BW, Virzi L, Gaynor JW; Pediatric Heart Network Investigators. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. *N Engl J Med*. 2010;362:1980–1992. doi: 10.1056/NEJMoa0912461
48. Karamlou T, Diggs BS, Person T, Ungerleider RM, Welke KF. National practice patterns for management of adult congenital heart disease: operation by pediatric heart surgeons decreases in-hospital death. *Circulation*. 2008;118:2345–2352. doi: 10.1161/CIRCULATIONAHA.108.776963
49. Kempny A, Diller GP, Dimopoulos K, Alonso-Gonzalez R, Uebing A, Li W, Babu-Narayan S, Swan L, Wort SJ, Gatzoulis MA. Determinants of outpatient clinic attendance amongst adults with congenital heart disease and outcome. *Int J Cardiol*. 2016;203:245–250. doi: 10.1016/j.ijcard.2015.10.081
50. Dorfman AT, Marino BS, Wernovsky G, Tabbutt S, Ravishankar C, Godinez RI, Priestley M, Dodds KM, Rychik J, Gruber PJ, Gaynor JW, Levy RJ, Nicolson SC, Montenegro LM, Spray TL, Dominguez TE. Critical heart disease in the neonate: presentation and outcome at a tertiary care center. *Pediatr Crit Care Med*. 2008;9:193–202. doi: 10.1097/PCC.0b013e318166eda5
51. Arth AC, Tinker SC, Simeone RM, Ailes EC, Cragan JD, Grosse SD. Inpatient hospitalization costs associated with birth defects among persons of all ages: United States, 2013. *MMWR Morb Mortal Wkly Rep*. 2017;66:41–46. doi: 10.15585/mmwr.mm6602a1
52. Faraoni D, Nasr VG, DiNardo JA. Overall hospital cost estimates in children with congenital heart disease: analysis of the 2012 Kid's Inpatient Database. *Pediatr Cardiol*. 2016;37:37–43. doi: 10.1007/s00246-015-1235-0
53. Dean PN, Hillman DG, McHugh KE, Gutgesell HP. Inpatient costs and charges for surgical treatment of hypoplastic left heart syndrome. *Pediatrics*. 2011;128:e1181–e1186. doi: 10.1542/peds.2010-3742
54. Pasquali SK, Sun JL, d'Almada P, Jaquiss RD, Lodge AJ, Miller N, Kemper AR, Lannon CM, Li JS. Center variation in hospital costs for patients undergoing congenital heart surgery. *Circ Cardiovasc Qual Outcomes*. 2011;4:306–312. doi: 10.1161/CIRCOUTCOMES.110.958959
55. Mackie AS, Tran DT, Marelli AJ, Kaul P. Cost of congenital heart disease hospitalizations in Canada: a population-based study. *Can J Cardiol*. 2017;33:792–798. doi: 10.1016/j.cjca.2017.01.024
56. Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, Elixson M, Warnes CA, Webb CL. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. *Circulation*. 2007;115:2995–3014. doi: 10.1161/CIRCULATIONAHA.106.183216
57. Patel SS, Burns TL. Nongenetic risk factors and congenital heart defects. *Pediatr Cardiol*. 2013;34:1535–1555. doi: 10.1007/s00246-013-0775-4
58. Herskind AM, Almind Pedersen D, Christensen K. Increased prevalence of congenital heart defects in monozygotic and dizygotic twins. *Circulation*. 2013;128:1182–1188. doi: 10.1161/CIRCULATIONAHA.113.002453
59. Pettit KE, Merchant M, Machin GA, Tacy TA, Norton ME. Congenital heart defects in a large, unselected cohort of monochorionic twins. *J Perinatol*. 2013;33:457–461. doi: 10.1038/jp.2012.145
60. Snijder CA, Vlot IJ, Burdorf A, Obermann-Borst SA, Helbing WA, Wildhagen MF, Steegers EA, Steegers-Theunissen RP. Congenital heart defects and parental occupational exposure to chemicals. *Hum Reprod*. 2012;27:1510–1517. doi: 10.1093/humrep/des043
61. Wilson PD, Loffredo CA, Correa-Villaseñor A, Ferencz C. Attributable fraction for cardiac malformations. *Am J Epidemiol*. 1998;148:414–423.
62. Lee LJ, Lupo PJ. Maternal smoking during pregnancy and the risk of congenital heart defects in offspring: a systematic review and metaanalysis. *Pediatr Cardiol*. 2013;34:398–407. doi: 10.1007/s00246-012-0470-x
63. Sullivan PM, Dervan LA, Reiger S, Buddhe S, Schwartz SM. Risk of congenital heart defects in the offspring of smoking mothers: a population-based study. *J Pediatr*. 2015;166:978–984.e2. doi: 10.1016/j.jpeds.2014.11.042
64. Alverson CJ, Strickland MJ, Gilboa SM, Correa A. Maternal smoking and congenital heart defects in the Baltimore-Washington Infant Study. *Pediatrics*. 2011;127:e647–e653. doi: 10.1542/peds.2010-1399
65. Malik S, Cleves MA, Honein MA, Romitti PA, Botto LD, Yang S, Hobbs CA; National Birth Defects Prevention Study. Maternal smoking and congenital heart defects. *Pediatrics*. 2008;121:e810–e816. doi: 10.1542/peds.2007-1519
66. Patel SS, Burns TL, Botto LD, Riehle-Colarusso TJ, Lin AE, Shaw GM, Romitti PA; National Birth Defects Prevention Study. Analysis of selected maternal exposures and non-syndromic atrioventricular septal defects in the National Birth Defects Prevention Study, 1997-2005. *Am J Med Genet A*. 2012;158A:2447–2455. doi: 10.1002/ajmg.a.35555
67. Tanner JP, Salemi JL, Stuart AL, Yu H, Jordan MM, DuClos C, Cavicchia P, Correia JA, Watkins SM, Kirby RS. Associations between exposure to ambient benzene and PM(2.5) during pregnancy and the risk of selected birth defects in offspring. *Environ Res*. 2015;142:345–353. doi: 10.1016/j.envres.2015.07.006
68. Mateja WA, Nelson DB, Kroelinger CD, Ruzek S, Segal J. The association between maternal alcohol use and smoking in early pregnancy and congenital cardiac defects. *J Womens Health (Larchmt)*. 2012;21:26–34. doi: 10.1089/jwh.2010.2582
69. Baardman ME, Kerstjens-Frederikse WS, Corpeleijn E, de Walle HE, Hofstra RM, Berger RM, Bakker MK. Combined adverse effects of maternal smoking and high body mass index on heart development in offspring: evidence for interaction? *Heart*. 2012;98:474–479. doi: 10.1136/heartjnl-2011-300822
70. Cai GJ, Sun XX, Zhang L, Hong Q. Association between maternal body mass index and congenital heart defects in offspring: a systematic review. *Am J Obstet Gynecol*. 2014;211:91–117. doi: 10.1016/j.ajog.2014.03.028
71. Waller DK, Shaw GM, Rasmussen SA, Hobbs CA, Canfield MA, Siega-Riz AM, Gallaway MS, Correa A; National Birth Defects

Prevention Study. Prepregnancy obesity as a risk factor for structural birth defects. *Arch Pediatr Adolesc Med*. 2007;161:745–750. doi: 10.1001/archpedi.161.8.745
72. Øyen N, Diaz LJ, Leirgul E, Boyd HA, Priest J, Mathiesen ER, Quertermous T, Wohlfahrt J, Melbye M. Prepregnancy diabetes and offspring risk of congenital heart disease: a nationwide cohort study. *Circulation*. 2016;133:2243–2253. doi: 10.1161/CIRCULATIONAHA.115.017465
73. Simeone RM, Devine OJ, Marcinkevage JA, Gilboa SM, Razzaghi H, Bardenheier BH, Sharma AJ, Honein MA. Diabetes and congenital heart defects: a systematic review, meta-analysis, and modeling project. *Am J Prev Med*. 2015;48:195–204. doi: 10.1016/j.amepre.2014.09.002
74. Priest JR, Yang W, Reaven G, Knowles JW, Shaw GM. Maternal midpregnancy glucose levels and risk of congenital heart disease in offspring. *JAMA Pediatr*. 2015;169:1112–1116. doi: 10.1001/jamapediatrics.2015.2831
75. Auger N, Fraser WD, Healy-Profitós J, Arbour L. Association between preeclampsia and congenital heart defects. *JAMA*. 2015;314:1588–1598. doi: 10.1001/jama.2015.12505
76. Scanlon KS, Ferencz C, Loffredo CA, Wilson PD, Correa-Villaseñor A, Khoury MJ, Willett WC. Preconceptional folate intake and malformations of the cardiac outflow tract: Baltimore-Washington Infant Study Group. *Epidemiology*. 1998;9:95–98.
77. Ionescu-Ittu R, Marelli AJ, Mackie AS, Pilote L. Prevalence of severe congenital heart disease after folic acid fortification of grain products: time trend analysis in Quebec, Canada. *BMJ*. 2009;338:b1673. doi: 10.1136/bmj.b1673
78. Dong DY, Binongo JN, Kancherla V. Maternal chlamydia infection during pregnancy and risk of cyanotic congenital heart defects in the offspring. *Matern Child Health J*. 2016;20:66–76. doi: 10.1007/s10995-015-1804-0
79. Oster ME, Riehle-Colarusso T, Correa A. An update on cardiovascular malformations in congenital rubella syndrome. *Birth Defects Res A Clin Mol Teratol*. 2010;88:1–8. doi: 10.1002/bdra.20621
80. Zheng JY, Tian HT, Zhu ZM, Li B, Han L, Jiang SL, Chen Y, Li DT, He JC, Zhao Z, Cao Y, Qiu YG, Li TC. Prevalence of symptomatic congenital heart disease in Tibetan school children. *Am J Cardiol*. 2013;112:1468–1470. doi: 10.1016/j.amjcard.2013.07.028
81. US Department of Health and Human Services, Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. The addition of critical congenital cyanotic heart disease to the committee's recommended uniform screening panel. October 15, 2010. https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/reports-recommendations/letter-to-sec-congenital-cyanotic.pdf. Accessed July 31, 2014.
82. Mahle WT, Martin GR, Beekman RH 3rd, Morrow WR; Section on Cardiology and Cardiac Surgery Executive Committee. Endorsement of Health and Human Services recommendation for pulse oximetry screening for critical congenital heart disease. *Pediatrics*. 2012;129:190–192. doi: 10.1542/peds.2011-3211
83. Glidewell J, Olney RS, Hinton C, Pawelski J, Sontag M, Wood T, Kucik JE, Daskalov R, Hudson J; Centers for Disease Control and Prevention (CDC). State legislation, regulations, and hospital guidelines for newborn screening for critical congenital heart defects: United States, 2011-2014. *MMWR Morb Mortal Wkly Rep*. 2015;64:625–630.
84. de-Wahl Granelli A, Wennergren M, Sandberg K, Mellander M, Bejlum C, Inganäs L, Eriksson M, Segerdahl N, Agren A, Ekman-Joelsson BM, Sunnegårdh J, Verdicchio M, Ostman-Smith I. Impact of pulse oximetry screening on the detection of duct dependent congenital heart disease: a Swedish prospective screening study in 39,821 newborns. *BMJ*. 2009;338:a3037. doi: 10.1136/bmj.a3037
85. Meberg A, Brügmann-Pieper S, Due R Jr, Eskedal L, Fagerli I, Farstad T, Frøisland DH, Sannes CH, Johansen OJ, Keljalic J, Markestad T, Nygaard EA, Røsvik A, Silberg IE. First day of life pulse oximetry screening to detect congenital heart defects [published correction appears in *J Pediatr*. 2009;154:629]. *J Pediatr*. 2008;152:761–765. doi: 10.1016/j.jpeds.2007.12.043
86. Riede FT, Wörner C, Dähnert I, Möckel A, Kostelka M, Schneider P. Effectiveness of neonatal pulse oximetry screening for detection of critical congenital heart disease in daily clinical routine: results from a prospective multicenter study. *Eur J Pediatr*. 2010;169:975–981. doi: 10.1007/s00431-010-1160-4
87. Peterson C, Grosse SD, Oster ME, Olney RS, Cassell CH. Cost-effectiveness of routine screening for critical congenital heart disease in US newborns. *Pediatrics*. 2013;132:e595–e603. doi: 10.1542/peds.2013-0332
88. Ailes EC, Gilboa SM, Honein MA, Oster ME. Estimated number of infants detected and missed by critical congenital heart defect screening. *Pediatrics*. 2015;135:1000–1008. doi: 10.1542/peds.2014-3662
89. Hartman RJ, Rasmussen SA, Botto LD, Riehle-Colarusso T, Martin CL, Cragan JD, Shin M, Correa A. The contribution of chromosomal abnormalities to congenital heart defects: a population-based study. *Pediatr Cardiol*. 2011;32:1147–1157. doi: 10.1007/s00246-011-0034-5
90. Peterson C, Ailes E, Riehle-Colarusso T, Oster ME, Olney RS, Cassell CH, Fixler DE, Carmichael SL, Shaw GM, Gilboa SM. Late detection of critical congenital heart disease among US infants: estimation of the potential impact of proposed universal screening using pulse oximetry. *JAMA Pediatr*. 2014;168:361–370. doi: 10.1001/jamapediatrics.2013.4779
91. Abouk R, Grosse SD, Ailes EC, Oster ME. Association of US state implementation of newborn screening policies for critical congenital heart disease with early infant cardiac deaths [published correction appears in *JAMA*. 2018;320:1288]. *JAMA*. 2017;318:2111–2118. doi: 10.1001/jama.2017.17627
92. Jawin V, Ang HL, Omar A, Thong MK. Beyond critical congenital heart disease: newborn screening using pulse oximetry for neonatal sepsis and respiratory diseases in a middle-income country. *PLoS One*. 2015;10:e0137580. doi: 10.1371/journal.pone.0137580
93. Wang X, Li P, Chen S, Xi L, Guo Y, Guo A, Sun K. Influence of genes and the environment in familial congenital heart defects. *Mol Med Rep*. 2014;9:695–700. doi: 10.3892/mmr.2013.1847
94. Nora JJ, Dodd PF, McNamara DG, Hattwick MA, Leachman RD, Cooley DA. Risk to offspring of parents with congenital heart defects. *JAMA*. 1969;209:2052–2053.
95. Korbel JO, Tirosh-Wagner T, Urban AE, Chen XN, Kasowski M, Dai L, Grubert F, Erdman C, Gao MC, Lange K, Sobel EM, Barlow GM, Aylsworth AS, Carpenter NJ, Clark RD, Cohen MY, Doran E, Falik-Zaccai T, Lewin SO, Lott IT, McGillivray BC, Moeschler JB, Pettenati MJ, Pueschel SM, Rao KW, Shaffer LG, Shohat M, Van Riper AJ, Warburton D, Weissman S, Gerstein MB, Snyder M, Korenberg JR. The genetic architecture of Down syndrome phenotypes revealed by high-resolution analysis of human segmental trisomies. *Proc Natl Acad Sci U S A*. 2009;106:12031–12036. doi: 10.1073/pnas.0813248106
96. Soemedi R, Wilson IJ, Bentham J, Darlay R, Töpf A, Zelenika D, Cosgrove C, Setchfield K, Thornborough C, Granados-Riveron J, Blue GM, Breckpot J, Hellens S, Zwolinkski S, Glen E, Mamasoula C, Rahman TJ, Hall D, Rauch A, Devriendt K, Gewillig M, O' Sullivan J, Winlaw DS, Bu'Lock F, Brook JD, Bhattacharya S, Lathrop M, Santibanez-Koref M, Cordell HJ, Goodship JA, Keavney BD. Contribution of global rare copy-number variants to the risk of sporadic congenital heart disease. *Am J Hum Genet*. 2012;91:489–501. doi: 10.1016/j.ajhg.2012.08.003
97. Zaidi S, Brueckner M. Genetics and genomics of congenital heart disease. *Circ Res*. 2017;120:923–940. doi: 10.1161/CIRCRESAHA.116.309140
98. Preuss C, Capredon M, Wünnemann F, Chetaille P, Prince A, Godard B, Leclerc S, Sobreira N, Ling H, Awadalla P, Thibeault M, Khairy P, Samuels ME, Andelfinger G; MIBAVA Leducq Consortium. Family based whole exome sequencing reveals the multifaceted role of notch signaling in congenital heart disease. *PLoS Genet*. 2016;12:e1006335. doi: 10.1371/journal.pgen.1006335
99. Zaidi S, Choi M, Wakimoto H, Ma L, Jiang J, Overton JD, Romano-Adesman A, Bjornson RD, Breitbart RE, Brown KK, Carriero NJ, Cheung YH, Deanfield J, DePalma S, Fakhro KA, Glessner J, Hakonarson H, Italia MJ, Kaltman JR, Kaski J, Kim R, Kline JK, Lee T, Leipzig J, Lopez A, Mane SM, Mitchell LE, Newburger JW, Parfenov M, Pe'er I, Porter G, Roberts AE, Sachidanandam R, Sanders SJ, Seiden HS, State MW, Subramanian S, Tikhonova IR, Wang W, Warburton D, White PS, Williams IA, Zhao H, Seidman JG, Brueckner M, Chung WK, Gelb BD, Goldmuntz E, Seidman CE, Lifton RP. De novo mutations in histone-modifying genes in congenital heart disease. *Nature*. 2013;498:220–223. doi: 10.1038/nature12141
100. Hoang TT, Goldmuntz E, Roberts AE, Chung WK, Kline JK, Deanfield JE, Giardini A, Aleman A, Gelb BD, Mac Neal M, Porter GA Jr, Kim R, Brueckner M, Lifton RP, Edman S, Woyciechowski S, Mitchell LE, Agopian AJ. The Congenital Heart Disease Genetic Network Study: cohort description. *PLoS One*. 2018;13:e0191319. doi: 10.1371/journal.pone.0191319
101. Global Burden of Disease Study 2016. Global Burden of Disease Study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and

Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed May 1, 2018.
102. Kumar A, Singh S. BCG site reactivation in Kawasaki disease. *Arthritis Rheumatol*. 2016;68:2026. doi: 10.1002/art.39708
103. Gordon JB, Daniels LB, Kahn AM, Jimenez-Fernandez S, Vejar M, Numano F, Burns JC. The spectrum of cardiovascular lesions requiring intervention in adults after Kawasaki disease. *JACC Cardiovasc Interv*. 2016;9:687–696. doi: 10.1016/j.jcin.2015.12.011
104. Xie X, Shi X, Liu M. The roles of genetic factors in Kawasaki disease: a systematic review and meta-analysis of genetic association studies. *Pediatr Cardiol*. 2018;39:207–225. doi: 10.1007/s00246-017-1760-0
105. Nakamura Y. Kawasaki disease: epidemiology and the lessons from it. *Int J Rheum Dis*. 2018;21:16–19. doi: 10.1111/1756-185X.13211
106. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, Kobayashi T, Wu MH, Saji TT, Pahl E; on behalf of the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135:e927–e999. doi: 10.1161/CIR.0000000000000484
107. Yorifuji T, Tsukahara H, Doi H. Breastfeeding and risk of Kawasaki disease: a nationwide longitudinal survey in Japan. *Pediatrics*. 2016;137:e20153919. doi: 10.1542/peds.2015-3919
108. Holman RC, Belay ED, Christensen KY, Folkema AM, Steiner CA, Schonberger LB. Hospitalizations for Kawasaki syndrome among children in the United States, 1997–2007. *Pediatr Infect Dis J*. 2010;29:483–488. doi: 10.1097/INF.0b013e318cf8705
109. Holman RC, Christensen KY, Belay ED, Steiner CA, Effler PV, Miyamura J, Forbes S, Schonberger LB, Melish M. Racial/ethnic differences in the incidence of Kawasaki syndrome among children in Hawaii. *Hawaii Med J*. 2010;69:194–197.
110. Sudo D, Nakamura Y. Nationwide surveys show that the incidence of recurrent Kawasaki disease in Japan has hardly changed over the last 30 years. *Acta Paediatr*. 2017;106:796–800. doi: 10.1111/apa.13773
111. Manlhiot C, O'Shea S, Bernknopf B, LaBelle M, Chahal N, Dillenburg RF, Lai LS, Bock D, Lew B, Masood S, Mathew M, McCrindle BW. Epidemiology of Kawasaki disease in Canada 2004 to 2014: comparison of surveillance using administrative data vs periodic medical record review. *Can J Cardiol*. 2018;34:303–309. doi: 10.1016/j.cjca.2017.12.009
112. Maddox RA, Holman RC, Uehara R, Callinan LS, Guest JL, Schonberger LB, Nakamura Y, Yashiro M, Belay ED. Recurrent Kawasaki disease: USA and Japan. *Pediatr Int*. 2015;57:1116–1120. doi: 10.1111/ped.12733
113. Taddio A, Rossi ED, Monasta L, et al. Describing Kawasaki shock syndrome: results from a retrospective study and literature review. *Clin Rheumatol*. 2017;36:223–228. doi: 10.1007/s10067-016-3316-8
114. Ogata S, Tremoulet AH, Sato Y, Ueda K, Shimizu C, Sun X, Jain S, Silverstein L, Baker AL, Tanaka N, Ogihara Y, Ikehara S, Takatsuki S, Sakamoto N, Kobayashi T, Fuse S, Matsubara T, Ishii M, Saji T, Newburger JW, Burns JC. Coronary artery outcomes among children with Kawasaki disease in the United States and Japan. *Int J Cardiol*. 2013;168:3825–3828. doi: 10.1016/j.ijcard.2013.06.027
115. Salgado AP, Ashouri N, Berry EK, Sun X, Jain S, Burns JC, Tremoulet AH. High risk of coronary artery aneurysms in infants younger than 6 months of age with Kawasaki disease. *J Pediatr*. 2017;185:112–116.e1. doi: 10.1016/j.jpeds.2017.03.025
116. Satoh K, Wakejima Y, Gau M, Kiguchi T, Matsuda N, Takasawa R, Takasawa K, Nishioka M, Shimohira M. Risk of coronary artery lesions in young infants with Kawasaki disease: need for a new diagnostic method. *Int J Rheum Dis*. 2018;21:746–754. doi: 10.1111/1756-185X.13223
117. Yamashita M, Ae R, Yashiro M, Aoyama Y, Sano T, Makino N, Nakamura Y. Difference in risk factors for subtypes of acute cardiac lesions resulting from Kawasaki disease. *Pediatr Cardiol*. 2017;38:375–380. doi: 10.1007/s00246-016-1525-1
118. Holman RC, Curns AT, Belay ED, Steiner CA, Schonberger LB. Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. *Pediatrics*. 2003;112(pt 1):495–501.
119. Chang RK. Hospitalizations for Kawasaki disease among children in the United States, 1988-1997. *Pediatrics*. 2002;109:e87.
120. Makino N, Nakamura Y, Yashiro M, Sano T, Ae R, Kosami K, Kojo T, Aoyama Y, Kotani K, Yanagawa H. Epidemiological observations of Kawasaki disease in Japan, 2013–2014. *Pediatr Int*. 2018;60:581–587. doi: 10.1111/ped.13544
121. García-Pavón S, Yamazaki-Nakashimada MA, Báez M, Borjas-Aguilar KL, Murata C. Kawasaki disease complicated with macrophage activation syndrome: a systematic review. *J Pediatr Hematol Oncol*. 2017;39:445–451. doi: 10.1097/MPH.0000000000000872
122. Lin MT, Sun LC, Wu ET, Wang JK, Lue HC, Wu MH. Acute and late coronary outcomes in 1073 patients with Kawasaki disease with and without intravenous γ-immunoglobulin therapy. *Arch Dis Child*. 2015;100:542–547. doi: 10.1136/archdischild-2014-306427
123. Manlhiot C, Millar K, Golding F, McCrindle BW. Improved classification of coronary artery abnormalities based only on coronary artery z-scores after Kawasaki disease. *Pediatr Cardiol*. 2010;31:242–249. doi: 10.1007/s00246-009-9599-7
124. Suda K, Iemura M, Nishiono H, Teramachi Y, Koteda Y, Kishimoto S, Kudo Y, Itoh S, Ishii H, Ueno T, Tashiro T, Nobuyoshi M, Kato H, Matsuishi T. Long-term prognosis of patients with Kawasaki disease complicated by giant coronary aneurysms: a single-institution experience. *Circulation*. 2011;123:1836–1842. doi: 10.1161/CIRCULATIONAHA.110.978213
125. Miura M, Kobayashi T, Kaneko T, Ayusawa M, Fukazawa R, Fukushima N, Fuse S, Hamaoka K, Hirono K, Kato T, Mitani Y, Sato S, Shimoyama S, Shiono J, Suda K, Suzuki H, Maeda J, Waki K, Kato H, Saji T, Yamagishi H, Ozeki A, Tomotsune M, Yoshida M, Akazawa Y, Aso K, Doi S, Fukasawa Y, Furuno K, Hayabuchi Y, Hayashi M, Honda T, Horita N, Ikeda K, Ishii M, Iwashima S, Kamada M, Kaneko M, Katyama H, Kawamura Y, Kitagawa A, Komori A, Kuraishi K, Masuda H, Matsuda S, Matsuzaki S, Mii S, Miyamoto T, Moritou Y, Motoki N, Nagumo K, Nakamura T, Nishihara E, Nomura Y, Ogata S, Ohashi H, Okumura K, Omori D, Sano T, Suganuma E, Takahashi T, Takatsuki S, Takeda A, Terai M, Toyono M, Watanabe K, Watanabe M, Yamamoto M, Yamamura K; and the Z-score Project 2nd Stage Study Group. Association of severity of coronary artery aneurysms in patients with Kawasaki disease and risk of later coronary events. *JAMA Pediatr*. 2018;172:e180030. doi: 10.1001/jamapediatrics.2018.0030
126. Daniels LB, Tjajadi MS, Walford HH, Jimenez-Fernandez S, Trofimenko V, Fick DB Jr, Phan HA, Linz PE, Nayak K, Kahn AM, Burns JC, Gordon JB. Prevalence of Kawasaki disease in young adults with suspected myocardial ischemia. *Circulation*. 2012;125:2447–2453. doi: 10.1161/CIRCULATIONAHA.111.082107
127. Wardle AJ, Connolly GM, Seager MJ, Tulloh RM. Corticosteroids for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev*. 2017;1:CD011188. doi: 10.1002/14651858.CD011188.pub2
128. Dionne A, Bakloul M, Manlhiot C, McCrindle BW, Hosking M, Houde C, Pepelassis D, Dahdah N. Coronary artery bypass grafting and percutaneous coronary intervention after Kawasaki disease: the Pediatric Canadian Series. *Pediatr Cardiol*. 2017;38:36–43. doi: 10.1007/s00246-016-1480-x
129. Kim GB, Park S, Eun LY, Han JW, Lee SY, Yoon KL, Yu JJ, Choi JW, Lee KY. Epidemiology and clinical features of Kawasaki disease in South Korea, 2012-2014. *Pediatr Infect Dis J*. 2017;36:482–485. doi: 10.1097/INF.0000000000001474
130. Wu MH, Lin MT, Chen HC, Kao FY, Huang SK. Postnatal risk of acquiring Kawasaki disease: a nationwide birth cohort database study. *J Pediatr*. 2017;180:80–86.e2. doi: 10.1016/j.jpeds.2016.09.052
131. Chen JJ, Ma XJ, Liu F, Yan WL, Huang MR, Huang M, Huang GY; Shanghai Kawasaki Disease Research Group. Epidemiologic features of Kawasaki disease in Shanghai from 2008 through 2012. *Pediatr Infect Dis J*. 2016;35:7–12. doi: 10.1097/INF.0000000000000914
132. Nakamura Y, Yashiro M, Yamashita M, Aoyama N, Otaki U, Ozeki Y, Sano T, Kojo T, Ae R, Aoyama Y, Makino N, Kotani K. Cumulative incidence of Kawasaki disease in Japan. *Pediatr Int*. 2018;60:19–22. doi: 10.1111/ped.13450
133. Jakob A, Whelan J, Kordecki M, Berner R, Stiller B, Arnold R, von Kries R, Neumann E, Roubinis N, Robert M, Grohmann J, Höhn R, Hufnagel M. Kawasaki disease in Germany: a prospective, population-based study adjusted for underreporting. *Pediatr Infect Dis J*. 2016;35:129–134. doi: 10.1097/INF.0000000000000953
134. Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. *Arch Dis Child*. 2015;100:1084–1088. doi: 10.1136/archdischild-2014-307536
135. Cimaz R, Fanti E, Mauro A, Voller F, Rusconi F. Epidemiology of Kawasaki disease in Italy: surveillance from national

hospitalization records. *Eur J Pediatr*. 2017;176:1061–1065. doi: 10.1007/s00431-017-2947-3
136. Sánchez-Manubens J, Antón J, Bou R, Iglesias E, Calzada-Hernandez J, Rodó X, Morguí JA; el Grupo de Trabajo en Enfermedad de Kawasaki en Cataluña. Kawasaki disease is more prevalent in rural areas of Catalonia (Spain) [in Spanish]. *An Pediatr (Barc)*. 2017;87:226–231. doi: 10.1016/j.anpedi.2016.12.009
137. Gilboa SM, Devine OJ, Kucik JE, Oster ME, Riehle-Colarusso T, Nembhard WN, Xu P, Correa A, Jenkins K, Marelli AJ. Congenital heart defects in the United States: estimating the magnitude of the affected population in 2010. *Circulation*. 2016;134:101–109. doi: 10.1161/CIRCULATIONAHA.115.019307
138. Ma M, Gauvreau K, Allan CK, Mayer JE Jr, Jenkins KJ. Causes of death after congenital heart surgery. *Ann Thorac Surg*. 2007;83:1438–1445. doi: 10.1016/j.athoracsur.2006.10.073

16. DISORDERS OF HEART RHYTHM

See Table 16-1 and Charts 16-1 through 16-11

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Arrhythmias (Disorders of Heart Rhythm)

2016: Mortality—52 015. Any-mention mortality—536 092.

Abbreviations Used in Chapter 16

ACCORD	Action to Control Cardiovascular Risk in Diabetes
AF	atrial fibrillation
AMI	acute myocardial infarction
ARIC	Atherosclerosis Risk in Communities
ASSERT	Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial
AV	atrioventricular
BiomarCaRE	Biomarker for Cardiovascular Risk Assessment in Europe
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
CABG	coronary artery bypass graft
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CHA_2DS_2-VASc	Clinical prediction rule for estimating the risk of stroke based on congestive heart failure, hypertension, diabetes mellitus, and sex (1 point each); age ≥75 y and stroke/transient ischemic attack/thromboembolism (2 points each); plus history of vascular disease, age 65–74 y, and (female) sex category
$CHADS_2$	Clinical prediction rule for estimating the risk of stroke based on congestive heart failure, hypertension, age ≥75 y, diabetes mellitus (1 point each), and prior stroke/transient ischemic attack/thromboembolism (2 points)
CHARGE-AF	Cohorts for Heart and Aging Research in Genomic Epidemiology–Atrial Fibrillation
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CPAP	continuous positive airway pressure
CVD	cardiovascular disease
DALY	disability-adjusted life-year
DM	diabetes mellitus
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ED	emergency department
EF	ejection fraction
EMPHASIS-HF	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
EPIC	European Prospective Investigation Into Cancer and Nutrition
ESRD	end-stage renal disease
FHS	Framingham Heart Study
GBD	Global Burden of Disease
GWAS	genome-wide association studies
GWTG	Get With The Guidelines
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HCM	hypertrophic cardiomyopathy
HCUP	Healthcare Cost and Utilization Project

(Continued)

Abbreviations Used in Chapter 16 Continued

HD	heart disease
HF	heart failure
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
ICD-10	*International Classification of Diseases, 10th Revision*
IQR	interquartile range
IRR	incidence rate ratio
Look AHEAD	Look: Action for Health in Diabetes
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MESA	Multi-Ethnic Study of Atherosclerosis
MET	metabolic equivalent
MI	myocardial infarction
NAMCS	National Ambulatory Medical Care Survey
NCDR	National Cardiovascular Data Registry
NCHS	National Center for Health Statistics
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHDS	National Hospital Discharge Survey
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NSTEMI	non–ST-segment–elevation myocardial infarction
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
ORBIT-AF	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
OSA	obstructive sleep apnea
PA	physical activity
PAD	peripheral artery disease
PAR	population attributable risk
PINNACLE	Practice Innovation and Clinical Excellence
PREDIMED	Prevención con Dieta Mediterránea
PREVEND	Prevention of Renal and Vascular End-Stage Disease
QALY	quality-adjusted life-year
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RE-LY	Randomized Evaluation of Long-term Anticoagulant Therapy
RR	relative risk
SBP	systolic blood pressure
SCD	sudden cardiac death
SES	socioeconomic status
SNP	single-nucleotide polymorphism
STEMI	ST-segment–elevation myocardial infarction
STROKESTOP	Systematic ECG Screening for Atrial Fibrillation Among 75-Year-Old Subjects in the Region of Stockholm and Halland, Sweden
SVT	supraventricular tachycardia
UI	uncertainty interval
USD	US dollars
VF	ventricular fibrillation
WPW	Wolff-Parkinson-White

Bradyarrhythmias *ICD-9* 426.0, 426.1, 427.81; *ICD-10* I44.0 to I44.3, I49.5.

2016: Mortality—1163. Any-mention mortality—6411.
2014: Hospital discharges—94 000.
Pacemakers: *ICD-9-CM* 37.7 to 37.8, 00.50, 00.53.

<zjs;AHA Statistical Update> • <zjss;10163> • <zdoi;10.1161/CIR.0000000000000659>

Mean hospital charges: $83 521; in-hospital death rate: 1.46%; mean length of stay: 5.1 days.

AV Block

Prevalence and Incidence

- In a healthy sample of participants from the ARIC study (mean age 53 years), the prevalence of first-degree AV block was 7.8% in black males, 3.0% in black females, 2.1% in white males, and 1.3% in white females.[1] Lower prevalence estimates were noted in the relatively younger population (mean age 45 years) of the CARDIA study at its year 20 follow-up examination: 2.6% in black males, 1.9% in black females, 1.2% in white males, and 0.1% in white females.[2]
- The prevalence of PR interval prolongation was observed to be 2.1% in Finnish middle-aged adults, but the authors noted that the PR interval normalized in follow-up in 30% of these people.[3]
- No population-based studies have reported the prevalence of second-degree AV block. On the basis of results from clinical series, Mobitz II second-degree AV block is rare in healthy individuals (≈0.003%), whereas Mobitz I (Wenckebach) is observed in 1% to 2% of healthy young people, especially during sleep.[4]
- The prevalence of third-degree AV block in the general adult population is very low. The prevalence was 0.04% in the Tecumseh Study[5] and the Icelandic Reykjavik Study[6] and 0.6% in a large sample of people with hypertension and without DM enrolled with Veterans Health Administration hospitals.[7]
- In 122 815 recordings from 122 454 unique patients prescribed 14-day continuous electrocardiographic monitoring with the Zio patch device between 2011 and 2013, prevalence of high-grade AV block (defined as either Mobitz II or complete heart block) was 1.2% (1486 of all tracings).[8]
- An English registry study estimated the incidence of infant complete AV block as 2.1 per 100 000 live births.[9] Congenital complete heart block could be attributable to transplacental transfer of maternal anti-SSA/Ro or SSB/La antibodies.[10]

Complications (See Chart 16-1)

- In the FHS, PR interval prolongation (>200 ms) was associated with increased risk of AF (HR, 2.06 [95% CI, 1.36–3.12]), pacemaker implantation (HR, 2.89 [95% CI, 1.83–4.57]), and all-cause mortality (HR, 1.44 [95% CI, 1.09–1.91]).[11] Compared with people with a PR interval ≤200 ms, those with a PR interval >200 ms had an absolute increased risk per year of 1.0% for AF, 0.5% for pacemaker implantation, and 2.1% for death (Chart 16-1).[11]
- Decisions about the need for a pacemaker are influenced by the presence or absence of symptoms directly attributable to bradycardia and the likelihood of the arrhythmia to progress to complete heart block. Permanent pacing improves survival in patients with third-degree AV block, especially if syncope has occurred.[12]
- In a large, prospective, regional French registry of 6662 STEMI patients (2006–2013), high-degree AV block was noted in 3.5% of individuals. In 64% of cases, high-degree AV block was present on admission. Although patients with high-degree AV block on admission or occurring during the first 24 hours of hospitalization had higher in-hospital mortality rates than patients without heart block, it was not an independent predictor of mortality after multivariable analysis (HR, 0.99 [95% CI, 0.60–1.66]).[13]
- Little evidence exists to suggest that pacemakers improve survival in patients with isolated first-degree AV block.[14] However, marked first-degree AV block (PR >300 ms) can lead to symptoms even in the absence of higher degrees of AV block, with uncontrolled studies suggesting that those patients benefit from pacemaker implantation.[12,15]

Risk Factors

- In healthy individuals without CVD or its risk factors from MESA, PR interval was longer with advancing age, in males compared with females, and in blacks compared with whites.[16]
- Although first-degree AV block and Mobitz type I second-degree AV block can occur in apparently healthy people, presence of Mobitz II second- or third-degree AV block usually indicates underlying HD, including CHD, and HF.[4]
- Reversible causes of AV block include electrolyte abnormalities, drug-induced AV block, perioperative AV block attributable to hypothermia, or inflammation near the AV conduction system after surgery in this region. Some conditions may warrant pacemaker implantation because of the potential for disease progression even if the AV block reverses transiently (eg, sarcoidosis, amyloidosis, and neuromuscular diseases).[12]
- Long sinus pauses and AV block can occur during sleep apnea. In the absence of symptoms, these abnormalities are reversible and do not require pacing.[12,17]

Prevention

- Detection and correction of reversible causes of acquired AV block could be of potential importance in preventing symptomatic bradycardia and other complications of AV block.[12]

Sinus Node Dysfunction

Prevalence and Incidence

- There are no accurate estimates of the prevalence of sinus node dysfunction in the general population.
- According to a survey of members of the North American Society of Pacing and Electrophysiology, sick sinus syndrome accounted for 48% of implantations of first permanent pacemakers in the United States in 1997.[18,19]
- Sinus node dysfunction is commonly present with other causes of bradyarrhythmias (carotid sinus hypersensitivity in 42% of patients and advanced AV conduction abnormalities in 17%).[20,21]
- Incidence rates of sinus node dysfunction hospitalization among Medicare beneficiaries >65 years of age were 207 per 100 000 person-years in 1998. Rates increased with age and were higher in males than females and in whites than blacks.[22]
- The incidence rate of sick sinus syndrome was 0.8 per 1000 person-years of follow-up in 2 biracial US cohorts, ARIC and CHS.[23] The incidence increased with advancing age (HR, 1.73 [95% CI, 1.47–2.05] per 5-year increment), and blacks were at 41% lower risk of sick sinus syndrome than their white counterparts (HR, 0.59 [95% CI, 0.37–0.98]). Investigators projected that in the United States, the number of new cases of sick sinus syndrome per year would rise from 78 000 in 2012 to 172 000 in 2060.[23]

Complications (See Chart 16-2)

- In a small prospective study of 35 patients ≥45 years of age with sinus node dysfunction that was left untreated, 57% experienced cardiovascular events over a 4-year follow-up period; 31% experienced syncope over the same period.[24]
- The survival of patients with sinus node dysfunction appears to depend primarily on the severity of underlying cardiac disease, is not different from survival in the general population when treated with pacemaker, and is not significantly changed by type of pacemaker therapy.[25–27]
- In a retrospective study[28] of patients with sinus node dysfunction who had pacemaker therapy, mortality among those with ventricular pacing only was 63% compared with 40% among those with DDD pacing at 7-year follow-up.
- In 19 893 males and females >45 years of age from the ARIC and CHS cohorts, incidence of sick sinus syndrome was associated with increased mortality (HR, 1.4 [95% CI, 1.1–1.7]), CHD (HR, 1.7 [95% CI, 1.1–2.7]), HF (HR, 2.9 [95% CI, 2.2–3.8]), stroke (HR, 1.6 [95% CI, 1.0–2.5]), AF (HR, 5.8 [95% CI, 4.4–7.5]), and pacemaker implantation (HR, 53.7 [95% CI, 42.9–67.2]).[29]
- In a multicenter study from the Netherlands of people with bradycardia treated with pacemaker implantation, the actuarial 1-, 3-, 5-, and 7-year survival rates were 93%, 81%, 69%, and 61%, respectively. Individuals without CVD at baseline had similar survival rates as age- and sex-matched control subjects.[30]
- With sinus node dysfunction, the incidence of sudden death is extremely low, and pacemaker implantation does not appear to alter longevity.[12,31] SVT including AF was prevalent in 53% of patients with sinus node dysfunction.[26]
- On the basis of records from the NIS, pacemaker implantation rates per million increased from 291 in 1993 to 616 in 2009, although overall use plateaued in 2001. The patients' mean age and number of comorbidities at implantation increased over time. Total hospital charges associated with pacemaker implantation increased 45% from $53 693 in 1993 to $78 015 in 2009 (in 2011 dollars).[32]
- On the basis of NHDS data, the escalating implantation rate was attributable to increasing implantation for isolated sinus node dysfunction; implantation for sinus node dysfunction increased by 102%, whereas implantation for all other indications did not increase (Chart 16-2).[33]
- A study at a single academic institution compared older adult outpatients (>60 years old) with (N=470) and without (N=2090) asymptomatic bradycardia. Over a mean follow-up of 7.2 years, patients with asymptomatic bradycardia had a higher adjusted incidence of pacemaker insertion (HR, 2.14 [95% CI, 1.30–3.51]; *P*=0.003), which appeared after a lag time of 4 years. However, the absolute rate of pacemaker implantation was low (<1% per year), and asymptomatic bradycardia was not associated with a higher risk of death.[34]
- In 5831 participants of the MESA cohort, a heart rate lower than 50 beats per minute was not associated with mortality or incident CVD among individuals not taking heart rate–modifying drugs compared with those with heart rate between 50 and 59 beats per minute.[35]

Risk Factors

- The causes of sinus node dysfunction can be classified as intrinsic (secondary to pathological conditions involving the sinus node) or extrinsic (caused by depression of sinus node function by external factors such as drugs or autonomic influences).[36]
- Idiopathic degenerative disease is probably the most common cause of sinus node dysfunction.[37]
- Investigators collected data from 28 different studies on atrial pacing for sinus node dysfunction that showed a median annual incidence of second- and third-degree AV block of 0.6% (range, 0%–4.5%) and an overall prevalence of 2.1% (range, 0%–11.9%). This suggests that the degenerative process also affects the specialized conduction system, although the rate of progression is slow and does not dominate the clinical course of disease.[38]
- In the CHS and ARIC studies, factors associated with incident sick sinus syndrome included white (versus black) race, higher mean BMI, height, prevalent hypertension, lower heart rate, right bundle-branch block, N-terminal pro-BNP, cystatin C, and history of a major cardiovascular event.[23]

SVT (Excluding AF and Atrial Flutter) *ICD-9* 427.0; *ICD-10* I47.1.

2016: Mortality—146. Any-mention mortality—1440. Hospital discharges—15 000 (6000 male; 9000 female).

Prevalence and Incidence (See Chart 16-3)

- Data from the Marshfield Epidemiologic Study Area in Wisconsin suggested the incidence of documented paroxysmal SVT was 35 per 100 000 person-years, whereas the prevalence was 225 per 100 000 people. The mean age at SVT onset was 57 years, and both female sex (RR, 2.0) and age ≥65 years (versus <65 years: RR, 5.3) were significant risk factors (Chart 16-3).[39]
- A review of ED visits in US hospitals using NHAMCS data from 1993 to 2003 revealed that an estimated 550 000 visits were for SVT (0.05% of all visits [95% CI, 0.04%–0.06%]), or ≈50 000 visits per year (incidence rate of 1.8 ED visits per 10 000 person-years [95% CI, 1.4–2.3]). Of these patients, 24% (95% CI, 15%–34%) were admitted to the hospital, and 44% (95% CI, 32%–56%) were discharged without specific follow-up.[40] Rates were higher in individuals ≥65 years of age than in those <65 years of age (3.9 versus 1.5 per 10 000 person-years) and lower in males than in females (1.1 versus 2.6 per 10 000 person-years).
- The prevalence of SVT that is clinically undetected is likely much greater than the estimates from ED visits and electrophysiology procedures would suggest. Among 26 751 individual patients receiving a Zio Patch monitor (a 14-day single-lead electrocardiographic monitor) for clinical indications, prevalence of SVT defined as at least a single run of ≥8 beats was 31%.[41]
- Of 1383 participants in the Baltimore Longitudinal Study of Aging undergoing maximal exercise testing, 6% exhibited SVT during the test; increasing age was a significant risk factor. Only 16% exhibited >10 beats of SVT, and only 4% were symptomatic. Over an average of 6 years of follow-up, people with exercise-induced SVT were more likely to develop SVT or AF.[42]
- In a study of 3554 consecutive males 17 to 21 years of age applying for a pilot's license, the surface ECG revealed that the prevalence of ectopic atrial tachycardia was estimated to be 0.34% in asymptomatic applicants and 0.46% in symptomatic applicants.[43]

Complications

- Rare cases of incessant SVT can lead to a tachycardia-induced cardiomyopathy,[44] and rare cases of sudden death attributed to SVT as a trigger have been described.[45]
- Among 2 350 328 pregnancies included in Taiwan's national insurance database between 2001 and 2012, 769 females experienced paroxysmal SVT during pregnancy. Compared with those females without paroxysmal SVT during pregnancy, paroxysmal SVT during pregnancy was associated with a higher risk for poor maternal outcomes (severe morbidity and cesarean delivery) and poor fetal outcomes (low birth weight, preterm labor, fetal stress, and obvious fetal abnormalities).[46]
- A California administrative database study of almost 5 million patients suggested that after the exclusion of people with diagnosed AF, SVT was associated with an adjusted doubling of the risk of stroke in follow-up (HR, 2.10 [95% CI, 1.69–2.62]). The absolute stroke rate was low, however. The cumulative stroke rate was 0.94% (95% CI, 0.76%–1.16%) over 1 year in patients with SVT versus 0.21% (95% CI, 0.21%–0.22%; P<0.001, log-rank test) in those without SVT.[47]
- In a Swedish study of 214 patients (51% females) with paroxysmal SVT undergoing ablation, females had a longer history of symptomatic arrhythmia (16.2±14.6 versus 9.9±13.1 years), were more likely to report not being taken seriously when consulting for their symptoms (17% versus 7%), and were more symptomatic after 6 months of ablation than males.[48]

Specific Types

- Among those presenting for invasive electrophysiological study and ablation, AV nodal reentrant tachycardia (a circuit that requires 2 AV nodal pathways) is the most common mechanism of SVT[49,50] and usually represents the majority of cases (56% in one series of 1754 cases).[50]
- AV reentrant tachycardia (an arrhythmia that requires the presence of an extranodal connection between the atria and ventricles or specialized conduction tissue) is the second most common type of SVT (27% in the study by Porter et al[50]), and atrial tachycardia is the third most common (17% in the series of 1754 SVT cases from Porter et al[50]).
- In a US-based national pediatric electrophysiology registry study, AV reentrant tachycardia was the most common SVT mechanism (68%), whereas the remainder of the patients had AV nodal reentrant tachycardia (32%).[51]
- AV reentrant tachycardia prevalence decreases with age, whereas AV nodal reentrant tachycardia and atrial tachycardia prevalence increase with advancing age.[50]
- The majority of patients with AV reentrant tachycardia were males (55%), whereas females constituted the majority with AV nodal reentrant tachycardia (70%) or atrial tachycardia (62%) in the study by Porter et al.[50]
- Multifocal atrial tachycardia is an arrhythmia that is commonly confused with AF and is characterized by 3 distinct P-wave morphologies, irregular R-R intervals, and a rate >100 beats per minute. It is uncommon in both children[52] and adults,[53] with a prevalence in hospitalized adults estimated at 0.05% to 0.32%.[53] The average age of onset in adults is 70 to 72 years. Adults with multifocal atrial tachycardia have a high mortality rate, with estimates around 45%, but this is generally ascribed to the underlying condition(s).[53] In a study of older ambulatory adults in a Greece, the mortality in follow-up did not differ by whether or not multifocal atrial rhythms were detected on baseline ECG.[54]

WPW Syndrome

Prevalence

- A WPW electrocardiographic pattern was observed in 0.11% of males and 0.04% of females among 47 358 ECGs from adults participating in 4 large Belgian epidemiological studies.[55] In a study of 32 837 Japanese students who were required by law to receive ECGs before entering school, a WPW electrocardiographic pattern was reported in 0.07%, 0.07%, and 0.17% of elementary, junior high, and high school students, respectively.[56]

Complications

- WPW syndrome, a diagnosis reserved for those with both ventricular preexcitation (evidence of an anterograde conducting AV accessory pathway on a 12-lead ECG) and tachyarrhythmias, deserves special attention because of the associated risk of sudden death. Sudden death is generally attributed to rapid heart rates in AF conducting down an accessory pathway and leading to VF.[57]
- A cohort study from Intermountain Healthcare with ≈8 years of follow-up reported that rates of cardiac arrest were low and similar between WPW and control patients without WPW. In follow-up, WPW was associated with a significantly higher risk of AF (HR, 1.55 [95% CI, 1.29–1.87]); 7.0% of the WPW patients developed AF compared with 3.8% of those without WPW.[58]
- Asymptomatic adults with ventricular preexcitation appear to be at no increased risk of sudden death compared with the general population,[59–62] although certain characteristics found during an invasive electrophysiological study (including inducibility of AV reentrant tachycardia or AF, accessory pathway refractory period, and the shortest R-R interval during AF) can help risk stratify these patients.[59]
- In a single-center prospective registry study of 2169 patients who agreed to undergo an electrophysiology study for WPW syndrome from 2005 to 2010, 1168 patients (206 asymptomatic) underwent radiofrequency ablation, none of whom had malignant arrhythmias or VF in up to 8 years of follow-up. Of those who did not receive radiofrequency ablation (N=1001; 550 asymptomatic) in follow-up, 1.5% had VF, most of whom (13 of 15) were children. The authors noted that poor prognosis was related to accessory pathway electrophysiological properties rather than patient symptoms.[63]
- In a meta-analysis of 20 studies involving 1869 asymptomatic patients with a WPW electrocardiographic pattern followed up for a total of 11 722 person-years, the rate of sudden death in a random effects model that was used because of heterogeneity across studies was estimated to be 1.25 (95% CI, 0.57–2.19) per 1000 person-years. Risk factors for sudden death included male sex, inclusion in a study of children (<18 years of age), and inclusion in an Italian study.[64]
- Several studies in asymptomatic children with ventricular preexcitation detected by screening suggested a benign prognosis.[62,65] A referral-based registry study reported that electrophysiological testing can identify a group of asymptomatic children with a risk of sudden death or VF as high as 11% over 19 months of follow-up.[66] In a pediatric

hospital retrospective review of 446 children with WPW syndrome, 64% were symptomatic at presentation, and 20% had onset of symptoms during a median of 3 years follow-up. The incidence of sudden death was 1.1 per 1000 person-years in patients without structural HD.[67]

AF and Atrial Flutter

Prevalence (See Chart 16-4)

- Estimates of the prevalence of AF in the United States ranged from ≈2.7 million to 6.1 million in 2010,[68,69] and AF prevalence is estimated to rise to 12.1 million in 2030 (Chart 16-4).[70]
- In the European Union, the prevalence of AF in adults >55 years of age was estimated to be 8.8 million (95% CI, 6.5–12.3 million) in 2010 and was projected to rise to 17.9 million in 2060 (95% CI, 13.6–23.7 million).[71]
- Data from a California health plan suggested that compared with whites, blacks (OR, 0.49 [95% CI, 0.47–0.52]), Asians (OR, 0.68 [95% CI, 0.64–0.72]), and Hispanics (OR, 0.58 [95% CI, 0.55–0.61]) have a significantly lower adjusted prevalence of AF.[72]
- Among Medicare patients aged ≥65 years who were diagnosed from 1993 to 2007, the prevalence of AF increased ≈5% per year, from ≈41.1 per 1000 beneficiaries to 85.5 per 1000 beneficiaries.[73]
  - In 2007 in the 5% Medicare sample, there were 105 701 older adults with AF: 3.7% were black, 93.8% were white, and 2.6% were other/unknown race.[73]
  - The prevalence rate per 1000 beneficiaries was 46.3 in blacks, 90.8 in whites, and 47.5 in other/unknown race.[73]

Incidence (See Table 16-1 and Chart 16-5)

- In a Medicare sample, per 1000 person-years, the age- and sex-standardized incidence of AF was 27.3 in 1993 and 28.3 in 2007, representing a 0.2% mean annual change (P=0.02). Of individuals with incident AF in 2007, ≈55% were females, 91% were white, 84% had hypertension, 36% had HF, and 30% had cerebrovascular disease.[73]
- Investigators from MESA estimated the age- and sex-adjusted incidence rate of hospitalized AF per 1000 person-years (95% CI) as 11.2 (9.8–12.8) in NH whites, 6.1 (4.7–7.8) in Hispanics, 5.8 (4.8–7.0) in NH blacks, and 3.9 (2.5–6.1) in Chinese.[74]
- Data from California administrative databases were analyzed with regard to racial variation in incidence of AF. After adjustment for AF risk factors, compared with their white counterparts, lower incidence rates were found in blacks (HR, 0.84 [95% CI, 0.82–0.85]; P<0.001), Hispanics (HR, 0.78 [95% CI, 0.77–0.79]; P<0.001), and Asians (HR, 0.78 [95% CI, 0.77–0.79]; P<0.001) (Chart 16-5).[75]
- Racial variation in AF incidence is also observed in other countries. For instance, in a study of the UK Clinical Practice Research Datalink cohort ≥45 years of age, the incidence rates per 1000 person-years standardized to the UK population were 8.1 (95% CI, 8.1–8.2) in whites versus 5.4 (95% CI, 4.6–6.3) in Asians and 4.6 (95% CI, 4.0–5.3) in black patients.[76]
- Using data from a health insurance claims database covering 5% of the United States, the incidence of AF was estimated at 1.2 million cases in 2010 and was projected to increase to 2.6 million cases in 2030.[70]

Lifetime Risk and Cumulative Risk (See Chart 16-6)

- Previously, the lifetime risks of AF have been estimated to be ≈1 in 4 in individuals from the FHS and Rotterdam Study.[77,78]
- However, in more recent studies from Framingham and the European BiomarCaRE Consortium, the lifetime risk estimates for AF in individuals of European ancestry have increased to ≈1 in 3.
  - In the BiomarCaRE study based on 4 European community-based studies, the incidence increased after age 50 years in males and 60 years in females, but the cumulative incidence of AF was similar, at >30%, by age 90 years.[79]
  - In an FHS report based on participants with DNA collected after 1980, the lifetime risk of AF after age 55 years was 37.1%, which was influenced by both clinical and genetic risk.[80] In a subsequent study from Framingham, the lifetime risk of AF varied by risk factor burden. In individuals with optimal risk profile, the lifetime risk was 23.4% (95% CI, 1.8%–34.5%), whereas the risk was 33.4% (95% CI, 27.9–38.9) with a borderline risk profile and 38.4% (95% CI, 35.5%–41.4%) with an elevated risk profile.[81]
- In a medical insurance database study from the Yunnan Province in China, the estimated lifetime risk of AF at age 55 years was 21.1% (95% CI, 19.3%–23.0%) for females and 16.7% (95% CI, 15.4%–18.0%) for males.[82] In a Taiwanese study, the lifetime risk of AF was estimated to be 16.9

(95% CI, 16.7–14.2) in males and 14.6 (95% CI, 14.4–14.9) in females.[83]

- Investigators from the NHLBI-sponsored ARIC study observed that the lifetime risk of AF was 36% in white males (95% CI, 32%–38%), 30% in white females (95% CI, 26%–32%), 21% in African American males (95% CI, 13%–24%), and 22% in African American females (95% CI, 16%–25%).[84]

Mortality (See Chart 16-7)
2016 ICD-9 427.3; ICD-10 I48.

In 2016, AF was the underlying cause of death in 24 855 people and was listed on 15 816 US death certificates (any-mention mortality).

- The age-adjusted mortality rate from AF was 6.5 per 100 000 people in 2016.[85]
- In adjusted analyses from the FHS, AF was associated with an increased risk of death in both males (OR, 1.5 [95% CI, 1.2–1.8]) and females (OR, 1.9 [95% CI, 1.5–2.2]).[86] Furthermore, there was an interaction with sex, such that AF appeared to diminish the survival advantage typically observed in females.
- Although there was significant between-study heterogeneity (*P*<0.001), a meta-analysis confirmed that the adjusted risk of death was significantly stronger in females than in males with AF (RR, 1.12 [95% CI, 1.07–1.17]).[87]
- In Medicare beneficiaries ≥65 years of age with new-onset AF, mortality decreased modestly but significantly between 1993 and 2007. In 2007, the age- and sex-adjusted mortality at 30 days was 11%, and at 1 year, it was 25%.[73]
- An observational study of Olmsted County, MN, residents with first diagnosis of AF or atrial flutter between 2000 and 2010 reported a high early mortality compared with individuals of similar age and sex; the standardized mortality ratio was 19.4 (95% CI, 17.3–21.7) in the first 30 days and 4.2 (95% CI, 3.5–5.0) for days 31 to 90.[88]
- Although stroke is the most feared complication of AF, the RE-LY clinical trial reported that stroke accounted for only ≈7.0% of deaths in AF, with SCD (22.25%), progressive HF (15.1%), and noncardiovascular death (35.8%) accounting for the majority of deaths.[89]
- AF is also associated with increased mortality in subgroups of individuals, including the following:
  - — Individuals with other cardiovascular conditions and procedures, including HCM,[90] MI,[91,92] post-CABG[91–94] (both short-term[93] and long-term[93,94]), post– transcatheter aortic valve implantation,[95] PAD,[96] and stroke.[97]
  - — Individuals with AF have increased mortality with concomitant HF,[98,99] HF with preserved EF,[100,101] and HF with reduced EF.[100] In a meta-analysis that examined the timing of AF in relation to HF onset with regard to mortality, the risk of death associated with incident AF was higher (RR, 2.21 [95% CI, 1.96–2.49]) than with prevalent AF (RR, 1.19 [95% CI, 1.03–1.38]; $P_{interaction}$<0.001).[102]
  - — AF is also associated with an increased risk of death in other conditions, including DM,[103,104] ESRD,[105] sepsis,[106,107] and noncardiac surgery.[108]
- In a Medicare unadjusted analysis, blacks and Hispanics had a higher risk of death than their white counterparts with AF; however, after adjustment for comorbidities, blacks (HR, 0.95 [95% CI, 0.93–0.96]; *P*<0.001) and Hispanics (HR, 0.82 [95% CI, 0.80–0.84]; *P*<0.001) had a lower risk of death than whites with AF.[109] In contrast, in the population-based ARIC study, the rate difference for all-cause mortality for individuals with versus without AF per 1000 person-years was 106.0 (95% CI, 86.0–125.9)[103] in blacks, which was higher than the 55.9 (95% CI, 48.1–63.7) rate difference in mortality observed for whites.[110]
- In a US-based study, there was substantial variation in mortality with AF in US counties from 1980 to 2014.[111] Investigators estimated there were ≈22 700 (95% UI, 19 300–26 300) deaths attributable to AF in 2014 and 191 500 (95% UI, 168 000–215 300) years of life lost. In an examination of county-level data, the age-standardized CVD mortality rates were 5.6 per 100 000 for the 10th percentile and 9.7 per 100 000 for the 90th percentile. The counties with age-standardized death rates greater than the 90th percentile were clustered in Oregon, California, Utah, Idaho, northeastern Montana, areas east of Kansas City, MO, and southwest West Virginia.[111]
- In a Swedish study based on 75 primary care centers, an adjusted analysis of patients diagnosed with AF revealed that males living in low SES neighborhoods were 49% (HR, 1.49 [95% CI, 1.13–1.96]) more likely to die than their counterparts living in middle-income neighborhoods. The results were similar in models that additionally adjusted for anticoagulant and statin treatment (HR, 1.39 [95% CI, 1.05–1.83]).[112] In another study from the same group, unmarried and divorced males and males with lower educational levels with AF had higher risk of mortality than their married and better-educated male counterparts.[113]

Complications

- Five years after diagnosis with AF, the cumulative incidence rate of mortality, HF, MI, stroke, and gastrointestinal bleeding was higher in older age groups (80–84, 85–89, and ≥90 years of age) than in younger age groups (67–69, 70–74, and 75–79 years of age) (Table 16-1).[114]

Extracranial Systemic Embolic Events

- In a Danish population-based registry of individuals 50 to 89 years of age discharged from the hospital, individuals with new-onset AF had an elevated risk of thromboembolic events to the aorta and renal mesenteric, pelvic, and peripheral arteries. The excess thromboembolic event rate was 3.6 in males and 6.3 in females per 1000 person-years of follow-up. Compared with referents in the Danish population, the RR of diagnosed extracranial embolism was 4.0 (95% CI, 3.5–4.6) in males and 5.7 (95% CI, 5.1–6.3) in females.[115]
- Investigators pooled data from 4 large, contemporary, randomized anticoagulation trials and observed 221 systemic emboli in 91 746 person-years of follow-up. The systemic embolic event rate was 0.24 versus a stroke rate of 1.92 per 100 person-years. Compared with individuals experiencing stroke, patients experiencing systemic emboli were more likely to be females (56% versus 47%; *P*=0.01) but had similar mean age and $CHADS_2$ score as those with stroke. Both stroke (RR, 6.79 [95% CI, 6.22–7.41]) and systemic emboli (RR, 4.33 [95% CI, 3.29–5.70]) were associated with an increased risk of death compared with patients with neither event.[116]

Stroke
(See Chart 16-7)

- Using a 5% Medicare sample from 2008 to 2014, investigators reported the annual stroke rate to be 2.02% (95% CI, 1.99%–2.05%) in patients with AF and 1.38% (95% CI, 1.22%–1.57%) in patients with atrial flutter. After adjustment for demographics and vascular risk factors, the risk of stroke was significantly lower in patients with atrial flutter than in those with AF (HR, 0.69 [95% CI, 0.61–0.79]).[117]
- A systematic review of prospective studies found wide variability in stroke risk between studies and between AF patients, ranging between 0.5% and 9.3% per year.[118]
- Before the widespread use of anticoagulant drugs, after accounting for standard stroke risk factors, AF was associated with a 4- to 5-fold increased risk of ischemic stroke. Although the RR of stroke associated with AF did not vary (≈3- to 5-fold increased risk) substantively with advancing age, the proportion of strokes attributable to AF increased significantly. In the FHS, AF accounted for ≈1.5% of strokes in individuals 50 to 59 years of age and ≈23.5% in those 80 to 89 years of age.[119]
- AF was also an independent risk factor for ischemic stroke severity, recurrence, and mortality.[97] In an observational study, at 5 years only 39.2% (95% CI, 31.5%–46.8%) of ischemic stroke patients with AF were alive, and 21.5% (95% CI, 14.5%–31.3%) had experienced recurrent stroke.[120]
- In Medicare analyses that were adjusted for comorbidities, blacks (HR, 1.46 [95% CI, 1.38–1.55]; *P*<0.001) and Hispanics (HR, 1.11 [95% CI, 1.03–1.18]; *P*<0.001) had a higher risk of stroke than whites with AF.[109] The increased risk persisted in analyses adjusted for anticoagulant therapy status.[109] Additional analyses from the Medicare registry demonstrated that the addition of African American race to the CHA_2DS_2-VASc scoring system significantly improved the prediction of stroke events among newly diagnosed AF patients ≥65 years of age.[121]
- A meta-analysis that examined stroke risk by sex and presence of AF reported that AF conferred a multivariable-adjusted 2-fold stroke risk in females compared with males (RR, 1.99 [95% CI, 1.46–2.71]); however, the studies were noted to be significantly heterogeneous.[87]

Cognition

- A meta-analysis of 21 studies indicated that AF was associated with increased risk of cognitive impairment in patients with (RR, 2.70 [95% CI, 1.82–4.00]) and without (RR 1.37 [95% CI, 1.08–1.73]) a history of stroke. The risk of dementia was similarly increased (RR, 1.38 [95% CI, 1.22–1.56]).[122]
- In individuals with AF without evidence of cognitive dysfunction or stroke from Olmsted County, MN, the cumulative rate of dementia at 1 and 5 years was 2.7% and 10.5%, respectively.[123]

Physical Disability and Subjective Health

- AF has been associated with physical disability, poor subjective health,[124,125] and diminished quality of life.[126] A recent systematic review suggested that among people with AF, moderate-intensity activity improved exercise capacity and quality of life.[127]

Falls

- In the REGARDS study, AF was significantly associated with an adjusted higher risk of falls (10%) than among those without AF (6.6%; OR, 1.22 [95% CI, 1.04–1.44]). The presence of a history of both AF and falls was associated with a significantly higher risk of mortality (per 1000 person-years: AF plus falls, 51.2; AF and no falls, 34.4; no AF and falls, 29.8; no AF and no falls, 15.6). Compared with those with neither AF nor falls, those with both conditions had an adjusted 2-fold increased risk of death (HR, 2.12 [95% CI, 1.64–2.74]).[128]

- A systematic review and Markov decision analytic modeling report focused on people with AF ≥65 years of age noted that warfarin treatment was associated with 12.9 QALYs per patient with typical risks of stroke and falls versus 10.2 QALYs for those treated with neither warfarin nor aspirin. Of interest, sensitivity analyses of the probability of falls or stroke did not substantively influence the results.[129]
- A Medicare study noted that patients at high risk for falls with a $CHADS_2$ score of at least 2 who had been prescribed warfarin had a 25% lower risk (HR, 0.75 [95% CI, 0.61–0.91]; *P*=0.004) of a composite cardiovascular outcome (out-of-hospital death or hospitalization for stroke, MI, or hemorrhage) than those who did not receive anticoagulant drugs.[130]

Heart Failure
(See Chart 16-7)

- AF and HF share many antecedent risk factors, and ≈40% of people with either AF or HF will develop the other condition.[99]
- In the community, estimates of the incidence of HF in individuals with AF ranged from 3.3[99] to 5.8[131] per 100 person-years of follow-up. In Olmsted County, MN, in individuals with AF, per 100 person-years of follow-up, the incidence of HF with preserved EF was 3.3 (95% CI, 3.0–3.7), which was more common than HF with reduced EF (2.1 [95% CI, 1.9–2.4]).[131]
- Among older adults with AF in Medicare, the 5-year event rate was high, with rates of death and HF exceeding those for stroke (Chart 16-7). Higher event rates after new-onset AF were associated with older age and higher mean $CHADS_2$ score.[114]
- Investigators examined the incidence rate of HF with systolic dysfunction versus preserved LVEF (<40% versus >50%, respectively) in a Netherlands community-based cohort study (PREVEND) by AF status. Per 1000 person-years, the incidence rate of systolic HF was 12.75 versus 1.99 for those with versus those without AF, with a multivariable-adjusted HR of AF of 5.79 (95% CI, 2.40–13.98). Corresponding numbers for preserved EF were 4.90 versus 0.85 with and without AF, with a multivariable-adjusted HR of AF of 4.80 (95% CI, 1.30–17.70).[132]
- A meta-analysis of 9 studies reported that individuals with AF have a 5-fold increased risk of HF (RR, 4.62 [95% CI, 3.13–6.83]).[133]

Myocardial Infarction
(See Chart 16-7)

A meta-analysis of 16 cohort studies reported that AF was associated with a 1.54 (95% CI, 1.26–1.85) increased risk of MI in follow-up.[133]

- In the REGARDS study in individuals with AF, the age-adjusted MI incidence rate per 1000 person-years was 12.0 (95% CI, 9.6–14.9) in those with AF compared with 6.0 (95% CI, 5.6–6.6) in those without AF.[134]
- Both REGARDS[134] and the ARIC study[135] observed that the risk of MI after AF was higher in females than in males.
- For individuals with AF in both REGARDS[134] and the CHS,[136] a higher risk of MI was observed in blacks than whites. For instance, the CHS observed that individuals with AF who were black had a higher risk of MI (HR, 3.1 [95% CI, 1.7–5.6]) than whites (HR, 1.6 [95% CI, 1.2–2.1]; $P_{interaction}$=0.03).[136]
- In ARIC, AF was associated with an adjusted increased risk of NSTEMI (HR, 1.80 [95% CI, 1.39–2.31]) but not STEMI (HR, 0.49 [95% CI, 0.18–0.34]; *P* for comparison of HR=0.004).[135]

Chronic Kidney Disease

- In a Japanese community-based study, individuals with AF had approximately a doubling in increased risk of developing kidney dysfunction or proteinuria, even in those without baseline DM or hypertension. Per 1000 person-years of follow-up, the incidence of kidney dysfunction was 6.8 in those without and 18.2 in those with AF at baseline.[137]
- In a Kaiser Permanente study of people with CKD, new-onset AF was associated with an adjusted 1.67-fold increased risk of developing ESRD compared with those without AF (74 versus 64 per 1000 person-years of follow-up).[138]

SCD and VF

- In a study that examined data from 2 population-based studies, AF was associated with a doubling in the risk of SCD after accounting for baseline and time-varying confounders. In ARIC, the unadjusted incidence rate per 1000 person-years was 1.30 (95% CI, 1.14–1.47) in those without AF and 2.89 (95% CI, 2.00–4.05) in those with AF; corresponding rates in CHS were 3.82 (95% CI, 3.35–4.35) and 12.00 (95% CI, 9.45–15.25), respectively. The multivariable-adjusted HR associated with AF for sudden death was 2.47 (95% CI, 1.95–3.13).[139]
- An increased risk of VF was observed in a community-based case-control study from the

Netherlands. Individuals with ECG-documented VF during OHCA were matched with non-VF community control subjects. The prevalence of AF in the 1397 VF cases was 15.4% versus 2.6% in the community referents. Individuals with AF had an overall adjusted 3-fold increased risk of VF (adjusted OR, 3.1 [95% CI, 2.1–4.5]). The association was similar across age and sex categories and was observed in analyses of individuals without comorbidities, without AMI, and not using antiarrhythmic or QT-prolonging drugs.[140]

- In a meta-analysis of 7 studies, individuals with AF had an RR of SCD of 1.88 (95% CI, 1.36–2.60).[141]

AF Type and Complications

- A meta-analysis of 12 studies reported that compared with paroxysmal AF, nonparoxysmal AF was associated with a multivariable-adjusted increased risk of thromboembolism (HR, 1.38 [95% CI, 1.19–1.61]; *P*<0.001) and death (HR, 1.22 [95% CI, 1.09–1.37]; *P*<0.001).[142]
- In the Canadian Registry of AF, 755 patients with paroxysmal AF were followed up for a median of 6.35 years. At 1, 5, and 10 years, 8.6%, 24.3%, and 36.3% had progressed to persistent AF. Within 10 years, >50% of the patients had progressed to persistent AF or had died.[143]
- In the FHS, atrial flutter had a much lower incidence rate (36 per 100 000 person-years) than AF (578 per 100 000 person-years). Although based on only 112 individuals, in age- and sex-adjusted analyses, incident atrial flutter was associated with a 5-fold hazard of AF (HR, 5.0 [95% CI, 3.1–8.0]).[144]
- A national Taiwanese study compared the prognosis of 175 420 patients with AF and 6239 patients with atrial flutter. Using propensity scoring, they observed that compared with atrial flutter, individuals with AF had significantly higher incidences of ischemic stroke (1.63-fold), HF hospitalization (1.70-fold), and all-cause mortality (1.08-fold).[145]

Hospitalizations and Ambulatory Care Visits

- According to HCUP data in 2014, there were 454 000 hospital discharges with AF and atrial flutter as the principal diagnosis, evenly split between males and females (unpublished NHLBI tabulation).[146]
  - — The rate per 100 000 discharges increased with advancing age, from 16.4 in those aged 18 to 44 years, 149.6 in those 45 to 64 years, and 593.1 in those 65 to 84 years, to 1159.5 in individuals ≥85 years; however, 52.4% of all hospital discharges for AF occurred in patients 65 to 84 years old.[146]
- In 2015, there were 6 431 000 physician office visits and 499 000 ED visits for AF (NAMCS, NHAMCS, NHLBI tabulation).[147,148]
- Using cross-sectional data (2006–2014) from the HCUP's Nationwide Emergency Department Sample, the NIS, and the National Vital Statistics System, investigators estimated that in 2014, AF listed as a primary diagnosis accounted for ≈599 790 ED visits and 453 060 hospitalizations, with a mean length of stay of 3.5 days. Including AF listed as a comorbid condition, there were ≈4 million (3.6% of total) ED visits and 3.5 million (12.0% of total) hospitalizations.[149]
- On the basis of Medicare and MarketScan databases, annually, people with AF (37.5%) are approximately twice as likely to be hospitalized as age- and sex-matched referents (17.5%).[150]

Cost
(See Chart 16-8)

- Investigators examined Medicare and Optum Touchstone databases (2004–2010) to estimate costs attributed to nonvalvular AF versus propensity-matched control subjects in 2014 US dollars[151]:
  - — For patients aged 18 to 64 years, average per capita medical spending was $38 861 (95% CI, $35 781–$41 950) versus $28 506 (95% CI, $28 409–$28 603) for matched patients without AF. Corresponding numbers for patients ≥65 years old were $25 322 for those with AF (95% CI, $25 049–$25 595) versus $21 706 (95% CI, $21 563–$21 849) for matched non-AF patients.
  - — The authors estimated that the incremental cost of AF was $10 355 for commercially insured patients and $3616 for Medicare patients.
  - — Estimating that the prevalence of diagnosed versus undiagnosed nonvalvular AF, respectively, was 0.83% versus 0.07% for individuals 18 to 64 years of age and 8.8% versus 1.1% for those ≥65 years of age, the investigators estimated that the incremental cost of undiagnosed AF was $3.1 billion (95% CI, $2.7–3.7 billion).
- Investigators examined Medicare and MarketScan databases (2004–2006) to estimate costs attributed to AF in 2008 US dollars (Chart 16-8):[152]
  - — Extrapolating to the US population, it was estimated that the incremental cost of AF was ≈$26 billion, of which $6 billion was attributed to AF, $9.9 billion to other cardiovascular expenses, and $10.1 billion to noncardiovascular expenses.
  - — Using cross-sectional data (2006–2014) from the HCUP's Nationwide Emergency

Department Sample, the NIS, and the National Vital Statistics System, investigators estimated that in 2014, for AF listed as a primary diagnosis, the mean charge for ED visits was ≈$4000, and the mean cost of hospitalizations was about $8819.[149]

- A systematic review that examined costs of ischemic stroke in individuals with AF included 16 studies from 9 countries. In international dollars adjusted to 2015 values, they estimated that stroke-related healthcare costs were $8184, $12 895, and $41 420 for lower middle, middle- and high-income economies, respectively.[153]
- Costs of AF have been estimated for many other countries. Investigators estimated that the 3-year societal costs of AF were approximately €20 403 to €26 544 per person and €219 to 295 million for Denmark as a whole.[154]

Secular Trends

- During 50 years of observation of the FHS (1958–1967 to 1998–2007), the age-adjusted prevalence and incidence of AF approximately quadrupled. However, when only AF that was ascertained on ECGs routinely collected in the FHS was considered, the prevalence but not the incidence increased, which suggests that part of the changing epidemiology was attributable to enhanced surveillance. Although the prevalence of most risk factors changed over time, the hazards associated with specific risk factors did not change. Hence, the PAR associated with BMI, hypertension treatment, and DM increased (consistent with increasing prevalence). Over time, the multivariable-adjusted hazards of stroke and mortality associated with AF declined by 74% and 25%, respectively.[155]
- Between 2000 and 2010 in Olmsted County, MN, age- and sex-adjusted incidence rates and survival did not change over time.[88] However, over a similar time frame in the United Kingdom (2001–2013), the incidence of nonvalvular AF in people ≥45 years of age increased modestly from 5.9 (95% CI, 5.8–6.1) to 6.9 (95% CI, 6.8–7.1) per 1000 patient-years, with the largest increase observed in those >80 years of age.[76]
- In data from the ARIC study, the prevalence of AF in the setting of MI increased slightly, from 11% to 15%, between 1987 and 2009; however, the increased risk of death (OR, 1.47 [95% CI, 1.07–2.01]) in the year after MI accompanied by AF did not change over time.[156]
- Between 1999 and 2013, among Medicare fee-for-service beneficiaries, rates of hospitalization for AF increased ≈1% per year. Although the median hospital length of stay, 3 days (IQR, 2.0–5.0 days), did not change, the mortality declined by 4% per year, and hospital readmissions at 30 days declined by 1% per year. During the same years, median Medicare inpatient costs per hospitalization increased substantially, from $2932 (IQR, $2232–$3870) to $4719 (IQR, $3124–$7209).[149]

Risk Factors (See Chart 16-9)

- On the basis of data from ARIC, the highest population attributable fraction for AF was hypertension, followed by BMI, smoking, cardiac disease, and DM (Chart 16-9).[157]

Smoking

- A meta-analysis of 8 studies suggested that current smoking was associated with an increased risk of AF (pooled RR, 1.39 [95% CI, 1.11–1.75]). Compared with noncurrent smokers, current smokers had a 21% higher risk of incident AF (pooled RR, 1.21 [95% CI, 1.03–1.42]), which suggests that smoking cessation is associated with a reduced risk of AF.[158]

Activity and Exercise

- Data from some studies suggested that vigorous-intensity exercise 5 to 7 days per week was associated with a slightly increased risk of AF.[127] In contrast, a meta-analysis suggested that more intensive PA was not associated with excess risk of AF (RR, 1.0 [95% CI, 0.82–1.22]), but the heterogeneity statistic was significant.[159]
- A multiracial longitudinal study from Detroit, MI, reported a dose-response relation between objectively assessed exercise capacity and lower risk of new-onset AF.[160] In unadjusted analyses, the incidence rates of AF over 5 years were 3.7%, 5.0%, 9.5%, and 18.8% for >11, 10 to 11, 6 to 9, and <6 METs, respectively. Every 1-higher peak MET was associated with an adjusted 7% lower risk of AF (HR, 0.93 [95% CI, 0.92–0.94]). The protective association of fitness was observed in all subgroups examined but was particularly beneficial in obese individuals.

BMI and Obesity

- In a meta-analysis of 16 studies involving >580 000 individuals, of whom ≈91 000 had obesity, AF developed in 6.3% of those who had obesity and 3.1% of those without it. Individuals with obesity had an RR of 1.51 for developing AF (95% CI, 1.35–1.68) compared with those without obesity.[161]
- Another meta-analysis of 29 studies examined various anthropometric components in relation to incident AF. A 5-unit increment in BMI was

associated with an RR of 1.28 (95% CI, 1.20–1.38) in relation to AF. The risk was nonlinear (*P*<0.0001), with stronger associations observed at higher BMIs, but a BMI of 22 to 24 kg/m² was still associated with excess risk compared with a BMI of 20 kg/m². Waist, waist-hip ratio, fat mass, and waist gain were also associated with increased risk of AF.[162]

- A causal relationship between higher BMI and incident AF gained further support from a genetic mendelian randomization study, which observed that a BMI gene score that included 39 SNPs was associated with a higher risk of AF.[163]

BP and Hypertension

- Hypertension accounted for ≈22%[157] of AF cases.
- In MESA, the population attributable fraction of AF attributable to hypertension appeared to be higher in US NH blacks (33.1%), Chinese (46.3%), and Hispanics (43.9%) than in NH whites (22.2%).[74]

DM and HbA_{1c}

- In a meta-analysis restricted to prospective studies, HbA_{1c} was associated with an increased risk of AF when analyzed as a continuous (RR, 1.11 [95% CI, 1.06–1.16]) or categorical (RR, 1.09 [95% CI, 1.00–1.18]) variable.[164]
- In a meta-analysis of observational studies (excluding a large outlier study) the RR of incident AF was 1.28 (31 cohort studies [95% CI, 1.22–1.35]) for DM and 1.20 (4 studies [95% CI, 1.03–1.39]) for prediabetes.[165]

Miscellaneous Risk Factors

- Other consistently reported risk factors for AF include clinical and subclinical[166] hyperthyroidism, CKD,[167,168] and moderate[169] or heavy alcohol consumption.[170]
- Central sleep apnea also is associated with an increased risk of incident AF.[171] For instance, in the Sleep Heart Health Study, a central sleep apnea index ≥5 was associated with an adjusted 3-fold higher odds (OR, 3.00 [95% CI, 1.40–6.44]) of incident AF.[172]
- Investigators from the Danish Diet, Cancer, and Health cohort reported that individuals with higher exposure to NO_2, a traffic-related air pollutant, had higher risk of AF (adjusted IRR, 1.08 [95% CI, 1.01–1.14] per 10 mcg/m³ higher 10-year time-weighted mean exposure to NO_2).[173]
- AF frequently occurs secondary to other comorbidities.
  - — In the FHS, 31% of AF was diagnosed in the context of a secondary, reversible condition. The most common triggers of AF were cardiothoracic surgery (30%), infection (23%), and AMI (18%). Paroxysmal AF in the context of a secondary precipitant frequently recurred over follow-up.[174]
  - — Sepsis is associated with an increased risk of AF. In a Medicare sample, 25.5% of patients with sepsis had AF; 18.3% of AF was preexisting, and 7.2% was newly diagnosed.[175] AF occurring in the context of sepsis is associated with an increased risk of stroke and death.[106]
  - — A meta-analysis reported that new-onset AF has been observed in 10.9% of patients undergoing noncardiac general surgery.[176]
- Prevalence of AF is particularly elevated in adults with congenital heart disease.[177]

Risk Prediction of AF

- In the biracial REGARDS study, better cardiovascular health, as classified by Life's Simple 7, predicted decreased risk of AF similarly between sexes and in blacks and whites. Individuals with optimal cardiovascular health (score 10–14 points) had an adjusted 32% lower risk of AF (OR, 0.68 [95% CI, 0.47 to 0.99]).[178]
- ARIC,[179] the FHS,[180] and the Women's Health Study[181] have developed risk prediction models to predict new-onset AF. Predictors of increased risk of new-onset AF include advancing age, European ancestry, body size (greater height and BMI), electrocardiographic features (LVH, left atrial enlargement), DM, BP (SBP and hypertension treatment), and presence of CVD (CHD, HF, valvular HD).
- More recently, the ARIC, CHS, and FHS investigators developed and validated a risk prediction model for AF in blacks and whites, which was replicated in 2 European cohorts.[182] The CHARGE-AF model has been validated in US multiethnic cohorts including Hispanics,[183] in MESA,[184] and in a United Kingdom cohort (EPIC Norfolk).[185]

Borderline Risk Factors

- Data from the ARIC study indicated that having at least 1 elevated risk factor explained 50% and having at least 1 borderline risk factor explained 6.5% of incident AF cases. The estimated overall incidence rate per 1000 person-years at a mean age of 54.2 years was 2.19 for those with optimal risk, 3.68 for those with borderline risk, and 6.59 for those with elevated risk factors.[157]

Subclinical Atrial Tachyarrhythmias, Unrecognized AF, Screening for AF

Device-Detected AF

- Cardiac implantable electronic devices (eg, pacemakers and defibrillators) have increased clinician awareness of the frequency of subclinical AF and atrial high-rate episodes in people without a documented history of AF. Several studies have suggested that device-detected high-rate atrial tachyarrhythmias are surprisingly frequent and are associated with an increased risk of AF and total mortality.[186,187]

- Investigators in the ASSERT study prospectively enrolled 2580 patients with a recent pacemaker or defibrillator implantation who were ≥65 years of age, had a history of hypertension, and had no history of AF. They classified individuals by presence versus absence of subclinical atrial tachyarrhythmias (defined as atrial rate >190 beats per minute for >6 minutes in the first 3 months) and conducted follow-up for 2.5 years.[188] Subclinical atrial tachyarrhythmias in the first 3 months occurred in 10.1% of the patients and were associated with the following[188]:
  - An almost 6-fold higher risk of clinical AF (HR, 5.6 [95% CI, 3.8–8.2])
  - A more than doubling in the adjusted risk of the primary end point, ischemic stroke or systemic embolism (HR, 2.5 [95% CI, 1.3–4.9])
  - An annual ischemic stroke or systemic embolism rate of 1.7% (versus 0.7% in those without)
  - A 13% PAR for ischemic stroke or systemic embolism
  - Over the subsequent 2.5 years of follow-up, an additional 35% of the patients had subclinical atrial tachyarrhythmias, which were 8-fold more frequent than clinical AF episodes.
- A pooled analysis of 5 prospective studies in patients without permanent AF revealed that over 2 years of follow-up, cardiac implanted electronic devices detected ≥5 minutes of AF in 43% of the patients (total N=10 016). AF burden was associated with an increased risk of stroke after adjustment for $CHADS_2$ score and anticoagulation.[189]
- The temporal association of AF and stroke risk was evaluated in a case-crossover analysis among 9850 patients with cardiac implantable electronic devices enrolled in the Veterans Health Administration healthcare system. The OR for an acute ischemic stroke was the highest within a 5-day period after a qualifying AF episode, which was defined as at least 5.5 hours of AF on a given day. This estimate reduced as the period after the AF occurrence extended beyond 30 days.[190]

Community Screening

- The prevalence of undiagnosed AF in the community is unknown. Using Medicare and commercials claims data, investigators have estimated that in 2009, ≈0.7 million (13.1%) of the ≈5.3 million AF cases in the United States were undiagnosed. Of the undiagnosed AF cases, investigators estimated 535 400 (95% CI, 331 900–804 400; 1.3%) were in individuals ≥65 years of age, and 163 500 (95% CI, 17 700–400 000; 0.09%) were in individuals 18 to 64 years old.[191]
- The incidence of detecting previously undiagnosed AF by screening depends on the underlying risk of AF in the population studied, the intensity and duration of screening, and the method used to detect AF.[192]
- Methods vary in their sensitivity and specificity in the detection of undiagnosed AF, increasing from palpation, to devices such as handheld single-lead ECGs, modified BP devices, and plethysmographs.[192]
- There has been increasing interest in the use of smart phone technology to aid in community screening.[193,194]
- In a community-based study in Sweden (STROKESTOP), half of the population 75 to 76 years of age were invited to a stepwise screening program for AF, and 7173 participated in the screening, of whom 218 had newly diagnosed AF (3.0% [95% CI, 2.7%–3.5%]) and an additional 666 (9.3% [95% CI, 8.6%–10.0%]) had previously diagnosed AF. Of the 218 newly diagnosed AF cases, only 37 were diagnosed by screening electrocardiography, whereas intermittent monitoring detected 4 times as many cases. Of those individuals with newly diagnosed AF, 93% initiated treatment with oral anticoagulant drugs.[195]
- There have been 2 systematic reviews regarding the effectiveness of screening to detect unknown AF.
  - Lowres et al[196] identified 30 separate studies that included outpatient clinics or community screening. In individuals without a prior diagnosis of AF, they observed that 1.0% (95% CI, 0.89%–1.04%) of those screened had AF (14 studies, N=67 772), whereas among those individuals ≥65 years of age, 1.4% (95% CI, 1.2%–1.6%; 8 studies, N=18 189) had AF.
  - Another systematic review by Moran et al[197] observed that in individuals >65 years of age, systematic screening (OR, 1.57 [95% CI, 1.08–2.26]) and opportunistic screening (OR, 1.58 [95% CI, 1.10–2.29]) were associated with enhanced detection of AF. The number needed to screen by either method was ≈170 individuals.
- At present, the detection of AF, even in an asymptomatic stage, is the basis for risk stratification for stroke and appropriate decision making on the need for anticoagulant drugs. Ongoing trials are

evaluating the risks and benefits of anticoagulation among patients at high risk for stroke but without a prior history of AF. The findings from these studies will help to determine optimal strategies for subclinical AF screening and treatment.[192] To date, no studies have demonstrated that AF screening reduces mortality or incidence of thromboembolic complications.

Family History and Genetics

Family History

- Although unusual, early-onset lone AF has long been recognized to cluster in families.[12,198] In the past decade, the heritability of AF in the community has been appreciated.
- In studies from the FHS:
  - — Adjusted for coexistent risk factors, having at least 1 parent with AF was associated with a 1.85-fold increased risk of AF in the adult offspring (multivariable-adjusted 95% CI, 1.12–3.06; *P*=0.02).[199]
  - — A history of a first-degree relative with AF also was associated with an increased risk of AF (HR, 1.40 [95% CI, 1.13–1.74]). The risk was greater if the first-degree relative's age of onset was ≤65 years (HR, 2.01 [95% CI, 1.49–2.71]) and with each additional affected first-degree relative (HR, 1.24 [95% CI, 1.05–1.46]).[200] Similar findings were reported from Sweden.[201]
- A Taiwanese population-based study reported that a history of a first-degree relative with AF was associated with a 1.92-fold (95% CI, 1.84–1.99) increased risk of newly diagnosed AF. They estimated that 19.9% of the increased risk was attributable to genetic (heritability) factors, with the remaining risk related to shared (3.5%) and nonshared (76.5%) environmental factors.[202]
- A study from the UK Biobank estimated that the heritability of AF was 22.1% (95% CI, 15.6%–28.5%). The heritability was similar by sex and in older (>65 years) versus younger (≤65 years) people. Most of the variation was explained by common (minor allele frequency ≥5%) genetic variation.[203]
- Racial variation in AF incidence is complex and not fully understood. One study of blacks and whites from CHS and ARIC suggested that genetic markers of European ancestry were associated with an increased risk of incident AF.[204]
- A recent meta-analysis of genetic studies in AF included GWASs with >17 000 case subjects and >115 000 referents and exome-wide association studies of >22 000 AF cases and >132 000 referents. The strongest common variant associated with AF was near the paired-like homeodomain transcription factor 2 (*PITX2*) gene.[205] The study identified a total of 26 loci, which were in or near genes encoding ion channels, sarcomeric proteins, and transcription factors. Japanese investigators were able to replicate 7 loci previously reported in cohorts predominantly of European ancestry and were able to identify 6 new loci.[206]
- A subsequent GWAS, which included >65 000 patients with AF, reported 97 AF-associated loci, 67 of which were novel in combined-ancestry analyses.[207]
- Whole exome/genome sequencing studies have identified rare mutations in additional genes, including *MYL4*.[208]
- Investigators in the FHS examined the lifetime risk of AF at age 55 years using both clinical and genetic risk factors. They derived polygenic risk scores of 1000 variants (many were subthreshold hits) associated with AF in the UK Biobank. They divided participants into tertiles of clinical and genetic risk and reported that individuals within the lowest tertile of clinical and of polygenic risk had a lifetime risk of AF of 22.3% (95% CI, 15.4%–29.1%), whereas those in the highest tertile of clinical and polygenic risk had a lifetime risk of 48.2% (95% CI, 41.3%–55.1%).[80]
- Some studies suggest that genetic markers of AF could improve risk prediction for AF over models that include clinical factors.[181]
- Genetic risk scores could also identify patients at higher risk of cardioembolic stroke[209]; however, the utility of clinical genetic testing for AF-related genetic variants is unclear.

Prevention (See Chart 16-9)

Primary Prevention: Observational Data

- An observational prospective Swedish study revealed that individuals having bariatric surgery had a 29% lower risk (HR, 0.79 [95% CI, 0.60–0.83]; *P*<0.001) of developing AF in 19 years of median follow-up than matched referents.[210]

Secondary Prevention of AF: Observational Data

- There are increasingly more data supporting the importance of risk factor modification for secondary prevention of AF recurrence and improved symptoms.
  - — In individuals referred for catheter ablation, those who agreed to aggressive risk factor modification had lower symptom burden in follow-up and higher adjusted AF-free survival (HR, 4.8 [95% CI, 2.0–11.4]; *P*<0.001).[211]
  - — The same Australian investigators reported that overweight and obese individuals with

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symptomatic AF who opted to participate in weight loss and aggressive risk factor management interventions had fewer hospitalizations, cardioversions, and ablation procedures than their counterparts who declined enrollment. The risk factor management group was associated with a predicted 10-year cost savings of $12 094 per patient.[212]

— In adjusted analyses, overweight and obese individuals with paroxysmal or persistent AF who achieved at least 10% weight loss were 6-fold more likely to be AF free (86.2% AF free; HR, 5.9 [95% CI, 3.4–10.3]; *P*<0.001) than those with <3% weight loss (39.6% AF free). In addition, individuals losing at least 10% weight reported fewer symptoms.[213]

— The same Australian group also reported that among consecutive overweight and obese patients with AF who agreed to participate in an exercise program, those who achieved less improvement in cardiorespiratory fitness (<2 METs gain) had lower AF-free survival (40%; HR, 3.9 [95% CI, 2.1–7.3]; *P*<0.001) than those with greater improvement in fitness (≥2 METs gain, 89% AF free).[214]

- Treatment of OSA has been noted to decrease risk of progression to permanent AF.[215] In a meta-analysis, CPAP was reported to be associated with a reduced risk of recurrent AF after ablation.[216] However, there is a lack of robust randomized data supporting the role of CPAP in the primary and secondary prevention of AF in individuals with sleep-disordered breathing.
- In a national outpatient registry of AF patients (ORBIT-AF), 94% had indications for guideline-based primary or secondary prevention in addition to oral anticoagulant drugs; however, only 47% received all guideline-indicated therapies, consistent with an underutilization of evidence-based preventive therapies for comorbid conditions in individuals with AF.[217] Predictors of not receiving all guideline-indicated therapies included frailty, comorbid illness, geographic region, and antiarrhythmic drug therapy. Factors most strongly associated with the 17% warfarin discontinuation rate in the first year prescribed included hospitalization because of bleeding (OR, 10.9 [95% CI, 7.9–15.0]), prior catheter ablation (OR, 1.8 [95% CI, 1.4–2.4]), noncardiovascular/nonbleeding hospitalization (OR, 1.8 [95% CI, 1.4–2.2]), cardiovascular hospitalization (OR, 1.6 [95% CI, 1.3–2.0]), and permanent AF (OR, 0.25 [95% CI, 0.17–0.36]).[218]
- A study of 2 national Canadian primary care audits similarly observed that 84.3% of individuals enrolled were eligible for at least 1 cardiovascular evidence-based therapy. The proportions receiving evidence-based therapy varied by diagnosis, at 40.8% of those with CAD, 48.9% of those with DM, 40.2% of those with HF, and 96.7% of those with hypertension.[219]

Prevention: Randomized Data

- Intensive glycemic control was not found to prevent incident AF in the ACCORD study.[104]
- In the Look AHEAD randomized trial of individuals with type 2 DM who were overweight to obese, an intensive lifestyle intervention associated with modest weight loss did not significantly affect the rate of incident AF (6.1 versus 6.7 cases per 1000 person-years of follow-up; multivariable HR, 0.99 [95% CI, 0.77–1.28]); however, AF was not prespecified as a primary or secondary outcome.[220]
- Randomized trials of overweight or obese patients referred to an Adelaide, Australia, arrhythmia clinic for management of symptomatic paroxysmal or persistent AF demonstrated that individuals randomized to a weight loss intervention reported lower symptom burden.[221]
- Meta-analyses have suggested that BP lowering might be useful in prevention of AF in trials of hypertension, after MI, in HF, and after cardioversion.[222,223] However, the studies were primarily secondary or post hoc analyses, the intervention duration was modest, and the results were fairly heterogeneous.
- Recently, in an analysis of the EMPHASIS-HF trial, in one of many secondary outcomes, eplerenone was nominally observed to reduce the incidence of new-onset AF. However, the number of AF events was modest.[224]
- A post hoc analysis of the PREDIMED randomized primary prevention study suggested a significant reduction in incident AF with the Mediterranean diet including extra virgin olive oil (HR, 0.62 [95% CI, 0.45–0.85]).[225]
- Although heterogeneous in their findings, modest-sized short-term studies suggested that the use of statins might prevent AF; however, larger longer-term studies do not provide support for the concept that statins are effective in AF prevention.[226]

Awareness

- In REGARDS, a US national biracial study, compared with whites, blacks had approximately one-third the likelihood (OR, 0.32 [95% CI, 0.20–0.52]) of being aware that they had AF.[227] The REGARDS investigators also reported that compared with individuals aware of their diagnosis, individuals who were unaware of their AF had a 94% higher risk of mortality in follow-up.[228]

- A study from Kaiser Permanente in California examined the relation between AF diagnosis (2006–2009) and self-report questionnaire data (2010). Of the more than 12 000 individuals with diagnosed AF, 14.5% were unaware of their diagnosis and 20.4% had inadequate health literacy. In adjusted analyses, low health literacy was associated with a lack of awareness of their AF diagnosis (literacy prevalence ratio, 0.96 [95% CI, 0.94–0.98]).[229]

Treatment and Control

Anticoagulation Undertreatment

- Studies have demonstrated underutilization of oral anticoagulation therapy. In a meta-analysis, males and individuals with prior stroke were more likely to receive warfarin, whereas factors associated with lower use included alcohol and drug abuse, noncompliance, warfarin contraindications, dementia, falls, both gastrointestinal and intracranial hemorrhage, renal impairment, and advancing age.[230] The underutilization of anticoagulation in AF has been demonstrated to be a global problem.[231]
- The GWTG–Stroke program conducted a retrospective analysis consisting of 1622 hospitals and 94 474 patients with acute ischemic stroke in the setting of known AF from 2012 to 2015. In that analysis, 79 008 of patients (83.6%) were not receiving therapeutic anticoagulation: 13.5% had a subtherapeutic international normalized ratio, 39.9% were receiving antiplatelet treatment only, and 30.3% were not receiving any antithrombotic therapy. In adjusted analyses versus patients receiving no antithrombotic medications, patients receiving antecedent therapeutic warfarin, non–vitamin K antagonist oral anticoagulants, or antiplatelet therapy had lower odds of moderate or severe stroke (adjusted OR [95% CI], 0.56 [0.51–0.60], 0.65 [0.61–0.71], and 0.88 [0.84–0.92], respectively) and lower in-hospital mortality.[232]
- Individuals who had AF and were not treated with anticoagulant drugs had a 2.1-fold increase in risk for recurrent stroke and a 2.4-fold increase in risk for recurrent severe stroke.[233]
- In the NCDR PINNACLE registry of outpatients with AF:
  - Less than half of high-risk patients, defined as those with a CHA_2DS_2-VASc score ≥4, were receiving an oral anticoagulant prescription.[234]
  - Between 2008 and 2014, in individuals with a CHA_2DS_2-VASc score >1, direct anticoagulant use increased from 0 to 24.8%, and use of warfarin decreased from 52.4% to 34.8%. Although over the time period, the prevalence of oral anticoagulation treatment increased from 52.4% to 60.7%, substantive gaps remain.[235]
  - In the PINNACLE registry, females were significantly less likely to receive oral anticoagulants at all levels of CHA_2DS_2-VASc scores (56.7% versus 61.3%; P<0.001).[236]
  - The PINNACLE registry investigators also reported that receipt of warfarin versus a direct oral anticoagulant varied significantly by type of insurance, with military, private, and Medicare insured patients more likely to receive newer anticoagulants than individuals with Medicaid and other insurance.[237]
- Disparities in treatment patterns have also been observed in Sweden. In adjusted analyses, compared with individuals with AF living in middle-income neighborhoods, those living in high-SES neighborhoods were more likely to be prescribed warfarin (males: OR, 1.44 [95% CI, 1.27–1.67]; females: OR, 1.19 [95% CI, 1.05–1.36]) and statins (males: OR, 1.23 [95% CI, 1.07–1.41]; females: OR, 1.23 [95% CI, 1.05–1.44]).[238]
- Investigators conducted multivariable cross-sectional analyses of the NIS between 2012 and 2014 and observed that patients admitted to rural hospitals had a 17% higher risk of death than those admitted to urban hospitals (OR, 1.17 [95% CI, 1.04–1.32]).[239]
- A systematic review and meta-analysis identified 3 studies of coordinated care systems of care that included 1383 patients.[240] The investigators reported that AF integrated care approaches were associated with reduced all-cause mortality (OR, 0.51 [95% CI, 0.32 to 0.80]; P=0.003) and cardiovascular hospitalizations (OR, 0.58 [95% CI, 0.44 to 0.77]; P=0.0002).

Global Burden of AF (See Charts 16-10 and 16-11)

- The vast majority of research on the epidemiology of AF has been conducted in Europe and North America. Investigators from the GBD project noted that the global prevalence, incidence, mortality, and DALYs associated with AF increased from 1990 to 2010.[241]
- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories.[242]
  - Total number of global deaths attributable to AF/atrial flutter was 200 000 in 2016 (100 000 in females and 100 000 in males).

— Globally, 46.3 million individuals had prevalent AF/atrial flutter in 2016 (23.1 million females and 23.2 million males).
— Mortality attributable to AF is highest in Northern Europe (Chart 16-10).
— Prevalence of AF is highest in Northern Europe and the United States (Chart 16-11).

- Investigators conducted a prospective registry of >15 000 AF patients presenting to EDs in 47 countries. They observed substantial regional variability in annual AF mortality: South America (17%) and Africa (20%) had double the mortality rate of North America, Western Europe, and Australia (10%; *P*<0.001). HF deaths (30%) exceeded deaths attributable to stroke (8%).[243]

Table 16-1. Cumulative Incidence Rate Over 5 Years After AF Diagnosis, by Age*

Age Group, y	Mortality	Heart Failure	Myocardial Infarction	Stroke	Gastrointestinal Bleeding
67–69	28.8	11.0	3.3	5.0	4.4
70–74	32.3	12.1	3.6	5.7	4.9
75–79	40.1	13.3	3.9	6.9	5.9
80–84	52.1	15.1	4.3	8.1	6.4
85–89	67.0	15.8	4.4	8.9	6.6
≥90	84.3	13.7	3.6	6.9	5.4

All values are percentages. AF indicates atrial fibrillation.
*See Chart 16-7.
Adapted from Piccini et al[114] by permission of the European Society of Cardiology. Copyright © 2013, The Authors.

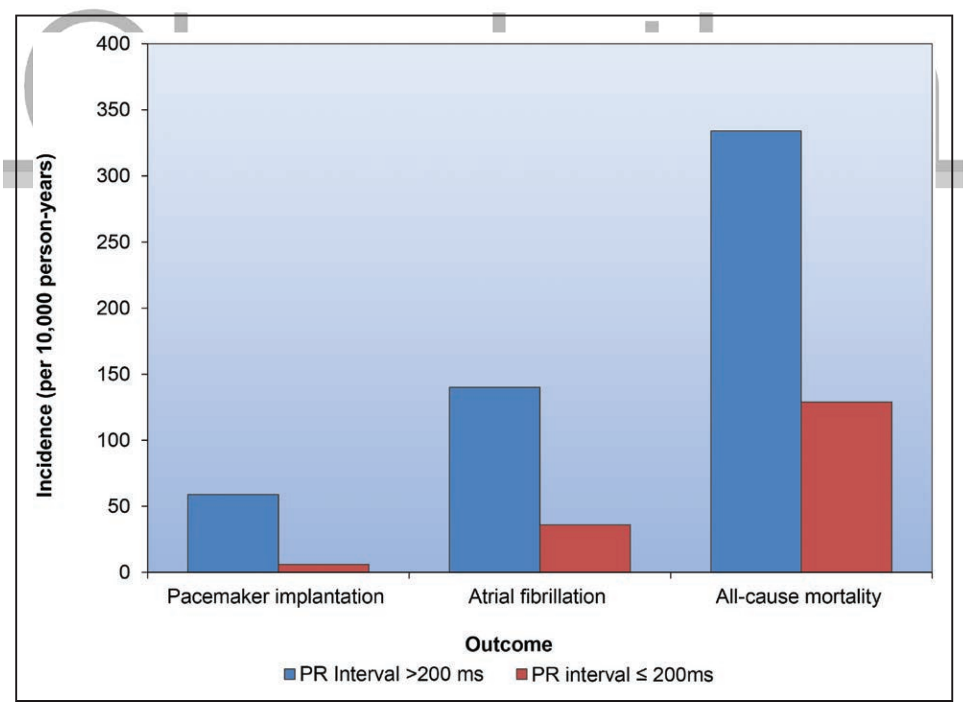

Chart 16-1. Long-term outcomes in individuals with prolonged PR interval (>200 ms; first-degree atrioventricular block) compared with individuals with normal PR interval in the FHS.
FHS indicates Framingham Heart Study.
Data derived from Cheng et al.[11]

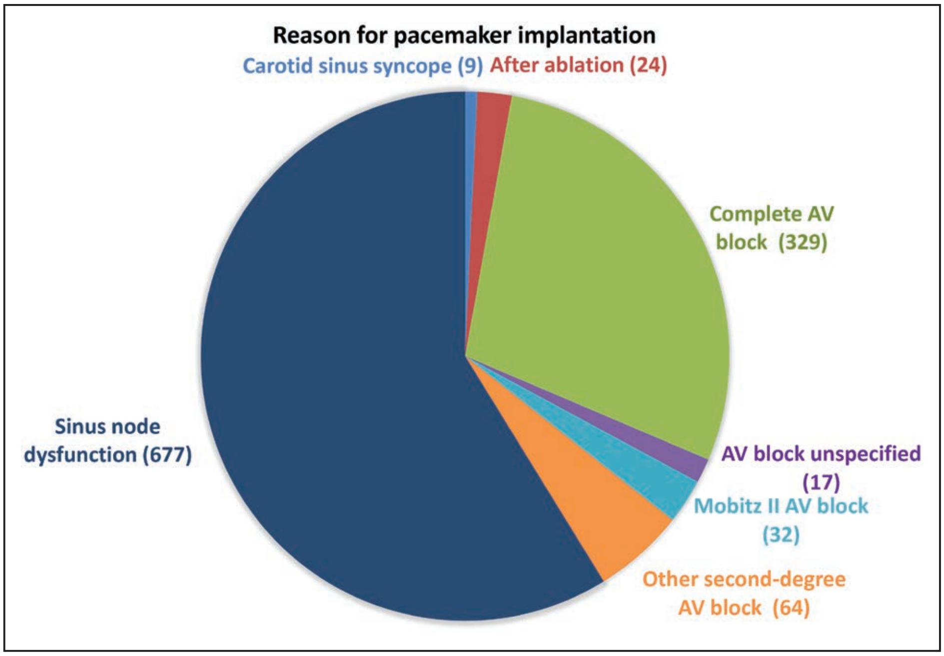

Chart 16-2. Primary indications (in thousands) for pacemaker placement between 1990 and 2002 from the NHDS, NCHS.
AV indicates atrioventricular; NCHS, National Center for Health Statistics; and NHDS, National Hospital Discharge Survey.
Data derived from Birnie et al.[33]

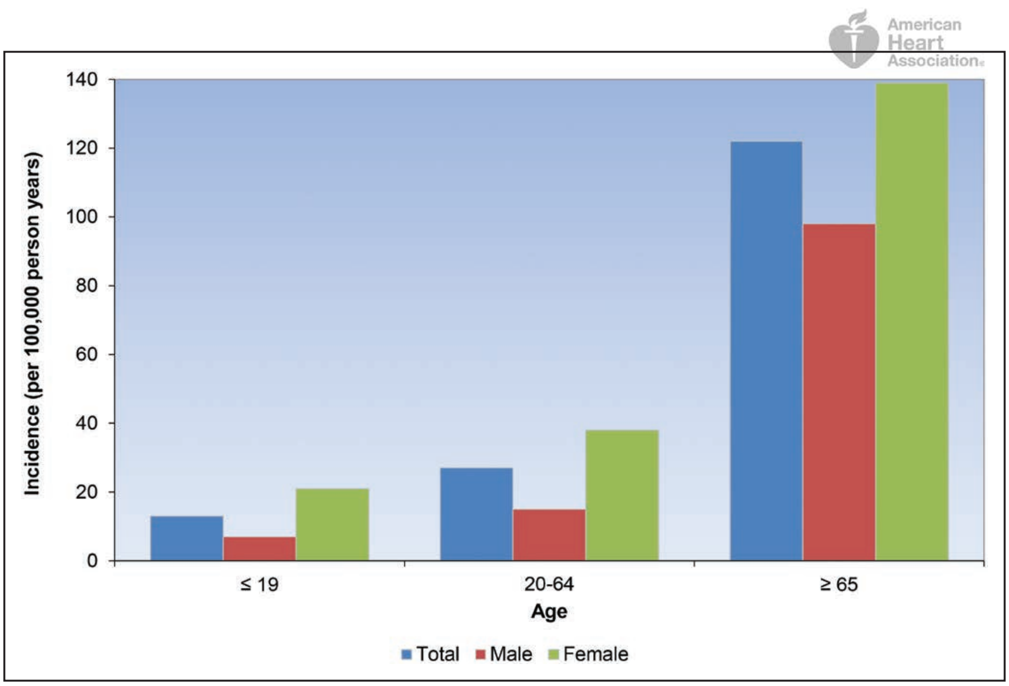

Chart 16-3. Incidence rate of paroxysmal supraventricular tachycardia per 100 000 person-years by age and sex.
Data derived from Orejarena et al.[39]

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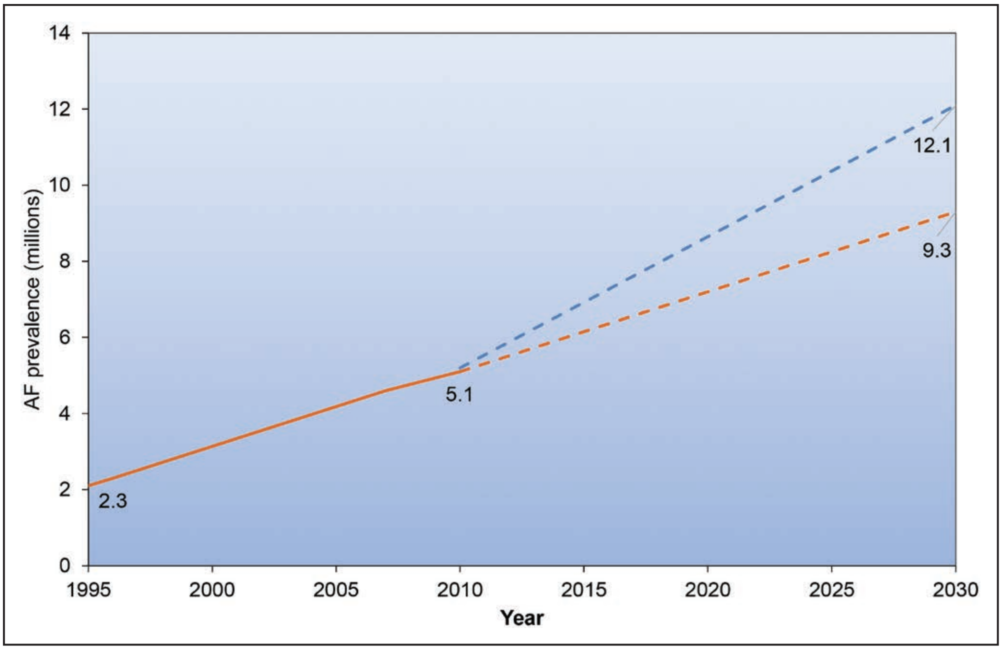

Chart 16-4. Current and future US prevalence projections for AF.
Projections assume no increase (red dashed line) or logarithmic growth (blue dashed line) in incidence of AF from 2007.
AF indicates atrial fibrillation.
Data derived from Go et al[68]; and modified from Colilla et al[70] with permission from Elsevier. Copyright © 2013, Elsevier Inc.

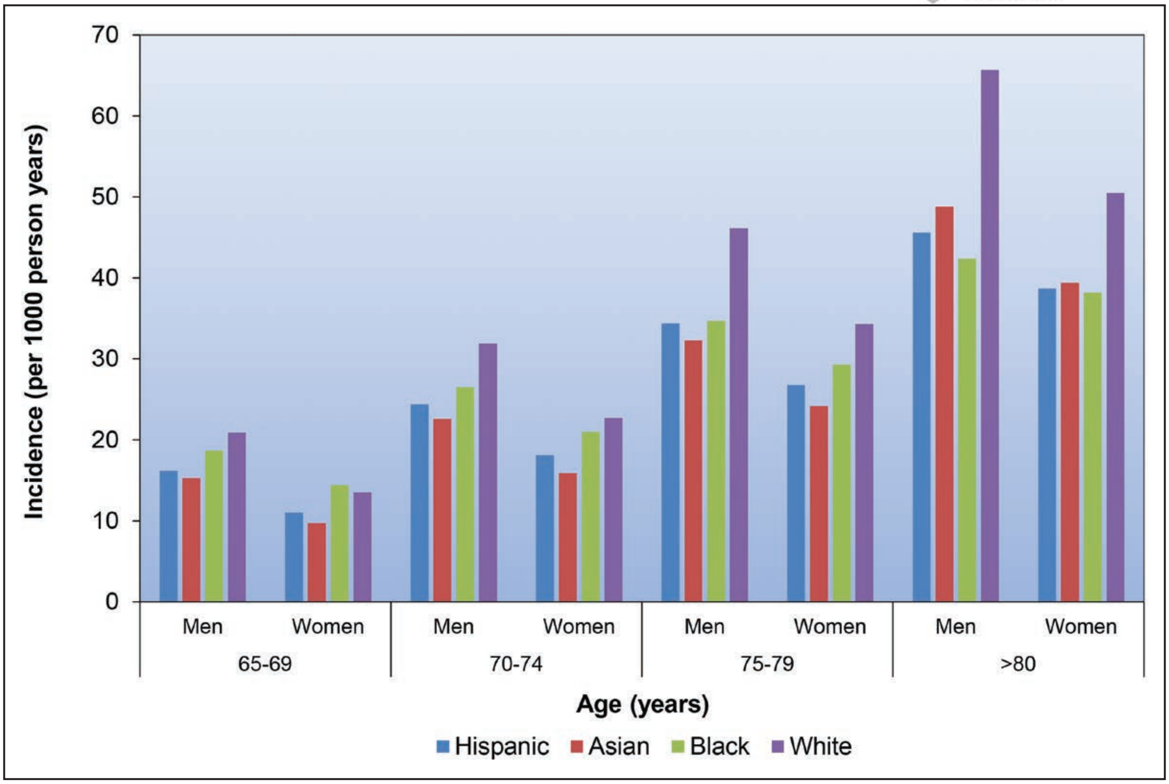

Chart 16-5. Atrial fibrillation incidence by race.
Incidence increases with advancing age among different races and sexes in the United States.
Data derived from Dewland et al.[75]

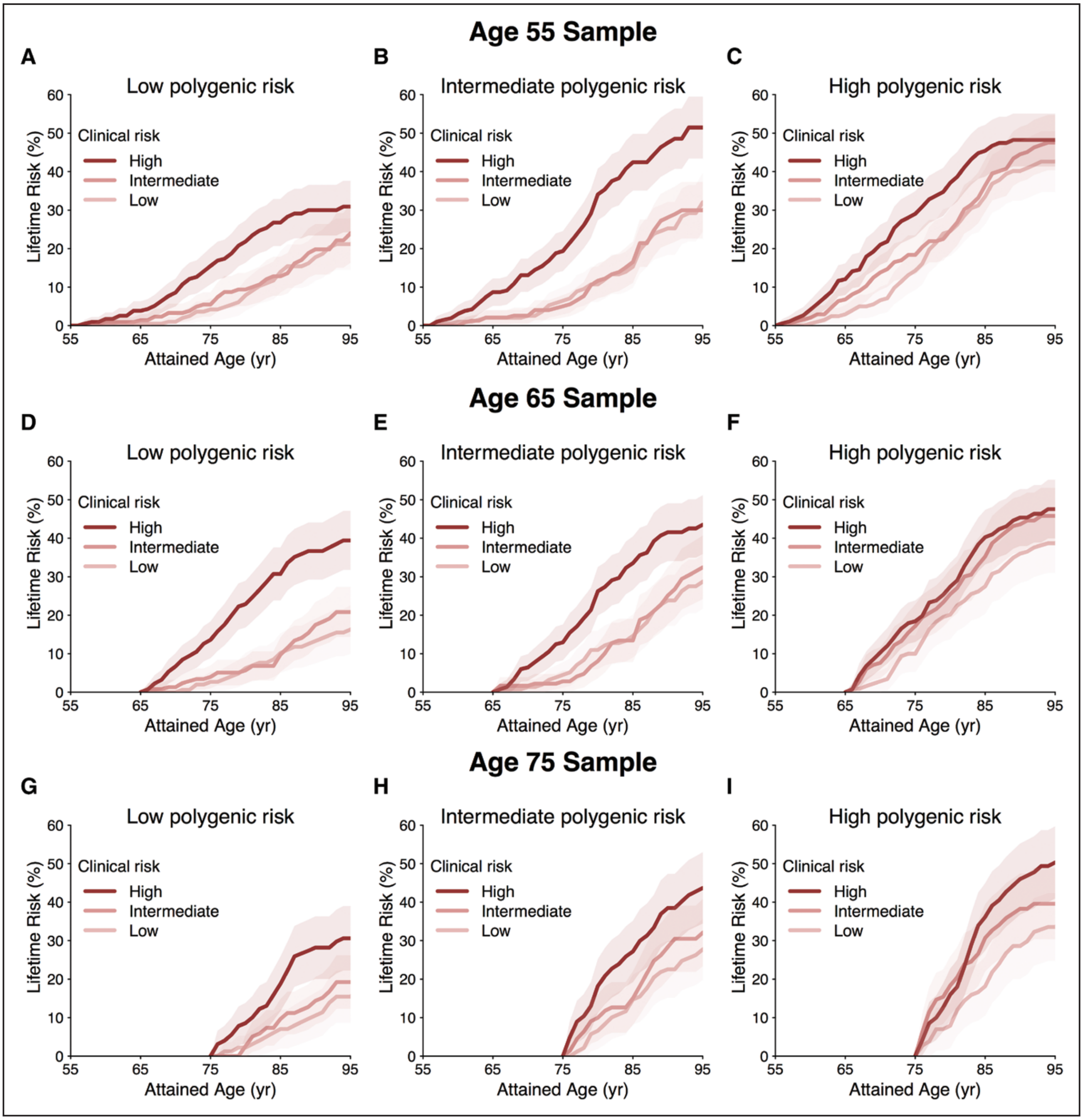

Chart 16-6. Lifetime cumulative risk for atrial fibrillation at different ages (through age 94 years) by sex.
Reprinted from Weng et al.[80]

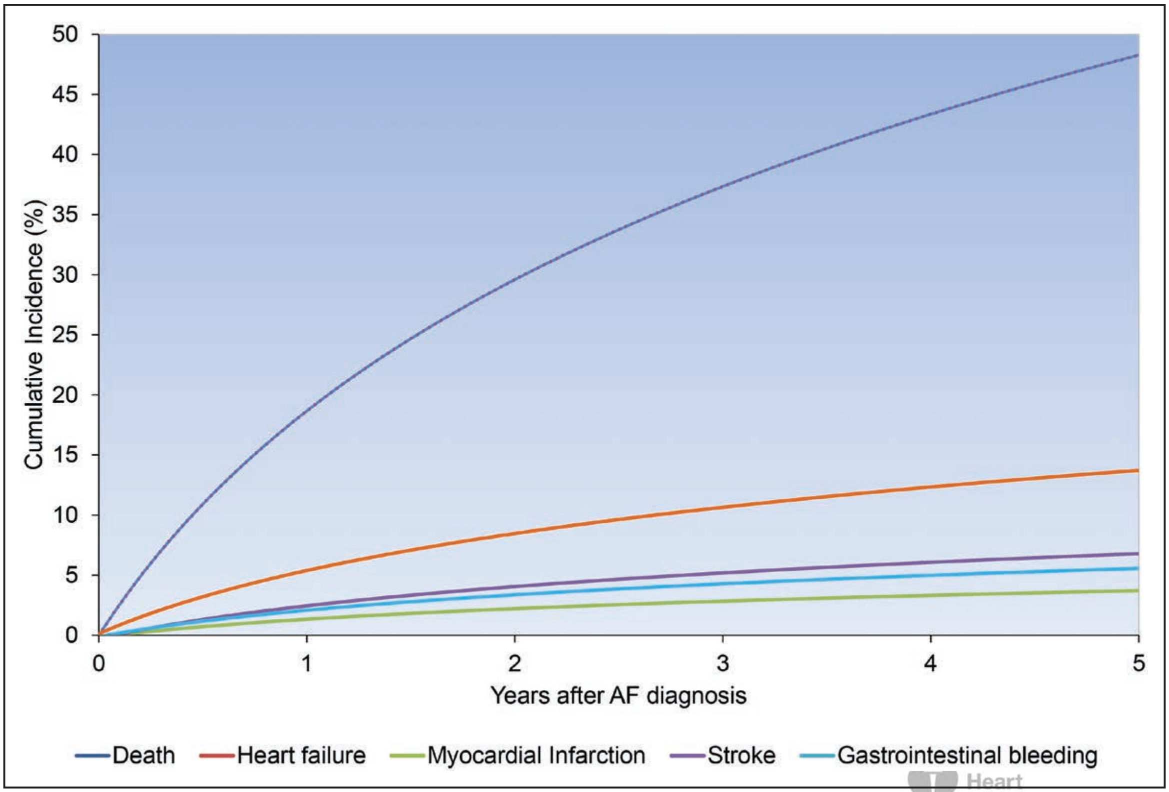

Chart 16-7. Cumulative incidence of events in the 5 years after diagnosis of incident AF in Medicare patients.
AF indicates atrial fibrillation.
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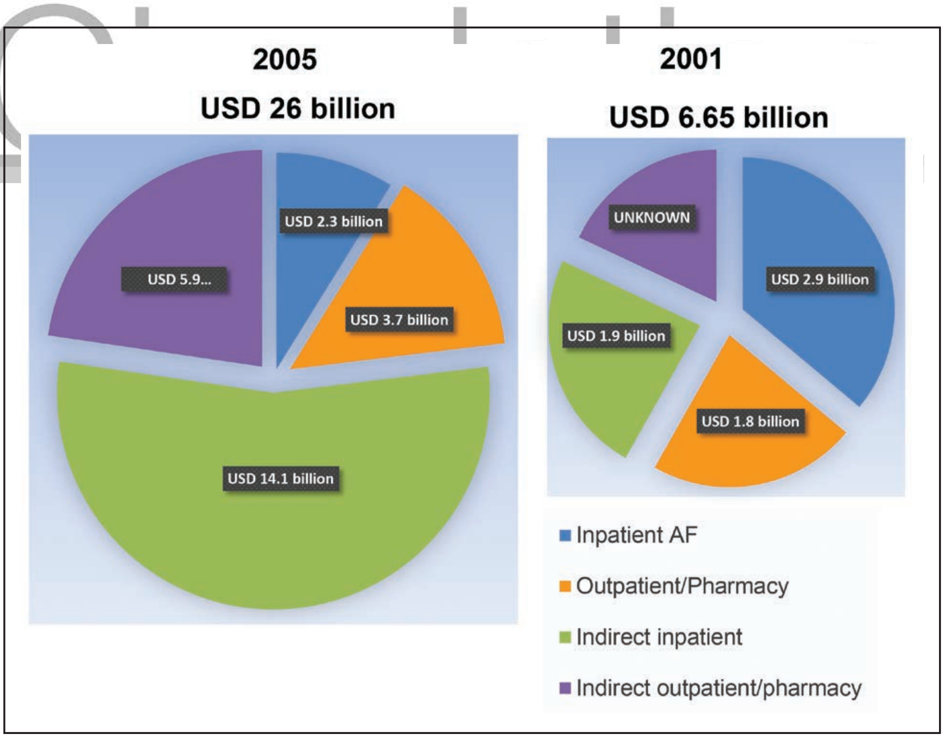

Chart 16-8. AF cost estimates, where AF is diagnosed in inpatient and outpatient encounters.
Indirect costs are incremental costs of inpatient and outpatient visits.
AF indicates atrial fibrillation; and USD, US dollars.
Adapted from Kim et al,[150] copyright © 2011, American Heart Association, Inc.; and from Coyne et al[152] with permission from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), copyright © 2006, International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

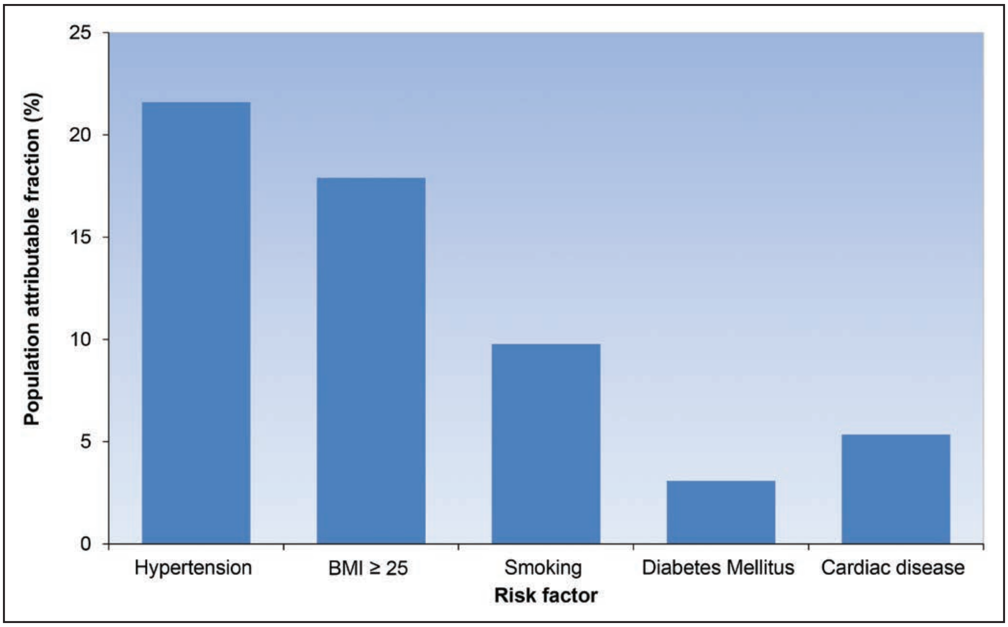

Chart 16-9. Population attributable fraction of major risk factors for atrial fibrillation in the ARIC study.
ARIC indicates Atherosclerosis Risk in Communities; BMI, body mass index (in kg/m²); cardiac disease, patients with history of coronary artery disease or heart failure; and smoking, current smoker.
Data derived from Huxley et al.[157]

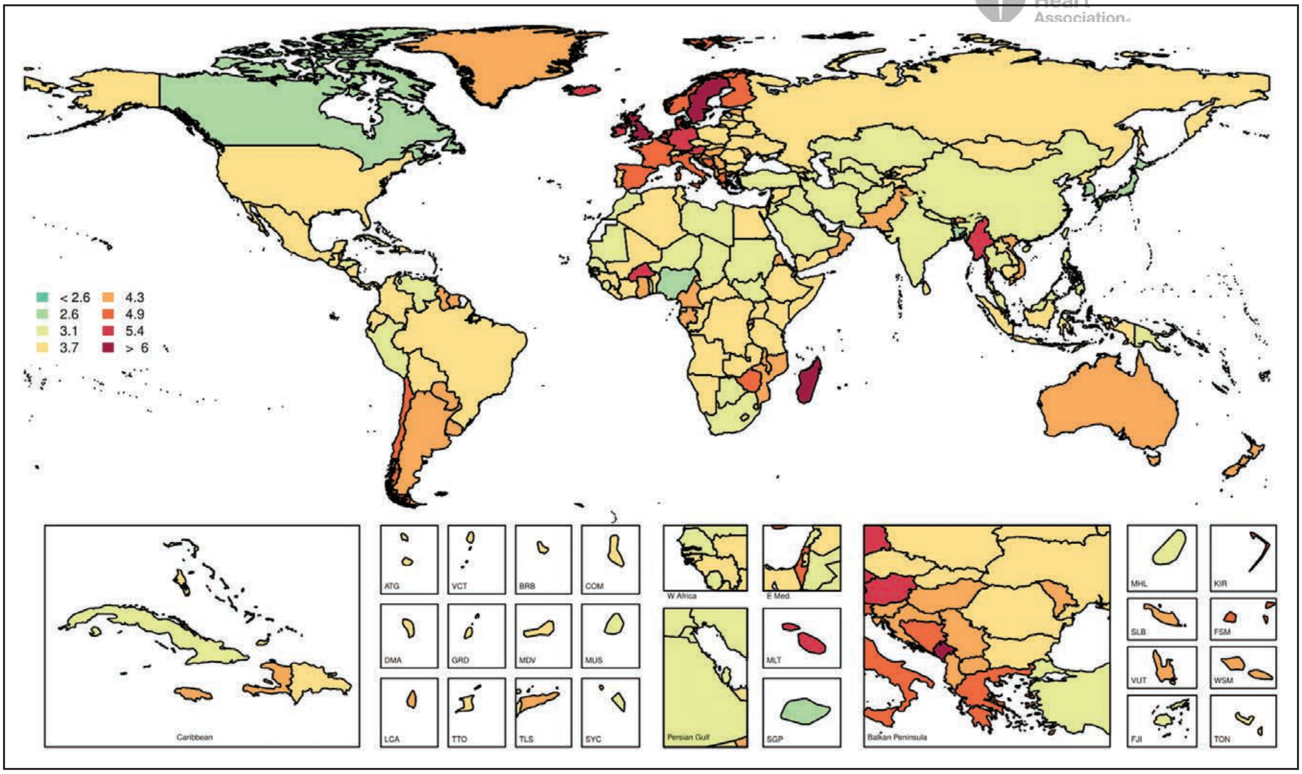

Chart 16-10. Age-standardized global mortality rates of atrial fibrillation and flutter per 100000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[242] Printed with permission.

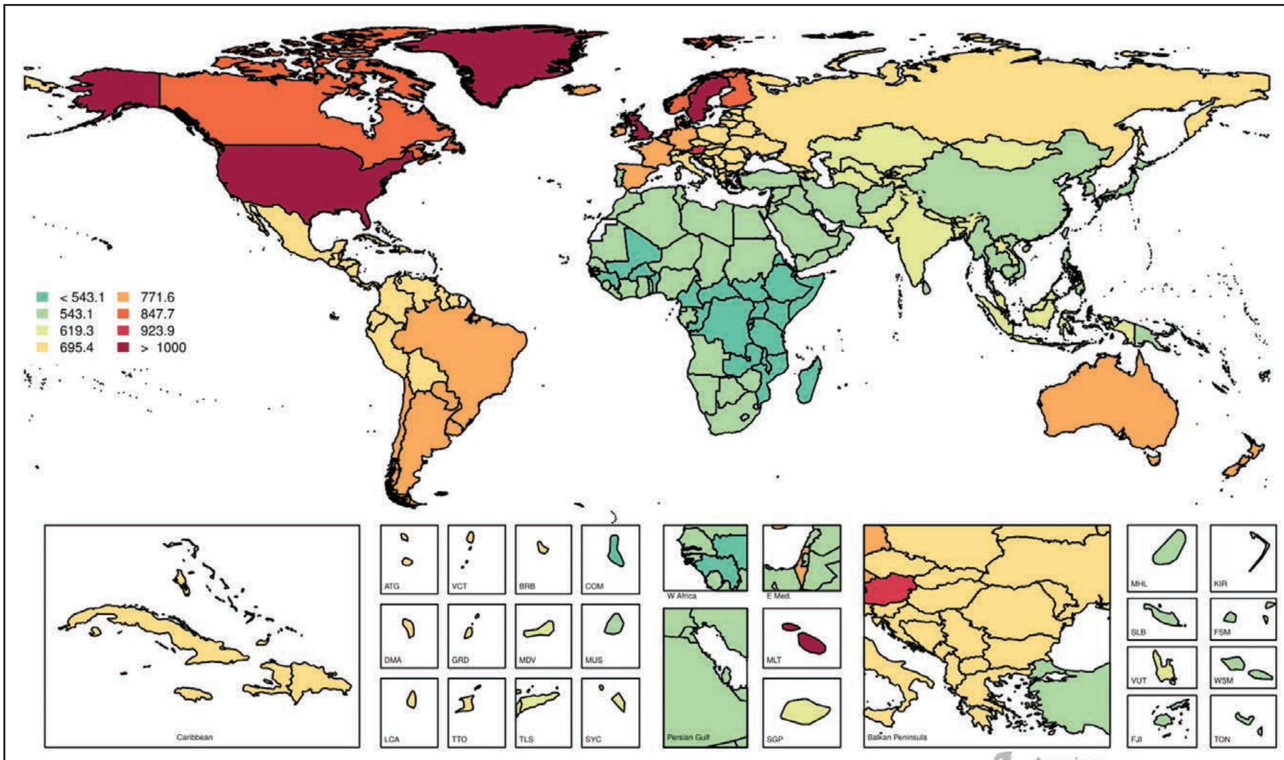

Chart 16-11. Age-standardized global prevalence rates of atrial fibrillation per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[242] Printed with permission. Copyright © 2017, University of Washington.

REFERENCES

1. Vitelli LL, Crow RS, Shahar E, Hutchinson RG, Rautaharju PM, Folsom AR; for the Atherosclerosis Risk in Communities (ARIC) Study Investigators. Electrocardiographic findings in a healthy biracial population. *Am J Cardiol*. 1998;81:453–459.
2. Walsh JA 3rd, Prineas R, Daviglus ML, Ning H, Liu K, Lewis CE, Sidney S, Schreiner PJ, Iribarren C, Lloyd-Jones DM. Prevalence of electrocardiographic abnormalities in a middle-aged, biracial population: Coronary Artery Risk Development in Young Adults study. *J Electrocardiol*. 2010;43:385.e1–385.e9. doi: 10.1016/j.jelectrocard.2010.02.001
3. Aro AL, Anttonen O, Kerola T, Junttila MJ, Tikkanen JT, Rissanen HA, Reunanen A, Huikuri HV. Prognostic significance of prolonged PR interval in the general population. *Eur Heart J*. 2014;35:123–129. doi: 10.1093/eurheartj/eht176
4. Wolbrette D, Naccarelli G. Bradycardias: sinus nodal dysfunction and atrioventricular conduction disturbances. In: Topol. EJ, ed. *Textbook of Cardiovascular Medicine.* 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:1038–1049.
5. Ostrander LD Jr, Brandt RL, Kjelsberg MO, Epstein FH. Electrocardiographic findings among the adult population of a total natural community, Tecumseh, Michigan. *Circulation*. 1965;31:888–898.
6. Kojic EM, Hardarson T, Sigfusson N, Sigvaldason H. The prevalence and prognosis of third-degree atrioventricular conduction block: the Reykjavik study. *J Intern Med*. 1999;246:81–86.
7. Movahed MR, Hashemzadeh M, Jamal MM. Increased prevalence of third-degree atrioventricular block in patients with type II diabetes mellitus. *Chest*. 2005;128:2611–2614. doi: 10.1378/chest.128.4.2611
8. Solomon MD, Yang J, Sung SH, Livingston ML, Sarlas G, Lenane JC, Go AS. Incidence and timing of potentially high-risk arrhythmias detected through long term continuous ambulatory electrocardiographic monitoring. *BMC Cardiovasc Disord*. 2016;16:35. doi: 10.1186/s12872-016-0210-x
9. Turner CJ, Wren C. The epidemiology of arrhythmia in infants: a population-based study. *J Paediatr Child Health*. 2013;49:278–281. doi: 10.1111/jpc.12155
10. Bordachar P, Zachary W, Ploux S, Labrousse L, Haissaguerre M, Thambo JB. Pathophysiology, clinical course, and management of congenital complete atrioventricular block. *Heart Rhythm*. 2013;10:760–766. doi: 10.1016/j.hrthm.2012.12.030
11. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, Benjamin EJ, Vasan RS, Wang TJ. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *JAMA*. 2009;301:2571–2577. doi: 10.1001/jama.2009.888
12. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2013;127:e283–e352. doi: 10.1161/CIR.0b013e318276ce9b
13. Auffret V, Loirat A, Leurent G, Martins RP, Filippi E, Coudert I, Hacot JP, Gilard M, Castellant P, Rialan A, Delaunay R, Rouault G, Druelles P, Boulanger B, Treuil J, Avez B, Bedossa M, Boulmier D, Le Guellec M, Daubert JC, Le Breton H. High-degree atrioventricular block complicating ST segment elevation myocardial infarction in the contemporary era. *Heart*. 2016;102:40–49. doi: 10.1136/heartjnl-2015-308260
14. Mymin D, Mathewson FA, Tate RB, Manfreda J. The natural history of primary first-degree atrioventricular heart block. *N Engl J Med*. 1986;315:1183–1187. doi: 10.1056/NEJM198611063151902
15. Barold SS, Ilercil A, Leonelli F, Herweg B. First-degree atrioventricular block. Clinical manifestations, indications for pacing, pacemaker management & consequences during cardiac resynchronization. *J Interv Card Electrophysiol*. 2006;17:139–152. doi: 10.1007/s10840-006-9065-x
16. Soliman EZ, Alonso A, Misialek JR, Jain A, Watson KE, Lloyd-Jones DM, Lima J, Shea S, Burke GL, Heckbert SR. Reference ranges of PR duration and P-wave indices in individuals free of cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Electrocardiol*. 2013;46:702–706. doi: 10.1016/j.jelectrocard.2013.05.006

17. Grimm W, Koehler U, Fus E, Hoffmann J, Menz V, Funck R, Peter JH, Maisch B. Outcome of patients with sleep apnea-associated severe bradyarrhythmias after continuous positive airway pressure therapy. *Am J Cardiol*. 2000;86:688–692, A9.
18. Bernstein AD, Parsonnet V. Survey of cardiac pacing and implanted defibrillator practice patterns in the United States in 1997. *Pacing Clin Electrophysiol*. 2001;24:842–855.
19. Rodriguez RD, Schocken DD. Update on sick sinus syndrome, a cardiac disorder of aging. *Geriatrics*. 1990;45:26–30, 33.
20. Brignole M, Menozzi C, Lolli G, Oddone D, Gianfranchi L, Bertulla A. Pacing for carotid sinus syndrome and sick sinus syndrome. *Pacing Clin Electrophysiol*. 1990;13(pt 2):2071–2075.
21. Sutton R, Kenny RA. The natural history of sick sinus syndrome. *Pacing Clin Electrophysiol*. 1986;9(pt 2):1110–1114.
22. Baine WB, Yu W, Weis KA. Trends and outcomes in the hospitalization of older Americans for cardiac conduction disorders or arrhythmias, 1991-1998. *J Am Geriatr Soc*. 2001;49:763–770.
23. Jensen PN, Gronroos NN, Chen LY, Folsom AR, deFilippi C, Heckbert SR, Alonso A. Incidence of and risk factors for sick sinus syndrome in the general population. *J Am Coll Cardiol*. 2014;64:531–538. doi: 10.1016/j.jacc.2014.03.056
24. Menozzi C, Brignole M, Alboni P, Boni L, Paparella N, Gaggioli G, Lolli G. The natural course of untreated sick sinus syndrome and identification of the variables predictive of unfavorable outcome. *Am J Cardiol*. 1998;82:1205–1209.
25. Alt E, Völker R, Wirtzfeld A, Ulm K. Survival and follow-up after pacemaker implantation: a comparison of patients with sick sinus syndrome, complete heart block, and atrial fibrillation. *Pacing Clin Electrophysiol*. 1985;8:849–855.
26. Lamas GA, Lee KL, Sweeney MO, Silverman R, Leon A, Yee R, Marinchak RA, Flaker G, Schron E, Orav EJ, Hellkamp AS, Greer S, McAnulty J, Ellenbogen K, Ehlert F, Freedman RA, Estes NA 3rd, Greenspon A, Goldman L; Mode Selection Trial in Sinus-Node Dysfunction. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. *N Engl J Med*. 2002;346:1854–1862. doi: 10.1056/NEJMoa013040
27. Simon AB, Janz N. Symptomatic bradyarrhythmias in the adult: natural history following ventricular pacemaker implantation. *Pacing Clin Electrophysiol*. 1982;5:372–383.
28. Hesselson AB, Parsonnet V, Bernstein AD, Bonavita GJ. Deleterious effects of long-term single-chamber ventricular pacing in patients with sick sinus syndrome: the hidden benefits of dual-chamber pacing. *J Am Coll Cardiol*. 1992;19:1542–1549.
29. Alonso A, Jensen PN, Lopez FL, Chen LY, Psaty BM, Folsom AR, Heckbert SR. Association of sick sinus syndrome with incident cardiovascular disease and mortality: the Atherosclerosis Risk in Communities study and Cardiovascular Health Study. *PLoS One*. 2014;9:e109662. doi: 10.1371/journal.pone.0109662
30. Udo EO, van Hemel NM, Zuithoff NP, Doevendans PA, Moons KG. Prognosis of the bradycardia pacemaker recipient assessed at first implantation: a nationwide cohort study. *Heart*. 2013;99:1573–1578. doi: 10.1136/heartjnl-2013-304445
31. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) [published correction appears in *Circulation*. 2009;120:e34–35]. *Circulation*. 2008;117:e350–e408. doi: 10.1161/CIRCUALTIONAHA.108.189742
32. Greenspon AJ, Patel JD, Lau E, Ochoa JA, Frisch DR, Ho RT, Pavri BB, Kurtz SM. Trends in permanent pacemaker implantation in the United States from 1993 to 2009: increasing complexity of patients and procedures. *J Am Coll Cardiol*. 2012;60:1540–1545. doi: 10.1016/j.jacc.2012.07.017
33. Birnie D, Williams K, Guo A, Mielniczuk L, Davis D, Lemery R, Green M, Gollob M, Tang A. Reasons for escalating pacemaker implants. *Am J Cardiol*. 2006;98:93–97. doi: 10.1016/j.amjcard.2006.01.069
34. Goldberger JJ, Johnson NP, Gidea C. Significance of asymptomatic bradycardia for subsequent pacemaker implantation and mortality in patients >60 years of age. *Am J Cardiol*. 2011;108:857–861. doi: 10.1016/j.amjcard.2011.04.035
35. Dharod A, Soliman EZ, Dawood F, Chen H, Shea S, Nazarian S, Bertoni AG; MESA Investigators. Association of asymptomatic bradycardia with incident cardiovascular disease and mortality: the Multi-Ethnic Study of Atherosclerosis (MESA). *JAMA Intern Med*. 2016;176:219–227. doi: 10.1001/jamainternmed.2015.7655
36. Issa Z, Miller J, Zipes D. *Clinical Arrhythmology and Electrophysiology: A Companion to Braunwald's Heart Disease*. Philadelphia, PA: Saunders Elsevier; 2008.
37. Dobrzynski H, Boyett MR, Anderson RH. New insights into pacemaker activity: promoting understanding of sick sinus syndrome. *Circulation*. 2007;115:1921–1932. doi: 10.1161/CIRCULATIONAHA.106.616011
38. Rosenqvist M, Obel IW. Atrial pacing and the risk for AV block: is there a time for change in attitude? *Pacing Clin Electrophysiol*. 1989;12(pt 1):97–101.
39. Orejarena LA, Vidaillet H Jr, DeStefano F, Nordstrom DL, Vierkant RA, Smith PN, Hayes JJ. Paroxysmal supraventricular tachycardia in the general population. *J Am Coll Cardiol*. 1998;31:150–157.
40. Murman DH, McDonald AJ, Pelletier AJ, Camargo CA Jr. U.S. emergency department visits for supraventricular tachycardia, 1993-2003. *Acad Emerg Med*. 2007;14:578–581. doi: 10.1197/j.aem.2007.01.013
41. Turakhia MP, Hoang DD, Zimetbaum P, Miller JD, Froelicher VF, Kumar UN, Xu X, Yang F, Heidenreich PA. Diagnostic utility of a novel leadless arrhythmia monitoring device. *Am J Cardiol*. 2013;112:520–524. doi: 10.1016/j.amjcard.2013.04.017
42. Maurer MS, Shefrin EA, Fleg JL. Prevalence and prognostic significance of exercise-induced supraventricular tachycardia in apparently healthy volunteers. *Am J Cardiol*. 1995;75:788–792.
43. Poutiainen AM, Koistinen MJ, Airaksinen KE, Hartikainen EK, Kettunen RV, Karjalainen JE, Huikuri HV. Prevalence and natural course of ectopic atrial tachycardia. *Eur Heart J*. 1999;20:694–700.
44. Wu EB, Chia HM, Gill JS. Reversible cardiomyopathy after radiofrequency ablation of lateral free-wall pathway-mediated incessant supraventricular tachycardia. *Pacing Clin Electrophysiol*. 2000;23:1308–1310.
45. Wang YS, Scheinman MM, Chien WW, Cohen TJ, Lesh MD, Griffin JC. Patients with supraventricular tachycardia presenting with aborted sudden death: incidence, mechanism and long-term follow-up. *J Am Coll Cardiol*. 1991;18:1711–1719.
46. Chang SH, Kuo CF, Chou IJ, See LC, Yu KH, Luo SF, Chiou MJ, Zhang W, Doherty M, Wen MS, Chen WJ, Yeh YH. Outcomes associated with paroxysmal supraventricular tachycardia during pregnancy. *Circulation*. 2017;135:616–618. doi: 10.1161/CIRCULATIONAHA.116.025064
47. Kamel H, Elkind MS, Bhave PD, Navi BB, Okin PM, Iadecola C, Devereux RB, Fink ME. Paroxysmal supraventricular tachycardia and the risk of ischemic stroke. *Stroke*. 2013;44:1550–1554. doi: 10.1161/STROKEAHA.113.001118
48. Carnlöf C, Iwarzon M, Jensen-Urstad M, Gadler F, Insulander P. Women with PSVT are often misdiagnosed, referred later than men, and have more symptoms after ablation. *Scand Cardiovasc J*. 2017;51:299–307. doi: 10.1080/14017431.2017.1385837
49. Brembilla-Perrot B, Houriez P, Beurrier D, Claudon O, Burger G, Vançon AC, Mock L. Influence of age on the electrophysiological mechanism of paroxysmal supraventricular tachycardias. *Int J Cardiol*. 2001;78:293–298.
50. Porter MJ, Morton JB, Denman R, Lin AC, Tierney S, Santucci PA, Cai JJ, Madsen N, Wilber DJ. Influence of age and gender on the mechanism of supraventricular tachycardia. *Heart Rhythm*. 2004;1:393–396. doi: 10.1016/j.hrthm.2004.05.007
51. Anand RG, Rosenthal GL, Van Hare GF, Snyder CS. Is the mechanism of supraventricular tachycardia in pediatrics influenced by age, gender or ethnicity? *Congenit Heart Dis*. 2009;4:464–468. doi: 10.1111/j.1747-0803.2009.00336.x
52. Bradley DJ, Fischbach PS, Law IH, Serwer GA, Dick M 2nd. The clinical course of multifocal atrial tachycardia in infants and children. *J Am Coll Cardiol*. 2001;38:401–408.
53. McCord J, Borzak S. Multifocal atrial tachycardia. *Chest*. 1998;113: 203–209.
54. Lazaros G, Chrysohoou C, Oikonomou E, Tsiachris D, Mazaris S, Venieri E, Zisimos K, Zaromytidou M, Kariori M, Kioufis S, Pitsavos C, Stefanadis C. The natural history of multifocal atrial rhythms in elderly outpatients: insights from the "Ikaria study." *Ann Noninvasive Electrocardiol*. 2014;19:483–489. doi: 10.1111/anec.12165
55. De Bacquer D, De Backer G, Kornitzer M. Prevalences of ECG findings in large population based samples of men and women. *Heart*. 2000;84:625–633.
56. Sano S, Komori S, Amano T, Kohno I, Ishihara T, Sawanobori T, Ijiri H, Tamura K. Prevalence of ventricular preexcitation in Japanese schoolchildren. *Heart*. 1998;79:374–378.

57. Blomström-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ, Campbell WB, Haines DE, Kuck KH, Lerman BB, Miller DD, Shaeffer CW Jr, Stevenson WG, Tomaselli GF. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias–executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias). *Circulation*. 2003;108:1871–1909. doi: 10.1161/01.CIR.0000091380.04100.84
58. Bunch TJ, May HT, Bair TL, Anderson JL, Crandall BG, Cutler MJ, Jacobs V, Mallender C, Muhlestein JB, Osborn JS, Weiss JP, Day JD. Long-term natural history of adult Wolff-Parkinson-White syndrome patients treated with and without catheter ablation. *Circ Arrhythm Electrophysiol*. 2015;8:1465–1471. doi: 10.1161/CIRCEP.115.003013
59. Leitch JW, Klein GJ, Yee R, Murdock C. Prognostic value of electrophysiology testing in asymptomatic patients with Wolff-Parkinson-White pattern [published correction appears in *Circulation*. 1991;83:1124]. *Circulation*. 1990;82:1718–1723.
60. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of electrocardiographic preexcitation in men: the Manitoba Follow-up Study. *Ann Intern Med*. 1992;116:456–460.
61. Munger TM, Packer DL, Hammill SC, Feldman BJ, Bailey KR, Ballard DJ, Holmes DR Jr, Gersh BJ. A population study of the natural history of Wolff-Parkinson-White syndrome in Olmsted County, Minnesota, 1953-1989. *Circulation*. 1993;87:866–873.
62. Goudevenos JA, Katsouras CS, Graekas G, Argiri O, Giogiakas V, Sideris DA. Ventricular pre-excitation in the general population: a study on the mode of presentation and clinical course. *Heart*. 2000;83:29–34.
63. Pappone C, Vicedomini G, Manguso F, Saviano M, Baldi M, Pappone A, Ciaccio C, Giannelli L, Ionescu B, Petretta A, Vitale R, Cuko A, Calovic Z, Fundaliotis A, Moscatiello M, Tavazzi L, Santinelli V. Wolff-Parkinson-White syndrome in the era of catheter ablation: insights from a registry study of 2169 patients. *Circulation*. 2014;130:811–819. doi: 10.1161/CIRCULATIONAHA.114.011154
64. Obeyesekere MN, Leong-Sit P, Massel D, Manlucu J, Modi S, Krahn AD, Skanes AC, Yee R, Gula LJ, Klein GJ. Risk of arrhythmia and sudden death in patients with asymptomatic preexcitation: a meta-analysis. *Circulation*. 2012;125:2308–2315. doi: 10.1161/CIRCULATIONAHA.111.055350
65. Inoue K, Igarashi H, Fukushige J, Ohno T, Joh K, Hara T. Long-term prospective study on the natural history of Wolff-Parkinson-White syndrome detected during a heart screening program at school. *Acta Paediatr*. 2000;89:542–545.
66. Pappone C, Manguso F, Santinelli R, Vicedomini G, Sala S, Paglino G, Mazzone P, Lang CC, Gulletta S, Augello G, Santinelli O, Santinelli V. Radiofrequency ablation in children with asymptomatic Wolff-Parkinson-White syndrome. *N Engl J Med*. 2004;351:1197–1205. doi: 10.1056/NEJMoa040625
67. Cain N, Irving C, Webber S, Beerman L, Arora G. Natural history of Wolff-Parkinson-White syndrome diagnosed in childhood. *Am J Cardiol*. 2013;112:961–965. doi: 10.1016/j.amjcard.2013.05.035
68. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370–2375.
69. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence [published correction appears in *Circulation*. 2006;114:e498]. *Circulation*. 2006;114:119–125. doi: 10.1161/CIRCULATIONAHA.105.595140
70. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol*. 2013;112:1142–1147. doi: 10.1016/j.amjcard.2013.05.063
71. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, Witteman JC, Stricker BH, Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J*. 2013;34:2746–2751. doi: 10.1093/eurheartj/eht280
72. Shen AY, Contreras R, Sobnosky S, Shah AI, Ichiuji AM, Jorgensen MB, Brar SS, Chen W. Racial/ethnic differences in the prevalence of atrial fibrillation among older adults: a cross-sectional study. *J Natl Med Assoc*. 2010;102:906–913.
73. Piccini JP, Hammill BG, Sinner MF, Jensen PN, Hernandez AF, Heckbert SR, Benjamin EJ, Curtis LH. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. *Circ Cardiovasc Qual Outcomes*. 2012;5:85–93. doi: 10.1161/CIRCOUTCOMES.111.962688
74. Rodriguez CJ, Soliman EZ, Alonso A, Swett K, Okin PM, Goff DC Jr, Heckbert SR. Atrial fibrillation incidence and risk factors in relation to race-ethnicity and the population attributable fraction of atrial fibrillation risk factors: the Multi-Ethnic Study of Atherosclerosis. *Ann Epidemiol*. 2015;25:71–6, 76.e1. doi: 10.1016/j.annepidem.2014.11.024
75. Dewland TA, Olgin JE, Vittinghoff E, Marcus GM. Incident atrial fibrillation among Asians, Hispanics, blacks, and whites. *Circulation*. 2013;128:2470–2477. doi: 10.1161/CIRCULATIONAHA.113.002449
76. Martinez C, Katholing A, Wallenhorst C, Granziera S, Cohen AT, Freedman SB. Increasing incidence of non-valvular atrial fibrillation in the UK from 2001 to 2013. *Heart*. 2015;101:1748–1754. doi: 10.1136/heartjnl-2015-307808
77. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004;110:1042–1046. doi: 10.1161/01.CIR.0000140263.20897.42
78. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip GY, Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J*. 2006;27:949–953. doi: 10.1093/eurheartj/ehi825.
79. Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Njølstad I, Vartiainen E, Sans S, Pasterkamp G, Hughes M, Costanzo S, Donati MB, Jousilahti P, Linneberg A, Palosaari T, de Gaetano G, Bobak M, den Ruijter HM, Mathiesen E, Jørgensen T, Söderberg S, Kuulasmaa K, Zeller T, Iacoviello L, Salomaa V, Schnabel RB; on behalf of the BiomarCaRE Consortium. Sex differences and similarities in atrial fibrillation epidemiology, risk factors, and mortality in community cohorts: results from the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe). *Circulation*. 2017;136:1588–1597. doi: 10.1161/CIRCULATIONAHA.117.028981
80. Weng LC, Preis SR, Hulme OL, Larson MG, Choi SH, Wang B, Trinquart L, McManus DD, Staerk L, Lin H, Lunetta KL, Ellinor PT, Benjamin EJ, Lubitz SA. Genetic predisposition, clinical risk factor burden, and lifetime risk of atrial fibrillation. *Circulation*. 2018;137:1027–1038. doi: 10.1161/CIRCULATIONAHA.117.031431
81. Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, McManus DD, Ko D, Weng LC, Lunetta KL, Frost L, Benjamin EJ, Trinquart L. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ*. 2018;361:k1453. doi: 10.1136/bmj.k1453
82. Guo Y, Tian Y, Wang H, Si Q, Wang Y, Lip GYH. Prevalence, incidence, and lifetime risk of atrial fibrillation in China: new insights into the global burden of atrial fibrillation. *Chest*. 2015;147:109–119. doi: 10.1378/chest.14-0321
83. Chao TF, Liu CJ, Tuan TC, Chen TJ, Hsieh MH, Lip GYH, Chen SA. Lifetime risks, projected numbers, and adverse outcomes in Asian patients with atrial fibrillation: a report from the Taiwan Nationwide AF Cohort Study. *Chest*. 2018;153:453–466. doi: 10.1016/j.chest.2017.10.001
84. Mou L, Norby FL, Chen LY, O'Neal WT, Lewis TT, Loehr LR, Soliman EZ, Alonso A. Lifetime risk of atrial fibrillation by race and socioeconomic status: the Atherosclerosis Risk in Communities (ARIC) study. *Circ Arrhythm Electrophysiol*. 2018;11:e006350. doi: 10.1161/CIRCEP.118.006350
85. National Center for Health Statistics. Centers for Disease Control and Prevention website. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2016. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed May 21, 2018.
86. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946–952.
87. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, Odutayo AA. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ*. 2016;532:h7013. doi: 10.1136/bmj.h7013
88. Chamberlain AM, Gersh BJ, Alonso A, Chen LY, Berardi C, Manemann SM, Killian JM, Weston SA, Roger VL. Decade-long trends in atrial fibrillation incidence and survival: a community study. *Am J Med*. 2015;128:260–7.e1. doi: 10.1016/j.amjmed.2014.10.030

89. Marijon E, Le Heuzey JY, Connolly S, Yang S, Pogue J, Brueckmann M, Eikelboom J, Themeles E, Ezekowitz M, Wallentin L, Yusuf S; for the RE-LY Investigators. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. *Circulation*. 2013;128:2192–2201. doi: 10.1161/CIRCULATIONAHA.112.000491
90. Masri A, Kanj M, Thamilarasan M, Wazni O, Smedira NG, Lever HM, Desai MY. Outcomes in hypertrophic cardiomyopathy patients with and without atrial fibrillation: a survival meta-analysis. *Cardiovasc Diagn Ther*. 2017;7:36–44. doi: 10.21037/cdt.2016.11.23
91. Jabre P, Jouven X, Adnet F, Thabut G, Bielinski SJ, Weston SA, Roger VL. Atrial fibrillation and death after myocardial infarction: a community study. *Circulation*. 2011;123:2094–2100. doi: 10.1161/CIRCULATIONAHA.110.990192
92. Jabre P, Roger VL, Murad MH, Chamberlain AM, Prokop L, Adnet F, Jouven X. Mortality associated with atrial fibrillation in patients with myocardial infarction: a systematic review and meta-analysis. *Circulation*. 2011;123:1587–1593. doi: 10.1161/CIRCULATIONAHA.110.986661
93. Kaw R, Hernandez AV, Masood I, Gillinov AM, Saliba W, Blackstone EH. Short- and long-term mortality associated with new-onset atrial fibrillation after coronary artery bypass grafting: a systematic review and meta-analysis. *J Thorac Cardiovasc Surg*. 2011;141:1305–1312. doi: 10.1016/j.jtcvs.2010.10.040
94. Phan K, Ha HS, Phan S, Medi C, Thomas SP, Yan TD. New-onset atrial fibrillation following coronary bypass surgery predicts long-term mortality: a systematic review and meta-analysis. *Eur J Cardiothorac Surg*. 2015;48:817–824. doi: 10.1093/ejcts/ezu551
95. Mojoli M, Gersh BJ, Barioli A, Masiero G, Tellaroli P, D'Amico G, Tarantini G. Impact of atrial fibrillation on outcomes of patients treated by transcatheter aortic valve implantation: a systematic review and meta-analysis. *Am Heart J*. 2017;192:64–75. doi: 10.1016/j.ahj.2017.07.005
96. Vrsalović M, Presečki AV. Atrial fibrillation and risk of cardiovascular events and mortality in patients with symptomatic peripheral artery disease: a meta-analysis of prospective studies. *Clin Cardiol*. 2017;40:1231–1235. doi: 10.1002/clc.22813
97. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB. Stroke severity in atrial fibrillation: the Framingham Study. *Stroke*. 1996;27:1760–1764.
98. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail*. 2009;11:676–683. doi: 10.1093/eurjhf/hfp085
99. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation*. 2003;107:2920–2925. doi: 10.1161/01.CIR.0000072767.89944.6E
100. Cheng M, Lu X, Huang J, Zhang J, Zhang S, Gu D. The prognostic significance of atrial fibrillation in heart failure with a preserved and reduced left ventricular function: insights from a meta-analysis. *Eur J Heart Fail*. 2014;16:1317–1322. doi: 10.1002/ejhf.187
101. Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study [published correction appears in *Circulation*. 2013;128:e465]. *Circulation*. 2013;128:1085–1093. doi: 10.1161/CIRCULATIONAHA.113.001475
102. Odutayo A, Wong CX, Williams R, Hunn B, Emdin CA. Prognostic importance of atrial fibrillation timing and pattern in adults with congestive heart failure: a systematic review and meta-analysis. *J Card Fail*. 2017;23:56–62. doi: 10.1016/j.cardfail.2016.08.005
103. Echouffo-Tcheugui JB, Shrader P, Thomas L, Gersh BJ, Kowey PR, Mahaffey KW, Singer DE, Hylek EM, Go AS, Peterson ED, Piccini JP, Fonarow GC. Care patterns and outcomes in atrial fibrillation patients with and without diabetes: ORBIT-AF registry. *J Am Coll Cardiol*. 2017;70:1325–1335. doi: 10.1016/j.jacc.2017.07.755
104. Fatemi O, Yuriditsky E, Tsioufis C, Tsachris D, Morgan T, Basile J, Bigger T, Cushman W, Goff D, Soliman EZ, Thomas A, Papademetriou V. Impact of intensive glycemic control on the incidence of atrial fibrillation and associated cardiovascular outcomes in patients with type 2 diabetes mellitus (from the Action to Control Cardiovascular Risk in Diabetes Study). *Am J Cardiol*. 2014;114:1217–1222. doi: 10.1016/j.amjcard.2014.07.045
105. Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM. Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis [published correction appears in *Nephrol Dial Transplant*. 2014;29:2152]. *Nephrol Dial Transplant*. 2012;27:3816–3822. doi: 10.1093/ndt/gfs416
106. Walkey AJ, Hammill BG, Curtis LH, Benjamin EJ. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. *Chest*. 2014;146:1187–1195. doi: 10.1378/chest.14-0003
107. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA*. 2011;306:2248–2254. doi: 10.1001/jama.2011.1615
108. van Diepen S, Bakal JA, McAlister FA, Ezekowitz JA. Mortality and readmission of patients with heart failure, atrial fibrillation, or coronary artery disease undergoing noncardiac surgery: an analysis of 38 047 patients. *Circulation*. 2011;124:289–296. doi: 10.1161/CIRCULATIONAHA.110.011130
109. Kabra R, Cram P, Girotra S, Vaughan Sarrazin M. Effect of race on outcomes (stroke and death) in patients >65 years with atrial fibrillation. *Am J Cardiol*. 2015;116:230–235. doi: 10.1016/j.amjcard.2015.04.012
110. Magnani JW, Norby FL, Agarwal SK, Soliman EZ, Chen LY, Loehr LR, Alonso A. Racial differences in atrial fibrillation-related cardiovascular disease and mortality: the Atherosclerosis Risk in Communities (ARIC) Study. *JAMA Cardiol*. 2016;1:433–441. doi: 10.1001/jamacardio.2016.1025
111. Roth GA, Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, Morozoff C, Naghavi M, Mokdad AH, Murray CJL. Trends and patterns of geographic variation in cardiovascular mortality among US counties, 1980-2014. *JAMA*. 2017;317:1976–1992. doi: 10.1001/jama.2017.4150
112. Wändell P, Carlsson AC, Gasevic D, Sundquist J, Sundquist K. Neighbourhood socio-economic status and all-cause mortality in adults with atrial fibrillation: a cohort study of patients treated in primary care in Sweden. *Int J Cardiol*. 2016;202:776–781. doi: 10.1016/j.ijcard.2015.09.027
113. Wandell P, Carlsson AC, Gasevic D, Holzmann MJ, Arnlov J, Sundquist J, Sundquist K. Socioeconomic factors and mortality in patients with atrial fibrillation-a cohort study in Swedish primary care [published online May 9, 2018]. *Eur J Public Health*. doi: 10.1093/eurpub/cky075
114. Piccini JP, Hammill BG, Sinner MF, Hernandez AF, Walkey AJ, Benjamin EJ, Curtis LH, Heckbert SR. Clinical course of atrial fibrillation in older adults: the importance of cardiovascular events beyond stroke. *Eur Heart J*. 2014;35:250–256. doi: 10.1093/eurheartj/eht483
115. Frost L, Engholm G, Johnsen S, Møller H, Henneberg EW, Husted S. Incident thromboembolism in the aorta and the renal, mesenteric, pelvic, and extremity arteries after discharge from the hospital with a diagnosis of atrial fibrillation. *Arch Intern Med*. 2001;161:272–276.
116. Bekwelem W, Connolly SJ, Halperin JL, Adabag S, Duval S, Chrolavicius S, Pogue J, Ezekowitz MD, Eikelboom JW, Wallentin LG, Yusuf S, Hirsch AT. Extracranial systemic embolic events in patients with nonvalvular atrial fibrillation: incidence, risk factors, and outcomes. *Circulation*. 2015;132:796–803. doi: 10.1161/CIRCULATIONAHA.114.013243
117. Al-Kawaz M, Omran SS, Parikh NS, Elkind MSV, Soliman EZ, Kamel H. Comparative risks of ischemic stroke in atrial flutter versus atrial fibrillation. *J Stroke Cerebrovasc Dis*. 2018;27:839–844. doi: 10.1016/j.jstrokecerebrovasdis.2017.10.025
118. Quinn GR, Severdija ON, Chang Y, Singer DE. Wide variation in reported rates of stroke across cohorts of patients with atrial fibrillation. *Circulation*. 2017;135:208–219. doi: 10.1161/CIRCULATIONAHA.116.024057
119. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983–988.
120. Hayden DT, Hannon N, Callaly E, Ní Chróinín D, Horgan G, Kyne L, Duggan J, Dolan E, O'Rourke K, Williams D, Murphy S, Kelly PJ. Rates and determinants of 5-year outcomes after atrial fibrillation-related stroke: a population study. *Stroke*. 2015;46:3488–3493. doi: 10.1161/STROKEAHA.115.011139
121. Kabra R, Girotra S, Vaughan Sarrazin M. Refining stroke prediction in atrial fibrillation patients by addition of African-American ethnicity to CHA2DS2-VASc score. *J Am Coll Cardiol*. 2016;68:461–470. doi: 10.1016/j.jacc.2016.05.044
122. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. *Ann Intern Med*. 2013;158(5 Pt 1):338–346. doi: 10.7326/0003-4819-158-5-201303050-00007
123. Miyasaka Y, Barnes ME, Petersen RC, Cha SS, Bailey KR, Gersh BJ, Casaclang-Verzosa G, Abhayaratna WP, Seward JB, Iwasaka T, Tsang TS. Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a community-based cohort. *Eur Heart J*. 2007;28:1962–1967. doi: 10.1093/eurheartj/ehm012

124. Rienstra M, Lubitz SA, Mahida S, Magnani JW, Fontes JD, Sinner MF, Van Gelder IC, Ellinor PT, Benjamin EJ. Symptoms and functional status of patients with atrial fibrillation: state of the art and future research opportunities. *Circulation*. 2012;125:2933–2943. doi: 10.1161/CIRCULATIONAHA.111.069450
125. Rienstra M, Lyass A, Murabito JM, Magnani JW, Lubitz SA, Massaro JM, Ellinor PT, Benjamin EJ. Reciprocal relations between physical disability, subjective health, and atrial fibrillation: the Framingham Heart Study. *Am Heart J*. 2013;166:171–178. doi: 10.1016/j.ahj.2013.02.025
126. Zhang L, Gallagher R, Neubeck L. Health-related quality of life in atrial fibrillation patients over 65 years: a review. *Eur J Prev Cardiol*. 2015;22:987–1002. doi: 10.1177/2047487314538855
127. Giacomantonio NB, Bredin SS, Foulds HJ, Warburton DE. A systematic review of the health benefits of exercise rehabilitation in persons living with atrial fibrillation. *Can J Cardiol*. 2013;29:483–491. doi: 10.1016/j.cjca.2012.07.003
128. O'Neal WT, Qureshi WT, Judd SE, Bowling CB, Howard VJ, Howard G, Soliman EZ. Effect of falls on frequency of atrial fibrillation and mortality risk (from the REasons for Geographic And Racial Differences in Stroke Study). *Am J Cardiol*. 2015;116:1213–1218. doi: 10.1016/j.amjcard.2015.07.036
129. Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med*. 1999;159:677–685.
130. Gage BF, Birman-Deych E, Kerzner R, Radford MJ, Nilasena DS, Rich MW. Incidence of intracranial hemorrhage in patients with atrial fibrillation who are prone to fall. *Am J Med*. 2005;118:612–617. doi: 10.1016/j.amjmed.2005.02.022
131. Chamberlain AM, Gersh BJ, Alonso A, Kopecky SL, Killian JM, Weston SA, Roger VL. No decline in the risk of heart failure after incident atrial fibrillation: a community study assessing trends overall and by ejection fraction. *Heart Rhythm*. 2017;14:791–798. doi: 10.1016/j.hrthm.2017.01.031
132. Vermond RA, Geelhoed B, Verweij N, Tieleman RG, Van der Harst P, Hillege HL, Van Gilst WH, Van Gelder IC, Rienstra M. Incidence of atrial fibrillation and relationship with cardiovascular events, heart failure, and mortality: a community-based study from the Netherlands. *J Am Coll Cardiol*. 2015;66:1000–1007. doi: 10.1016/j.jacc.2015.06.1314
133. Ruddox V, Sandven I, Munkhaugen J, Skattebu J, Edvardsen T, Otterstad JE. Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2017;24:1555–1566. doi: 10.1177/2047487317715769
134. Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, Thacker EL, Judd S, Howard VJ, Howard G, Herrington DM, Cushman M. Atrial fibrillation and the risk of myocardial infarction [published correction appears in *JAMA Intern Med*. 2014;174:308]. *JAMA Intern Med*. 2014;174:107–114. doi: 10.1001/jamainternmed.2013.11912
135. Soliman EZ, Lopez F, O'Neal WT, Chen LY, Bengtson L, Zhang ZM, Loehr L, Cushman M, Alonso A. Atrial fibrillation and risk of ST-segment-elevation versus non-ST-segment-elevation myocardial infarction: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2015;131:1843–1850. doi: 10.1161/CIRCULATIONAHA.114.014145
136. O'Neal WT, Sangal K, Zhang ZM, Soliman EZ. Atrial fibrillation and incident myocardial infarction in the elderly. *Clin Cardiol*. 2014;37:750–755. doi: 10.1002/clc.22339
137. Watanabe H, Watanabe T, Sasaki S, Nagai K, Roden DM, Aizawa Y. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. *Am Heart J*. 2009;158:629–636. doi: 10.1016/j.ahj.2009.06.031
138. Bansal N, Fan D, Hsu CY, Ordonez JD, Marcus GM, Go AS. Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. *Circulation*. 2013;127:569–574. doi: 10.1161/CIRCULATIONAHA.112.123992
139. Chen LY, Sotoodehnia N, Bůžková P, Lopez FL, Yee LM, Heckbert SR, Prineas R, Soliman EZ, Adabag S, Konety S, Folsom AR, Siscovick D, Alonso A. Atrial fibrillation and the risk of sudden cardiac death: the Atherosclerosis Risk in Communities Study and Cardiovascular Health Study. *JAMA Intern Med*. 2013;173:29–35. doi: 10.1001/2013.jamainternmed.744
140. Bardai A, Blom MT, van Hoeijen DA, van Deutekom HW, Brouwer HJ, Tan HL. Atrial fibrillation is an independent risk factor for ventricular fibrillation: a large-scale population-based case-control study. *Circ Arrhythm Electrophysiol*. 2014;7:1033–1039. doi: 10.1161/CIRCEP.114.002094
141. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *BMJ*. 2016;354:i4482. doi: 10.1136/bmj.i4482
142. Ganesan AN, Chew DP, Hartshorne T, Selvanayagam JB, Aylward PE, Sanders P, McGavigan AD. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J*. 2016;37:1591–1602. doi: 10.1093/eurheartj/ehw007
143. Padfield GJ, Steinberg C, Swampillai J, Qian H, Connolly SJ, Dorian P, Green MS, Humphries KH, Klein GJ, Sheldon R, Talajic M, Kerr CR. Progression of paroxysmal to persistent atrial fibrillation: 10-year follow-up in the Canadian Registry of Atrial Fibrillation. *Heart Rhythm*. 2017;14:801–807. doi: 10.1016/j.hrthm.2017.01.038
144. Rahman F, Wang N, Yin X, Ellinor PT, Lubitz SA, LeLorier PA, McManus DD, Sullivan LM, Seshadri S, Vasan RS, Benjamin EJ, Magnani JW. Atrial flutter: clinical risk factors and adverse outcomes in the Framingham Heart Study. *Heart Rhythm*. 2016;13:233–240. doi: 10.1016/j.hrthm.2015.07.031
145. Lin YS, Chen TH, Chi CC, Lin MS, Tung TH, Liu CH, Chen YL, Chen MC. Different implications of heart failure, ischemic stroke, and mortality between nonvalvular atrial fibrillation and atrial flutter: a view from a national cohort study. *J Am Heart Assoc*. 2017;6:e006406. doi: 10.1161/JAHA.117.006406
146. Agency for Healthcare Research and Quality website. Weighted national estimates from HCUP National (Nationwide) Inpatient Sample (NIS), [2014], Agency for Healthcare Research and Quality (AHRQ), based on data collected by individual States and provided to AHRQ by the states. https://www.ahrq.gov/data/hcup/index.html. Accessed November 14, 2018.
147. Centers for Disease Control and Prevention website. National Ambulatory Medical Care Survey: 2015 State and National Summary Tables. https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2015_namcs_web_tables.pdf. Accessed June 14, 2018.
148. Centers for Disease Control and Prevention website. National Hospital Ambulatory Medical Care Survey: 2015 Emergency Department Summary Tables. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2015_ed_web_tables.pdf. Accessed June 14, 2018.
149. Jackson SL, Tong X, Yin X, George MG, Ritchey MD. Emergency department, hospital inpatient, and mortality burden of atrial fibrillation in the United States, 2006 to 2014. *Am J Cardiol*. 2017;120:1966–1973. doi: 10.1016/j.amjcard.2017.08.017
150. Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes*. 2011;4:313–320. doi: 10.1161/CIRCOUTCOMES.110.958165
151. Turakhia MP, Shafrin J, Bognar K, Goldman DP, Mendys PM, Abdulsattar Y, Wiederkehr D, Trocio J. Economic burden of undiagnosed nonvalvular atrial fibrillation in the United States. *Am J Cardiol*. 2015;116:733–739. doi: 10.1016/j.amjcard.2015.05.045
152. Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health*. 2006;9:348–356. doi: 10.1111/j.1524-4733.2006.00124.x
153. Li X, Tse VC, Au-Doung LW, Wong ICK, Chan EW. The impact of ischaemic stroke on atrial fibrillation-related healthcare cost: a systematic review. *Europace*. 2017;19:937–947. doi: 10.1093/europace/euw093
154. Johnsen SP, Dalby LW, Täckström T, Olsen J, Fraschke A. Cost of illness of atrial fibrillation: a nationwide study of societal impact. *BMC Health Serv Res*. 2017;17:714. doi: 10.1186/s12913-017-2652-y
155. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, Seshadri S, Wolf PA, Vasan RS, Benjamin EJ, Levy D. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386:154–162. doi: 10.1016/S0140-6736(14)61774-8
156. Bengtson LG, Chen LY, Chamberlain AM, Michos ED, Whitsel EA, Lutsey PL, Duval S, Rosamond WD, Alonso A. Temporal trends in the occurrence and outcomes of atrial fibrillation in patients with acute myocardial infarction (from the Atherosclerosis Risk in Communities Surveillance Study). *Am J Cardiol*. 2014;114:692–697. doi: 10.1016/j.amjcard.2014.05.059
157. Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, Maclehose R, Konety S, Alonso A. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2011;123:1501–1508. doi: 10.1161/CIRCULATIONAHA.110.009035

158. Zhu W, Yuan P, Shen Y, Wan R, Hong K. Association of smoking with the risk of incident atrial fibrillation: a meta-analysis of prospective studies. *Int J Cardiol*. 2016;218:259–266. doi: 10.1016/j.ijcard.2016.05.013
159. Kwok CS, Anderson SG, Myint PK, Mamas MA, Loke YK. Physical activity and incidence of atrial fibrillation: a systematic review and meta-analysis. *Int J Cardiol*. 2014;177:467–476. doi: 10.1016/j.ijcard.2014.09.104
160. Qureshi WT, Alirhayim Z, Blaha MJ, Juraschek SP, Keteyian SJ, Brawner CA, Al-Mallah MH. Cardiorespiratory fitness and risk of incident atrial fibrillation: results from the Henry Ford Exercise Testing (FIT) Project. *Circulation*. 2015;131:1827–1834. doi: 10.1161/CIRCULATIONAHA.114.014833
161. Asad Z, Abbas M, Javed I, Korantzopoulos P, Stavrakis S. Obesity is associated with incident atrial fibrillation independent of gender: a meta-analysis. *J Cardiovasc Electrophysiol*. 2018;29:725–732. doi: 10.1111/jce.13458
162. Aune D, Sen A, Schlesinger S, Norat T, Janszky I, Romundstad P, Tonstad S, Riboli E, Vatten LJ. Body mass index, abdominal fatness, fat mass and the risk of atrial fibrillation: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol*. 2017;32:181–192. doi: 10.1007/s10654-017-0232-4
163. Chatterjee NA, Giulianini F, Geelhoed B, Lunetta KL, Misialek JR, Niemeijer MN, Rienstra M, Rose LM, Smith AV, Arking DE, Ellinor PT, Heeringa J, Lin H, Lubitz SA, Soliman EZ, Verweij N, Alonso A, Benjamin EJ, Gudnason V, Stricker BHC, Van Der Harst P, Chasman DI, Albert CM. Genetic obesity and the risk of atrial fibrillation: causal estimates from mendelian randomization. *Circulation*. 2017;135:741–754. doi: 10.1161/CIRCULATIONAHA.116.024921
164. Qi W, Zhang N, Korantzopoulos P, Letsas KP, Cheng M, Di F, Tse G, Liu T, Li G. Serum glycated hemoglobin level as a predictor of atrial fibrillation: a systematic review with meta-analysis and meta-regression. *PLoS One*. 2017;12:e0170955. doi: 10.1371/journal.pone.0170955
165. Aune D, Feng T, Schlesinger S, Janszky I, Norat T, Riboli E. Diabetes mellitus, blood glucose and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. *J Diabetes Complications*. 2018;32:501–511. doi: 10.1016/j.jdiacomp.2018.02.004
166. Baumgartner C, da Costa BR, Collet TH, Feller M, Floriani C, Bauer DC, Cappola AR, Heckbert SR, Ceresini G, Gussekloo J, den Elzen WPJ, Peeters RP, Luben R, Völzke H, Dörr M, Walsh JP, Bremner A, Iacoviello M, Macfarlane P, Heeringa J, Stott DJ, Westendorp RGJ, Khaw KT, Magnani JW, Aujesky D, Rodondi N; Thyroid Studies Collaboration. Thyroid function within the normal range, subclinical hypothyroidism, and the risk of atrial fibrillation. *Circulation*. 2017;136:2100–2116. doi: 10.1161/CIRCULATIONAHA.117.028753
167. Alonso A, Lopez FL, Matsushita K, Loehr LR, Agarwal SK, Chen LY, Soliman EZ, Astor BC, Coresh J. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2011;123:2946–2953. doi: 10.1161/CIRCULATIONAHA.111.020982
168. Bansal N, Zelnick LR, Alonso A, Benjamin EJ, de Boer IH, Deo R, Katz R, Kestenbaum B, Mathew J, Robinson-Cohen C, Sarnak MJ, Shlipak MG, Sotoodehnia N, Young B, Heckbert SR. eGFR and albuminuria in relation to risk of incident atrial fibrillation: a meta-analysis of the Jackson Heart Study, the Multi-Ethnic Study of Atherosclerosis, and the Cardiovascular Health Study. *Clin J Am Soc Nephrol*. 2017;12:1386–1398. doi: 10.2215/CJN.01860217
169. Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. *J Am Coll Cardiol*. 2014;64:281–289. doi: 10.1016/j.jacc.2014.03.048
170. Kodama S, Saito K, Tanaka S, Horikawa C, Saito A, Heianza Y, Anasako Y, Nishigaki Y, Yachi Y, Iida KT, Ohashi Y, Yamada N, Sone H. Alcohol consumption and risk of atrial fibrillation: a meta-analysis. *J Am Coll Cardiol*. 2011;57:427–436. doi: 10.1016/j.jacc.2010.08.641
171. May AM, Blackwell T, Stone PH, Stone KL, Cawthon PM, Sauer WH, Varosy PD, Redline S, Mehra R; MrOS Sleep (Outcomes of Sleep Disorders in Older Men) Study Group. Central sleep-disordered breathing predicts incident atrial fibrillation in older men. *Am J Respir Crit Care Med*. 2016;193:783–791. doi: 10.1164/rccm.201508-1523OC
172. Tung P, Levitzky YS, Wang R, Weng J, Quan SF, Gottlieb DJ, Rueschman M, Punjabi NM, Mehra R, Bertisch S, Benjamin EJ, Redline S. Obstructive and central sleep apnea and the risk of incident atrial fibrillation in a community cohort of men and women. *J Am Heart Assoc*. 2017;6:004500. doi: 10.1161/JAHA.116.004500
173. Monrad M, Sajadieh A, Christensen JS, Ketzel M, Raaschou-Nielsen O, Tjønneland A, Overvad K, Loft S, Sørensen M. Long-term exposure to traffic-related air pollution and risk of incident atrial fibrillation: a cohort study. *Environ Health Perspect*. 2017;125:422–427. doi: 10.1289/EHP392
174. Lubitz SA, Yin X, Rienstra M, Schnabel RB, Walkey AJ, Magnani JW, Rahman F, McManus DD, Tadros TM, Levy D, Vasan RS, Larson MG, Ellinor PT, Benjamin EJ. Long-term outcomes of secondary atrial fibrillation in the community: the Framingham Heart Study. *Circulation*. 2015;131:1648–1655. doi: 10.1161/CIRCULATIONAHA.114.014058
175. Walkey AJ, Greiner MA, Heckbert SR, Jensen PN, Piccini JP, Sinner MF, Curtis LH, Benjamin EJ. Atrial fibrillation among Medicare beneficiaries hospitalized with sepsis: incidence and risk factors. *Am Heart J*. 2013;165:949–955.e3. doi: 10.1016/j.ahj.2013.03.020
176. Chebbout R, Heywood EG, Drake TM, Wild JRL, Lee J, Wilson M, Lee MJ. A systematic review of the incidence of and risk factors for postoperative atrial fibrillation following general surgery. *Anaesthesia*. 2018;73:490–498. doi: 10.1111/anae.14118
177. Loomba RS, Buelow MW, Aggarwal S, Arora RR, Kovach J, Ginde S. Arrhythmias in adults with congenital heart disease: what are risk factors for specific arrhythmias? *Pacing Clin Electrophysiol*. 2017;40:353–361. doi: 10.1111/pace.12983
178. Garg PK, O'Neal WT, Ogunsua A, Thacker EL, Howard G, Soliman EZ, Cushman M. Usefulness of the American Heart Association's Life Simple 7 to predict the risk of atrial fibrillation (from the REasons for Geographic And Racial Differences in Stroke [REGARDS] Study). *Am J Cardiol*. 2018;121:199–204. doi: 10.1016/j.amjcard.2017.09.033
179. Chamberlain AM, Agarwal SK, Folsom AR, Soliman EZ, Chambless LE, Crow R, Ambrose M, Alonso A. A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol*. 2011;107:85–91. doi: 10.1016/j.amjcard.2010.08.049
180. Schnabel RB, Aspelund T, Li G, Sullivan LM, Suchy-Dicey A, Harris TB, Pencina MJ, D'Agostino RB Sr, Levy D, Kannel WB, Wang TJ, Kronmal RA, Wolf PA, Burke GL, Launer LJ, Vasan RS, Psaty BM, Benjamin EJ, Gudnason V, Heckbert SR. Validation of an atrial fibrillation risk algorithm in whites and African Americans. *Arch Intern Med*. 2010;170:1909–1917. doi: 10.1001/archinternmed.2010.434
181. Everett BM, Cook NR, Conen D, Chasman DI, Ridker PM, Albert CM. Novel genetic markers improve measures of atrial fibrillation risk prediction. *Eur Heart J*. 2013;34:2243–2251. doi: 10.1093/eurheartj/eht033
182. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, Sinner MF, Sotoodehnia N, Fontes JD, Janssens AC, Kronmal RA, Magnani JW, Witteman JC, Chamberlain AM, Lubitz SA, Schnabel RB, Agarwal SK, McManus DD, Ellinor PT, Larson MG, Burke GL, Launer LJ, Hofman A, Levy D, Gottdiener JS, Kääb S, Couper D, Harris TB, Soliman EZ, Stricker BH, Gudnason V, Heckbert SR, Benjamin EJ. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc*. 2013;2:e000102. doi: 10.1161/JAHA.112.000102
183. Shulman E, Kargoli F, Aagaard P, Hoch E, Di Biase L, Fisher J, Gross J, Kim S, Krumerman A, Ferrick KJ. Validation of the Framingham Heart Study and CHARGE-AF risk scores for atrial fibrillation in Hispanics, African-Americans, and non-Hispanic whites. *Am J Cardiol*. 2016;117:76–83. doi: 10.1016/j.amjcard.2015.10.009
184. Alonso A, Roetker NS, Soliman EZ, Chen LY, Greenland P and Heckbert SR. Prediction of atrial fibrillation in a racially diverse cohort: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Am Heart Assoc*. 2016;5:e003077. doi: 10.1161/JAHA.115.003077
185. Pfister R, Brägelmann J, Michels G, Wareham NJ, Luben R, Khaw KT. Performance of the CHARGE-AF risk model for incident atrial fibrillation in the EPIC Norfolk cohort. *Eur J Prev Cardiol*. 2015;22:932–939. doi: 10.1177/2047487314544045
186. Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinchak R, Cook J, Paraschos A, Love J, Radoslovich G, Lee KL, Lamas GA; for the MOST Investigators. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST). *Circulation*. 2003;107:1614–1619. doi: 10.1161/01.CIR.0000057981.70380.45
187. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, Miller C, Qi D, Ziegler PD. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol*. 2009;2:474–480. doi: 10.1161/CIRCEP.109.849638
188. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH; ASSERT Investigators. Subclinical

atrial fibrillation and the risk of stroke [published correction appears in *N Engl J Med*. 2016;374:998]. *N Engl J Med*. 2012;366:120–129. doi: 10.1056/NEJMoa1105575
189. Boriani G, Glotzer TV, Santini M, West TM, De Melis M, Sepsi M, Gasparini M, Lewalter T, Camm JA, Singer DE. Device-detected atrial fibrillation and risk for stroke: an analysis of >10,000 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices). *Eur Heart J*. 2014;35:508–516. doi: 10.1093/eurheartj/eht491
190. Turakhia MP, Ziegler PD, Schmitt SK, Chang Y, Fan J, Than CT, Keung EK, Singer DE. Atrial fibrillation burden and short-term risk of stroke: case-crossover analysis of continuously recorded heart rhythm from cardiac electronic implanted devices. *Circ Arrhythm Electrophysiol*. 2015;8:1040–1047. doi: 10.1161/CIRCEP.114.003057
191. Turakhia MP, Shafrin J, Bognar K, Trocio J, Abdulsattar Y, Wiederkehr D, Goldman DP. Estimated prevalence of undiagnosed atrial fibrillation in the United States. *PLoS One*. 2018;13:e0195088. doi: 10.1371/journal.pone.0195088
192. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, Albert CM, Anderson CS, Antoniou S, Benjamin EJ, Boriani G, Brachmann J, Brandes A, Chao TF, Conen D, Engdahl J, Fauchier L, Fitzmaurice DA, Friberg L, Gersh BJ, Gladstone DJ, Glotzer TV, Gwynne K, Hankey GJ, Harbison J, Hillis GS, Hills MT, Kamel H, Kirchhof P, Kowey PR, Krieger D, Lee VWY, Levin LÅ, Lip GYH, Lobban T, Lowres N, Mairesse GH, Martinez C, Neubeck L, Orchard J, Piccini JP, Poppe K, Potpara TS, Puererfellner H, Rienstra M, Sandhu RK, Schnabel RB, Siu CW, Steinhubl S, Svendsen JH, Svennberg E, Themistoclakis S, Tieleman RG, Turakhia MP, Tveit A, Uittenbogaart SB, Van Gelder IC, Verma A, Wachter R, Yan BP; AF-Screen Collaborators. Screening for atrial fibrillation: a report of the AF-SCREEN International Collaboration. *Circulation*. 2017;135:1851–1867. doi: 10.1161/CIRCULATIONAHA.116.026693
193. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J, Bennett AA, Briffa T, Bauman A, Martinez C, Wallenhorst C, Lau JK, Brieger DB, Sy RW, Freedman SB. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies: the SEARCH-AF study. *Thromb Haemost*. 2014;111:1167–1176. doi: 10.1160/TH14-03-0231
194. McManus DD, Lee J, Maitas O, Esa N, Pidikiti R, Carlucci A, Harrington J, Mick E, Chon KH. A novel application for the detection of an irregular pulse using an iPhone 4S in patients with atrial fibrillation. *Heart Rhythm*. 2013;10:315–319. doi: 10.1016/j.hrthm.2012.12.001
195. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation: the STROKESTOP Study. *Circulation*. 2015;131:2176–2184. doi: 10.1161/CIRCULATIONAHA.114.014343
196. Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation: a systematic review. *Thromb Haemost*. 2013;110:213–222. doi: 10.1160/TH13-02-0165
197. Moran PS, Flattery MJ, Teljeur C, Ryan M, Smith SM. Effectiveness of systematic screening for the detection of atrial fibrillation. *Cochrane Database Syst Rev*. 2013;4:CD009586. doi: 10.1002/14651858.CD009586.pub2
198. Wolff L. Familial auricular fibrillation. *N Engl J Med*. 1943;229:396–398.
199. Fox CS, Parise H, D'Agostino RB Sr, Lloyd-Jones DM, Vasan RS, Wang TJ, Levy D, Wolf PA, Benjamin EJ. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. *JAMA*. 2004;291:2851–2855. doi: 10.1001/jama.291.23.2851
200. Lubitz SA, Yin X, Fontes JD, Magnani JW, Rienstra M, Pai M, Villalon ML, Vasan RS, Pencina MJ, Levy D, Larson MG, Ellinor PT, Benjamin EJ. Association between familial atrial fibrillation and risk of new-onset atrial fibrillation. *JAMA*. 2010;304:2263–2269. doi: 10.1001/jama.2010.1690
201. Zöller B, Ohlsson H, Sundquist J, Sundquist K. High familial risk of atrial fibrillation/atrial flutter in multiplex families: a nationwide family study in Sweden. *J Am Heart Assoc*. 2012;2:e003384. doi: 10.1161/JAHA.112.003384
202. Chang SH, Kuo CF, Chou IJ, See LC, Yu KH, Luo SF, Huang LH, Zhang W, Doherty M, Wen MS, Kuo CT, Yeh YH. Association of a family history of atrial fibrillation with incidence and outcomes of atrial fibrillation: a population-based family cohort study. *JAMA Cardiol*. 2017;2:863–870. doi: 10.1001/jamacardio.2017.1855
203. Weng LC, Choi SH, Klarin D, Smith JG, Loh PR, Chaffin M, Roselli C, Hulme OL, Lunetta KL, Dupuis J, Benjamin EJ, Newton-Cheh C, Kathiresan S, Ellinor PT, Lubitz SA. Heritability of atrial fibrillation. *Circ Cardiovasc Genet*. 2017;10:e001838–2015. doi: 10.1161/CIRCGENETICS.117.001838
204. Marcus GM, Alonso A, Peralta CA, Lettre G, Vittinghoff E, Lubitz SA, Fox ER, Levitzky YS, Mehra R, Kerr KF, Deo R, Sotoodehnia N, Akylbekova M, Ellinor PT, Paltoo DN, Soliman EZ, Benjamin EJ, Heckbert SR; for the Candidate-Gene Association Resource (CARe) Study. European ancestry as a risk factor for atrial fibrillation in African Americans. *Circulation*. 2010;122:2009–2015. doi: 10.1161/CIRCULATIONAHA.110.958306
205. Christophersen IE, Rienstra M, Roselli C, Yin X, Geelhoed B, Barnard J, Lin H, Arking DE, Smith AV, Albert CM, Chaffin M, Tucker NR, Li M, Klarin D, Bihlmeyer NA, Low SK, Weeke PE, Müller-Nurasyid M, Smith JG, Brody JA, Niemeijer MN, Dörr M, Trompet S, Huffman J, Gustafsson S, Schurmann C, Kleber ME, Lyytikäinen LP, Seppälä I, Malik R, Horimoto ARVR, Perez M, Sinisalo J, Aeschbacher S, Thériault S, Yao J, Radmanesh F, Weiss S, Teumer A, Choi SH, Weng LC, Clauss S, Deo R, Rader DJ, Shah SH, Sun A, Hopewell JC, Debette S, Chauhan G, Yang Q, Worrall BB, Paré G, Kamatani Y, Hagemeijer YP, Verweij N, Siland JE, Kubo M, Smith JD, Van Wagoner DR, Bis JC, Perz S, Psaty BM, Ridker PM, Magnani JW, Harris TB, Launer LJ, Shoemaker MB, Padmanabhan S, Haessler J, Bartz TM, Waldenberger M, Lichtner P, Arendt M, Krieger JE, Kähönen M, Risch L, Mansur AJ, Peters A, Smith BH, Lind L, Scott SA, Lu Y, Bottinger EB, Hernesniemi J, Lindgren CM, Wong JA, Huang J, Eskola M, Morris AP, Ford I, Reiner AP, Delgado G, Chen LY, Chen YI, Sandhu RK, Li M, Boerwinkle E, Eisele L, Lannfelt L, Rost N, Anderson CD, Taylor KD, Campbell A, Magnusson PK, Porteous D, Hocking LJ, Vlachopoulou E, Pedersen NL, Nikus K, Orho-Melander M, Hamsten A, Heeringa J, Denny JC, Kriebel J, Darbar D, Newton-Cheh C, Shaffer C, Macfarlane PW, Heilmann-Heimbach S, Almgren P, Huang PL, Sotoodehnia N, Soliman EZ, Uitterlinden AG, Hofman A, Franco OH, Völker U, Jöckel KH, Sinner MF, Lin HJ, Guo X, Dichgans M, Ingelsson E, Kooperberg C, Melander O, Loos RJF, Laurikka J, Conen D, Rosand J, van der Harst P, Lokki ML, Kathiresan S, Pereira A, Jukema JW, Hayward C, Rotter JI, März W, Lehtimäki T, Stricker BH, Chung MK, Felix SB, Gudnason V, Alonso A, Roden DM, Kääb S, Chasman DI, Heckbert SR, Benjamin EJ, Tanaka T, Lunetta KL, Lubitz SA, Ellinor PT; METASTROKE Consortium of the ISGC; Neurology Working Group of the CHARGE Consortium; AFGen Consortium. Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation [published correction appears in *Nat Genet*. 2017;49:1286]. *Nat Genet*. 2017;49:946–952. doi: 10.1038/ng.3843
206. Low SK, Takahashi A, Ebana Y, Ozaki K, Christophersen IE, Ellinor PT, Ogishima S, Yamamoto M, Satoh M, Sasaki M, Yamaji T, Iwasaki M, Tsugane S, Tanaka K, Naito M, Wakai K, Tanaka H, Furukawa T, Kubo M, Ito K, Kamatani Y, Tanaka T; AFGen Consortium. Identification of six new genetic loci associated with atrial fibrillation in the Japanese population. *Nat Genet*. 2017;49:953–958. doi: 10.1038/ng.3842
207. Roselli C, Chaffin MD, Weng LC, Aeschbacher S, Ahlberg G, Albert CM, Almgren P, Alonso A, Anderson CD, Aragam KG, Arking DE, Barnard J, Bartz TM, Benjamin EJ, Bihlmeyer NA, Bis JC, Bloom HL, Boerwinkle E, Bottinger EB, Brody JA, Calkins H, Campbell A, Cappola TP, Carlquist J, Chasman DI, Chen LY, Chen YI, Choi EK, Choi SH, Christophersen IE, Chung MK, Cole JW, Conen D, Cook J, Crijns HJ, Cutler MJ, Damrauer SM, Daniels BR, Darbar D, Delgado G, Denny JC, Dichgans M, Dörr M, Dudink EA, Dudley SC, Esa N, Esko T, Eskola M, Fatkin D, Felix SB, Ford I, Franco OH, Geelhoed B, Grewal RP, Gudnason V, Guo X, Gupta N, Gustafsson S, Gutmann R, Hamsten A, Harris TB, Hayward C, Heckbert SR, Hernesniemi J, Hocking LJ, Hofman A, Horimoto ARVR, Huang J, Huang PL, Huffman J, Ingelsson E, Ipek EG, Ito K, Jimenez-Conde J, Johnson R, Jukema JW, Kääb S, Kähönen M, Kamatani Y, Kane JP, Kastrati A, Kathiresan S, Katschnig-Winter P, Kavousi M, Kessler T, Kietselaer BL, Kirchhof P, Kleber ME, Knight S, Krieger JE, Kubo M, Launer LJ, Laurikka J, Lehtimäki T, Leineweber K, Lemaitre RN, Li M, Lim HE, Lin HJ, Lin H, Lind L, Lindgren CM, Lokki ML, London B, Loos RJF, Low SK, Lu Y, Lyytikäinen LP, Macfarlane PW, Magnusson PK, Mahajan A, Malik R, Mansur AJ, Marcus GM, Margolin L, Margulies KB, März W, McManus DD, Melander O, Mohanty S, Montgomery JA, Morley MP, Morris AP, Müller-Nurasyid M, Natale A, Nazarian S, Neumann B, Newton-Cheh C, Niemeijer MN, Nikus K, Nilsson P, Noordam R, Oellers H, Olesen MS, Orho-Melander M, Padmanabhan S, Pak HN, Paré G, Pedersen NL, Pera J, Pereira A, Porteous D, Psaty BM, Pulit SL, Pullinger CR, Rader DJ, Refsgaard L, Ribasés M, Ridker PM, Rienstra M, Risch L, Roden DM, Rosand J, Rosenberg MA, Rost N, Rotter JI, Saba S, Sandhu RK, Schnabel RB, Schramm K, Schunkert H, Schurman C, Scott SA, Seppälä I, Shaffer C, Shah S, Shalaby AA, Shim J, Shoemaker MB, Siland JE, Sinisalo J, Sinner MF, Slowik A, Smith AV, Smith BH, Smith JG, Smith JD, Smith NL, Soliman EZ, Sotoodehnia N, Stricker BH, Sun A, Sun H, Svendsen JH, Tanaka T, Tanriverdi K, Taylor KD, Teder-Laving M, Teumer A, Thériault S, Trompet S, Tucker NR, Tveit

A, Uitterlinden AG, Van Der Harst P, Van Gelder IC, Van Wagoner DR, Verweij N, Vlachopoulou E, Völker U, Wang B, Weeke PE, Weijs B, Weiss R, Weiss S, Wells QS, Wiggins KL, Wong JA, Woo D, Worrall BB, Yang PS, Yao J, Yoneda ZT, Zeller T, Zeng L, Lubitz SA, Lunetta KL, Ellinor PT. Multi-ethnic genome-wide association study for atrial fibrillation. *Nat Genet*. 2018;50:1225–1233. doi: 10.1038/s41588-018-0133-9
208. Gudbjartsson DF, Helgason H, Gudjonsson SA, Zink F, Oddson A, Gylfason A, Besenbacher S, Magnusson G, Halldorsson BV, Hjartarson E, Sigurdsson GT, Stacey SN, Frigge ML, Holm H, Saemundsdottir J, Helgadottir HT, Johannsdottir H, Sigfusson G, Thorgeirsson G, Sverrisson JT, Gretarsdottir S, Walters GB, Rafnar T, Thjodleifsson B, Bjornsson ES, Olafsson S, Thorarinsdottir H, Steingrimsdottir T, Gudmundsdottir TS, Theodors A, Jonasson JG, Sigurdsson A, Bjornsdottir G, Jonsson JJ, Thorarensen O, Ludvigsson P, Gudbjartsson H, Eyjolfsson GI, Sigurdardottir O, Olafsson I, Arnar DO, Magnusson OT, Kong A, Masson G, Thorsteinsdottir U, Helgason A, Sulem P, Stefansson K. Large-scale whole-genome sequencing of the Icelandic population. *Nat Genet*. 2015;47:435–444. doi: 10.1038/ng.3247
209. Lubitz SA, Parsons OE, Anderson CD, Benjamin EJ, Malik R, Weng LC, Dichgans M, Sudlow CL, Rothwell PM, Rosand J, Ellinor PT, Markus HS, Traylor M; on behalf of the WTCCC2, International Stroke Genetics Consortium, and AFGen Consortia. Atrial fibrillation genetic risk and ischemic stroke mechanisms. *Stroke*. 2017;48:1451–1456. doi: 10.1161/STROKEAHA.116.016198
210. Jamaly S, Carlsson L, Peltonen M, Jacobson P, Sjöström L, Karason K. Bariatric surgery and the risk of new-onset atrial fibrillation in Swedish obese subjects. *J Am Coll Cardiol*. 2016;68:2497–2504. doi: 10.1016/j.jacc.2016.09.940
211. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, Kalman JM, Abhayaratna WP, Sanders P. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol*. 2014;64:2222–2231. doi: 10.1016/j.jacc.2014.09.028
212. Pathak RK, Evans M, Middeldorp ME, Mahajan R, Mehta AB, Meredith M, Twomey D, Wong CX, Hendriks JML, Abhayaratna WP, Kalman JM, Lau DH, Sanders P. Cost-effectiveness and clinical effectiveness of the risk factor management clinic in atrial fibrillation: the CENT Study. *JACC Clin Electrophysiol*. 2017;3:436–447. doi: 10.1016/j.jacep.2016.12.015
213. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, Twomey D, Elliott AD, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). *J Am Coll Cardiol*. 2015;65:2159–2169. doi: 10.1016/j.jacc.2015.03.002
214. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Hendriks JM, Twomey D, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: the CARDIO-FIT Study. *J Am Coll Cardiol*. 2015;66:985–996. doi: 10.1016/j.jacc.2015.06.488
215. Holmqvist F, Guan N, Zhu Z, Kowey PR, Allen LA, Fonarow GC, Hylek EM, Mahaffey KW, Freeman JV, Chang P, Holmes DN, Peterson ED, Piccini JP, Gersh BJ. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation: results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J*. 2015;169:647–654.e2. doi: 10.1016/j.ahj.2014.12.024
216. Qureshi WT, Nasir UB, Alqalyoobi S, O'Neal WT, Mawri S, Sabbagh S, Soliman EZ, Al-Mallah MH. Meta-analysis of continuous positive airway pressure as a therapy of atrial fibrillation in obstructive sleep apnea. *Am J Cardiol*. 2015;116:1767–1773. doi: 10.1016/j.amjcard.2015.08.046
217. Hess PL, Kim S, Piccini JP, Allen LA, Ansell JE, Chang P, Freeman JV, Gersh BJ, Kowey PR, Mahaffey KW, Thomas L, Peterson ED, Fonarow GC. Use of evidence-based cardiac prevention therapy among outpatients with atrial fibrillation. *Am J Med*. 2013;126:625–32.e1. doi: 10.1016/j.amjmed.2013.01.037
218. O'Brien EC, Simon DN, Allen LA, Singer DE, Fonarow GC, Kowey PR, Thomas LE, Ezekowitz MD, Mahaffey KW, Chang P, Piccini JP, Peterson ED. Reasons for warfarin discontinuation in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J*. 2014;168:487–494. doi: 10.1016/j.ahj.2014.07.002
219. Silberberg A, Tan MK, Yan AT, Angaran P, Dorian P, Bucci C, Gregoire JC, Bell AD, Gladstone DJ, Green MS, Gross PL, Skanes A, Demchuk AM, Kerr CR, Mitchell LB, Cox JL, Talajic M, Essebag V, Heilbron B, Ramanathan K, Fournier C, Wheeler BH, Lin PJ, Berall M, Langer A, Goldin L, Goodman SG; FREEDOM AF and CONNECT AF Investigators. Use of evidence-based therapy for cardiovascular risk factors in Canadian outpatients with atrial fibrillation: from the Facilitating Review and Education to Optimize Stroke Prevention in Atrial Fibrillation (FREEDOM AF) and Co-ordinated National Network to Engage Physicians in the Care and Treatment of Patients With Atrial Fibrillation (CONNECT AF). *Am J Cardiol*. 2017;120:582–587. doi: 10.1016/j.amjcard.2017.05.027
220. Alonso A, Bahnson JL, Gaussoin SA, Bertoni AG, Johnson KC, Lewis CE, Vetter M, Mantzoros CS, Jeffery RW, Soliman EZ; Look AHEAD Research Group. Effect of an intensive lifestyle intervention on atrial fibrillation risk in individuals with type 2 diabetes: the Look AHEAD randomized trial. *Am Heart J*. 2015;170:770–777.e5. doi: 10.1016/j.ahj.2015.07.026
221. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, Lorimer MF, Lau DH, Antic NA, Brooks AG, Abhayaratna WP, Kalman JM, Sanders P. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA*. 2013;310:2050–2060. doi: 10.1001/jama.2013.280521
222. Emdin CA, Callender T, Cao J, Rahimi K. Effect of antihypertensive agents on risk of atrial fibrillation: a meta-analysis of large-scale randomized trials. *Europace*. 2015;17:701–710. doi: 10.1093/europace/euv021
223. Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, Connolly SJ. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol*. 2005;45:1832–1839. doi: 10.1016/j.jacc.2004.11.070
224. Swedberg K, Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Shi H, Vincent J, Pitt B; EMPHASIS-HF Study Investigators. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study. *J Am Coll Cardiol*. 2012;59:1598–1603. doi: 10.1016/j.jacc.2011.11.063
225. Martínez-González MÁ, Toledo E, Arós F, Fiol M, Corella D, Salas-Salvadó J, Ros E, Covas MI, Fernández-Crehuet J, Lapetra J, Muñoz MA, Fitó M, Serra-Majem L, Pintó X, Lamuela-Raventós RM, Sorlí JV, Babio N, Buil-Cosiales P, Ruiz-Gutierrez V, Estruch R, Alonso A; PREDIMED Investigators. Extravirgin olive oil consumption reduces risk of atrial fibrillation: the PREDIMED (Prevención con Dieta Mediterránea) trial. *Circulation*. 2014;130:18–26. doi: 10.1161/CIRCULATIONAHA.113.006921
226. Rahimi K, Emberson J, McGale P, Majoni W, Merhi A, Asselbergs FW, Krane V, Macfarlane PW; PROSPER Executive. Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials. *BMJ*. 2011;342:d1250. doi: 10.1136/bmj.d1250
227. Meschia JF, Merrill P, Soliman EZ, Howard VJ, Barrett KM, Zakai NA, Kleindorfer D, Safford M, Howard G. Racial disparities in awareness and treatment of atrial fibrillation: the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Stroke*. 2010;41:581–587. doi: 10.1161/STROKEAHA.109.573907
228. O'Neal WT, Efird JT, Judd SE, McClure LA, Howard VJ, Howard G, Soliman EZ. Impact of awareness and patterns of nonhospitalized atrial fibrillation on the risk of mortality: the Reasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *Clin Cardiol*. 2016;39:103–110. doi: 10.1002/clc.22501
229. Reading SR, Go AS, Fang MC, Singer DE, Liu IA, Black MH, Udaltsova N, Reynolds K; for the Anticoagulation and Risk Factors in Atrial Fibrillation–Cardiovascular Research Network (ATRIA-CVRN) Investigators. Health literacy and awareness of atrial fibrillation. *J Am Heart Assoc*. 2017;6:e005128. doi: 10.1161/JAHA.116.005128
230. Baczek VL, Chen WT, Kluger J, Coleman CI. Predictors of warfarin use in atrial fibrillation in the United States: a systematic review and meta-analysis. *BMC Fam Pract*. 2012;13:5. doi: 10.1186/1471-2296-13-5
231. Gamra H, Murin J, Chiang CE, Naditch-Brûlé L, Brette S, Steg PG; RealiseAF investigators. Use of antithrombotics in atrial fibrillation in Africa, Europe, Asia and South America: insights from the International RealiseAF Survey. *Arch Cardiovasc Dis*. 2014;107:77–87. doi: 10.1016/j.acvd.2014.01.001
232. Xian Y, O'Brien EC, Liang L, Xu H, Schwamm LH, Fonarow GC, Bhatt DL, Smith EE, Olson DM, Maisch L, Hannah D, Lindholm B, Lytle BL, Pencina MJ, Hernandez AF, Peterson ED. Association of preceding antithrombotic treatment with acute ischemic stroke severity and in-hospital outcomes among patients with atrial fibrillation. *JAMA*. 2017;317:1057–1067. doi: 10.1001/jama.2017.1371
233. Penado S, Cano M, Acha O, Hernández JL, Riancho JA. Atrial fibrillation as a risk factor for stroke recurrence. *Am J Med*. 2003;114:206–210.

234. Hsu JC, Maddox TM, Kennedy KF, Katz DF, Marzec LN, Lubitz SA, Gehi AK, Turakhia MP, Marcus GM. Oral anticoagulant therapy prescription in patients with atrial fibrillation across the spectrum of stroke risk: insights from the NCDR PINNACLE Registry. *JAMA Cardiol*. 2016;1:55–62. doi: 10.1001/jamacardio.2015.0374
235. Marzec LN, Wang J, Shah ND, Chan PS, Ting HH, Gosch KL, Hsu JC, Maddox TM. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. *J Am Coll Cardiol*. 2017;69:2475–2484. doi: 10.1016/j.jacc.2017.03.540
236. Thompson LE, Maddox TM, Lei L, Grunwald GK, Bradley SM, Peterson PN, Masoudi FA, Turchin A, Song Y, Doros G, Davis MB, Daugherty SL. Sex differences in the use of oral anticoagulants for atrial fibrillation: a report from the National Cardiovascular Data Registry (NCDR) PINNACLE Registry. *J Am Heart Assoc*. 2017;6:e005801. doi: 10.1161/JAHA.117.005801
237. Yong CM, Liu Y, Apruzzese P, Doros G, Cannon CP, Maddox TM, Gehi A, Hsu JC, Lubitz SA, Virani S, Turakhia MP; ACC PINNACLE Investigators. Association of insurance type with receipt of oral anticoagulation in insured patients with atrial fibrillation: a report from the American College of Cardiology NCDR PINNACLE registry. *Am Heart J*. 2018;195:50–59. doi: 10.1016/j.ahj.2017.08.010
238. Carlsson AC, Wändell P, Gasevic D, Sundquist J, Sundquist K. Neighborhood deprivation and warfarin, aspirin and statin prescription: a cohort study of men and women treated for atrial fibrillation in Swedish primary care. *Int J Cardiol*. 2015;187:547–552. doi: 10.1016/j.ijcard.2015.04.005
239. O'Neal WT, Sandesara PB, Kelli HM, Venkatesh S, Soliman EZ. Urban-rural differences in mortality for atrial fibrillation hospitalizations in the United States. *Heart Rhythm*. 2018;15:175–179. doi: 10.1016/j.hrthm.2017.10.019
240. Gallagher C, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Hendriks JML. Integrated care in atrial fibrillation: a systematic review and meta-analysis. *Heart*. 2017;103:1947–1953. doi: 10.1136/heartjnl-2016-310952
241. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129:837–847. doi: 10.1161/CIRCULATIONAHA.113.005119
242. Global Burden of Disease Study 2016. Global Burden of Disease Study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed May 1, 2018.
243. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J, Commerford P, Jansky P, Avezum A, Sigamani A, Damasceno A, Reilly P, Grinvalds A, Nakamya J, Aje A, Almahmeed W, Moriarty A, Wallentin L, Yusuf S, Connolly SJ; RE-LY Atrial Fibrillation Registry and Cohort Study Investigators. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study [published correction appears in *Lancet*. 2017;389:602]. *Lancet*. 2016;388:1161–1169. doi: 10.1016/S0140-6736(16)30968-0

17. SUDDEN CARDIAC ARREST, VENTRICULAR ARRHYTHMIAS, AND INHERITED CHANNELOPATHIES

See Tables 17-1 through 17-5 and Charts 17-1 through 17-4

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Cardiac Arrest (Including VF and Ventricular Flutter) *ICD-9* 427.4, 427.5; *ICD-10* I46.0, I46.1, I46.9, I49.0.

2016: Mortality—17 661. Any-mention mortality—366 494.

Abbreviations Used in Chapter 17

AED	automated external defibrillator
AF	atrial fibrillation
AHA	American Heart Association
AMI	acute myocardial infarction
ARIC	Atherosclerosis Risk in Communities Study
ARVC	arrhythmogenic right ventricular cardiomyopathy
AV	atrioventricular
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CARES	Cardiac Arrest Registry to Enhance Survival
CASQ2	calsequestrin 2
CHS	Cardiovascular Health Study
CI	confidence interval
CLRD	chronic lower respiratory disease
CPC	Cerebral Performance Index
CPR	cardiopulmonary resuscitation
CPVT	catecholaminergic polymorphic ventricular tachycardia
CVD	cardiovascular disease
DCM	dilated cardiomyopathy
DM	diabetes mellitus
ECG	electrocardiogram
ED	emergency department
eGFR	estimated glomerular filtration rate
EMS	emergency medical services
ERP	early repolarization pattern
GWAS	genome-wide association studies
GWTG	Get With The Guidelines
HCM	hypertrophic cardiomyopathy
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
ICD-10	*International Classification of Diseases, 10th Revision*
ICU	intensive care unit
IHCA	in-hospital cardiac arrest
IQR	interquartile range
IRR	incidence rate ratio
KD	Kawasaki disease

(*Continued*)

Abbreviations Used in Chapter 17 Continued

LQTS	long-QT syndrome
LV	left ventricular
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MI	myocardial infarction
NH	non-Hispanic
NIS	National (Nationwide) Inpatient Sample
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
PEA	pulseless electrical activity
PVC	premature ventricular contraction
PVT	polymorphic ventricular tachycardia
QTc	corrected QT interval
RMVT	repetitive monomorphic ventricular tachycardia
ROC	Resuscitation Outcomes Consortium
RR	relative risk
RV	right ventricular
RYR2	ryanodine receptor 2
SBP	systolic blood pressure
SCA	sudden cardiac arrest
SCD	sudden cardiac death
SD	standard deviation
SE	standard error
STEMI	ST-segment–elevation myocardial infarction
SUDS	Sudden Unexpected Death Study
TdP	torsade de pointes
VF	ventricular fibrillation
VT	ventricular tachycardia
WPW	Wolff-Parkinson-White

Tachycardia *ICD-9* 427.0, 427.1, 427.2; *ICD-10* I47.1, I47.2, I47.9.

2016: Mortality—957. Any-mention mortality—7563.

2014: Hospital discharges— 64 000 (42 000 male, 22 000 female).

Cardiac arrest is the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation.[1] An operational definition of SCA is unexpected cardiac arrest that results in attempts to restore circulation. If resuscitation attempts are unsuccessful, this situation is referred to as SCD. SCA results from many disease processes; a consensus statement by the International Liaison Committee on Resuscitation recommends categorizing cardiac arrest into events with external causes (drowning, trauma, asphyxia, electrocution, and drug overdose) or medical causes.[2] Because of fundamental differences in underlying pathogenesis and the system of care, epidemiological data for OHCA and IHCA are collected and reported separately. For similar reasons, data for infants (aged <1 year), children (aged 1–18 years), and adults are reported separately.

- In a Swedish registry of 70 846 OHCAs from 1992 to 2014, 92% of cases had medical causes. Among nonmedical cases, trauma was the most common cause.[3]
- Adjudication of cause of death in 179 cases of SCA in middle school, high school, college, and

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professional athletes from 2014 to 2016 identified a cause in 117 (65.4%): HCM (16.2%), coronary artery anomalies (13.7%), idiopathic cardiomyopathy (11.1%), autopsy-negative sudden unexplained death (6.8%), WPW syndrome (6.8%). and LQTS (6.0%).[4]

Incidence (See Tables 17-1 through 17-5)

- The ROC clinical trial network maintained a registry of EMS-assessed and EMS-treated OHCA in multiple regions of the United States from 2005 to 2015 (Table 17-1).
- The ongoing CARES registry estimates the incidence of EMS-treated OHCA among individuals of any age in >1400 EMS agencies in the United States (Tables 17-1 through 17-4).
- Incidence of EMS-assessed OHCA in people of any age is 110.8 individuals per 100 000 population (95% CI, 108.9–112.6), or 356 461 people (quasi CI, 350 349–362 252), based on extrapolation from the ROC registry of OHCA (ROC Investigators, unpublished data, July 7, 2016) to the total population of the United States (325 193 000 as of June 9, 2017).[5]
- Incidence of EMS-treated OHCA of suspected cardiac cause in people of any age is 57 individuals per 100 000 population, based on the CARES registry of EMS-treated OHCA.[6]
- Among 3 686 296 hospital discharges from academic medical centers in 2012, 33 700 (0.91%) included a cardiac arrest diagnosis.[7]
- In the NIS for 2014, the weighted national estimate of hospital discharges that included *ICD-9-CM* codes for CPR was 116 205 (SE, 2055; incidence rate, 36 [SE, 0.6] per 100 000 people) (ROC Investigators, unpublished data, July 7, 2016).[8]
- In the National Emergency Department Sample for 2014, the weighted national estimate of ED visits that included a diagnosis of "cardiac arrest or ventricular fibrillation" was 405 200 (incidence rate, 127 per 100 000 people).[8]

OHCA: Adults (See Table 17-2)

- Incidence of EMS-assessed OHCA in adults is 140.7 individuals per 100 000 population (95% CI, 138.3–143.1), or 347 322 adults (95% CI, 341 397–353 246) based on extrapolation from the ROC registry of OHCA to the total population of the United States (ROC Investigators, unpublished data, July 7, 2016).[5]
- Incidence of EMS-treated OHCA in adults was 73.0 individuals per 100 000 population (95% CI, 71.2–74.7), or 180 202 adults (95% CI, 175 759–184 399) in the ROC registry. Approximately 52% of EMS-assessed adult OHCA had resuscitation attempted (ROC Investigators, unpublished data, July 7, 2016).
- In 2015, the incidence of EMS-treated OHCA was 66 per 100 000. Incidence of EMS-treated OHCA with initial shockable rhythm was 13.5 per 100 000 (ROC Investigators, unpublished data, July 7, 2016).
- Ten ambulance services serving almost 54 000 000 residents of England attended 28 729 EMS-treated cardiac arrests in 2014 (annual incidence 53 per 100 000 residents).[9]
- Location of OHCA in adults is most often a home or residence (69.5%), followed by public settings (18.8%) and nursing homes (11.7%) (Table 17-2).[10] OHCA in adults is witnessed by a layperson in 37% of cases or by an EMS provider in 12% of cases. For 51% of cases, collapse is not witnessed.[10]
- Initial recorded cardiac rhythm was VF or VT or shockable by an AED in 18.7% of EMS-treated OHCAs in 2017 (Table 17-2).
- Of 4729 patients with STEMI in Los Angeles County, CA, from 2011 to 2014, 422 (9%) had OHCA.[11]

IHCA: Adults (See Table 17-2)

- Incidence of IHCA is 209 000 people each year based on extrapolation of 2003 to 2007 GWTG data to the total population of hospitalized patients in the United States.[12]
- Incidence of adult IHCA events was a mean of 8.27 (SD, 10.01) per 1000 hospital admissions and 1.56 (SD, 1.36) per 1000 inpatient days in the 2017 GWTG data (GWTG–Resuscitation, unpublished data, 2017).
- Incidence of IHCA was 1.6 per 1000 hospital admissions, with a median across hospitals of 1.5 (IQR, 1.2–2.2) in the UK National Cardiac Arrest Audit database between 2011 and 2013 (144 hospitals and 22 628 patients ≥16 years of age).[13]
- IHCA incidence was 2.85 per 1000 hospital admissions, based on 838 465 patients in the United States ≥18 years old with IHCA in the NIS from 2003 to 2011.[14]
- Incidence of CPR in the hospital increased from 1.81 to 2.37 per 1000 hospitalizations from 2007 to 2012, based on 235 959 hospitalized patients aged 18 to 64 years in the NIS.[15]
- Incidence of IHCA was 4.0 per 1000 hospitalizations (range, 1.4–11.8 per 1000 hospitalizations) based on 2 205 123 hospitalizations at 101 Veterans Health Administration hospitals between 2008 and 2012.[16]

- According to 2017 GWTG data (GWTG–Resuscitation, unpublished data, 2017), location of adult IHCA was 53.5% in the ICU, operating room, or ED and 46.5% in noncritical care areas among 26 178 events at 311 hospitals (Table 17-4).
- Initial recorded cardiac rhythm was VF or VT or shockable in 15.3% of adult IHCAs in 2017 GWTG data (GWTG–Resuscitation, unpublished data, 2017) (Table 17-2).

OHCA: Children (See Tables 17-2 and 17-3)

- Age- and sex-adjusted incidence rate of EMS-assessed OHCA in children was 8.3 per 100 000 person-years (75.3 for infants [<1 years], 3.7 for children [1–11 years], and 6.3 for adolescents [12–19 years] per 100 000 person-years) in the ROC Epistry from 2007 to 2012.[17]
- Incidence of EMS-assessed OHCA was 7037 (quasi CI, 6214–7861) children in the United States based on extrapolation from ROC for individuals <18 years of age in the United States (ROC Investigators, unpublished data, July 7, 2016).
- Location of EMS-treated OHCA was at home for 90.6% of children ≤1 year old, 80.2% of children 1 to 12 years old, and 74.7% of children 13 to 18 years old in the CARES 2017 data. Location was in a public place for 9.3% of children ≤1 years old, 19.6% of children 1 to 12 years old, and 25.0% of children 13 to 18 years old (Table 17-2).[10]
- Annual incidence of pediatric OHCA was 8.7 per 100 000 population in Western Australia from 2011 to 2014.[18]

Sports-Related SCA/SCD

- Incidence of SCD was 0.24 per 100 000 athlete-years in high school athletes screened every 3 years between 1993 and 2012 with standard preparticipation evaluations during Minnesota State High School League activities.[19]
- Incidence of nontraumatic OHCA was 1 per 43 770 athlete participant-years in a longitudinal study of students 17 to 24 years of age participating in National Collegiate Athletic Association sports from 2004 to 2008. Incidence of cardiac arrest was higher among blacks than among whites and among males than among females.[20]
- Incidence of SCA was 0.54 per 100 000 participants (95% CI, 0.41–0.70) among 10.9 million registered participants in 40 marathons and 19 half marathons.[21] Those with cardiac arrest were more often male and were running a marathon versus a half marathon.
- Sports-related SCA accounted for 39% of SCAs for ages ≤18 years, 13% for ages 19 to 25 years, and 7% for ages 25 to 34 years in a prospective registry of 3775 SCAs in Portland, OR, between 2002 and 2015 that included 186 SCAs in young people (5–34 years old).[22]
- Incidence of SCA or SCD was 1 per 44 832 athlete-years for males and 1 per 237 510 athlete-years for females based on a 2007 to 2013 registry of 104 cases of SCA and SCD in high school athletes.[23]
- Incidence of SCA during competitive sports in people 12 to 45 years old was 0.76 per 100 000 athlete-years in a population-based registry of all paramedic responses in Toronto, Canada, from 2009 to 2014.[24]
- In the US National Registry of Sudden Death in Athletes from 1980 to 2011, there were 1306 SCDs in young athletes (mean 19±6 years of age) participating in organized sports. The most common causes of SCD in 842 young athletes with confirmed diagnoses were HCM (36%), coronary artery anomalies (19%), myocarditis (7%), ARVC (5%), CAD (4%), and commotio cordis (3%).[25]
- In 45 cases of SCD among National Collegiate Athletic Association athletes from 2004 to 2008, adjudication revealed a cause of death in 36 (80%): autopsy-negative sudden unexplained death (31%), coronary artery abnormalities (14%), DCM (8%), myocarditis related (8%), aortic dissection (8%), and idiopathic LVH/possible HCM (8%), HCM (3%), ARVC (3%), LQTS (3%), commotio cordis (3%), and KD (3%).[26]
- In a 2007 to 2013 registry of 104 cases of SCA and SCD in high school athletes, adjudication revealed a cause of death in 50 cases (73%): idiopathic LVH or possible cardiomyopathy (26%), autopsy-negative sudden unexplained death (18%), HCM (14%), and myocarditis (14%).[23]
- Adjudication of cause of death in 179 cases of SCA in middle school, high school, college, and professional athletes from 2014 to 2016 identified a cause in 117 (65.4%): HCM (16.2%), coronary artery anomalies (13.7%), idiopathic cardiomyopathy (11.1%), autopsy-negative sudden unexplained death (6.8%), WPW (6.8%), and LQTS (6.0%).[4]

IHCA: Children (See Table 17-2)

- Incidence of IHCA for children (30 days to 18 years old) was a mean 9.65 (SD, 16.92) per 1000 admissions and 1.75 (SD, 3.03) per 1000 inpatient days in 92 hospitals according to 2017 GWTG data (GWTG–Resuscitation, unpublished data, 2017).
- Incidence of pediatric IHCA was 0.78 per 1000 discharges based on 29 577 children with IHCA in the Kids' Inpatient Database from 1997 to 2012. Incidence of pediatric IHCA increased from 0.57 per 1000 discharges in 1997 to 1.01 per 1000 discharges in 2012.[27]

- Per 2017 GWTG data (GWTG–Resuscitation, unpublished data, 2017), location of IHCA for children (30 days to 18 years old) was 87.8% in the ICU, operating room, or ED and 12.2% in noncritical care areas among 897 events at 92 hospitals (Table 17-2).
- Incidence of IHCA was 1.8 CPR events per 100 pediatric (<18 years) ICU admissions (sites range from 0.6 to 2.3 per 100 ICU admissions) in the Collaborative Pediatric Critical Care Research Network dataset of 10078 pediatric ICU admissions from 2011 to 2013.[28]
- In a registry of 23 cardiac ICUs of the Pediatric Critical Care Consortium including 15098 children between 2014 and 2016, 3.1% of children in ICUs had a cardiac arrest, with substantial variation between centers (range 1%– 5.5%), for a mean incidence of 4.8 cardiac arrests per 1000 cardiac ICU days (range, 1.1–10.4 per 1000 cardiac ICU days).[29]
- Initial recorded cardiac arrest rhythm was VF or VT or shockable in 9.9% of 897 events at 92 hospitals in GWTG–Resuscitation in 2017 (GWTG–Resuscitation, unpublished data, 2017) (Table 17-2).

Lifetime Risk

- SCD appears among the multiple causes of death on 13.4% of death certificates in 2016 (366494 of 2744248), which suggests that 1 of every 7.5 people in the United States will die of SCD.[30] Because some people survive SCA, the lifetime risk of cardiac arrest is even higher.
- Infants have a higher incidence of SCD (12.8 per 100000) than older children (1.1–2.0 per 100000). Among adults, risk of SCD increases exponentially with age, surpassing the risk for infants by age 40 years (20.3 per 100000) (Chart 17-1).

Mortality (See Table 17-5 and Chart 17-1)

- In 2016, primary-cause SCD mortality was 17661, and any-mention SCD mortality in the United States was 366494 (Table 17-5).[30]
- Survival of hospitalization after cardiac arrest varied between academic medical centers and was higher in hospitals with higher cardiac arrest volume, higher surgical volume, greater availability of invasive cardiac services, and more affluent catchment areas.[7]
- Of 1452808 death certificates from 1999 to 2015 for US residents aged 1 to 34 years, 31492 listed SCD (2%) as the cause of death, for an SCD rate of 1.32 per 100000 individuals.[31]
  - — SCD rate varied by age, from 0.49 per 100000 (1–10 years) to 2.76 per 100000 (26–34 years).[31]
  - — The rate of SCD declined from 1999 to 2015, from 1.48 to 1.13 per 100000 individuals.[31]
- Among hospitalized patients aged 18 to 64 years in the NIS from 2007 to 2012, 235959 adults had CPR in the hospital, and 30.4% survived to hospital discharge.[15]
- Mortality rates for any mention of SCD by age are provided in Chart 17-1.

OHCA: Adults (See Tables 17-1, 17-2, and 17-4)

- Survival to hospital discharge after EMS-treated OHCA was 10.4%, and survival with good functional status was 8.4% based on 73910 cases in CARES for 2017.[10]
- Survival to hospital discharge after EMS-treated cardiac arrest was 11.4% (95% CI, 10.4%–12.4%) for patients of any age and 11.4% (95% CI, 10.3%–12.4%) for adults in the ROC Epistry (ROC Investigators, unpublished data, July 7, 2016) (Table 17-1).
- Large regional variations in survival to hospital discharge (range, 3.4%–22.0%) and survival with functional recovery (range, 0.8%–20.1%) are observed between 132 counties in the United States.[32] Variation in rates of layperson CPR and AED use explained much of this variation.
- Age-adjusted survival to hospital admission was lower for blacks (6.0%) and Hispanics (8.6%) than for whites (11.3%) among 4053 cardiac arrests in New York City in 2002 to 2003.[33] This disparity persisted to 30 days after hospital discharge.
- Survival to hospital admission after EMS-treated nontraumatic OHCA was 29.0% for all presentations, with higher survival rates in public places (39.5%) and lower survival rates in homes/residences (27.5%) and nursing homes (18.2%) in the 2017 CARES registry (Table 17-4).
- Survival to hospital discharge varies between regions of the United States, being higher in the Midwest (adjusted OR, 1.16 [95% CI, 1.02–1.32]) and the South (1.24 [95% CI, 1.09–1.40]) relative to the Northeast, in 154177 patients hospitalized after OHCA in the NIS (2002–2013).[34]
- Survival at 1, 5, 10, and 15 years, respectively, was 92.2%, 81.4%, 70.1%, and 62.3% among 3449 patients surviving to hospital discharge after OHCA from 2000 to 2014 in Victoria, Australia.[35]
- Patients with STEMI who had OHCA had higher in-hospital mortality (38%) than STEMI patients without OHCA (6%) in a Los Angeles, CA, registry of 4729 STEMI patients from 2011 to 2014.[11]

Sports-Related SCA/SCD

- Among runners with cardiac arrest during marathons or half marathons, 71% died; those who died were younger (mean±SD, 39±9 years of age) than those who did not die (mean±SD, 49±10 years of age), were more often male, and were more often running a full marathon.[21]
- In a population-based registry of all paramedic responses for SCA from 2009 to 2014, 43.8% of athletes with SCA during competitive sports survived to hospital discharge.[24]

IHCA: Adults (See Table 17-2 and Chart 17-2)

- Survival to hospital discharge was 25.6% of 26 178 adult IHCAs at 311 hospitals in GWTG 2017 (GWTG–Resuscitation, unpublished data, 2017) data (Table 17-2, Chart 17-2). Among survivors, 81.7% had good functional status (cerebral performance category 1 or 2) at hospital discharge.
- Unadjusted survival rate after IHCA was 18.4% in the UK National Cardiac Arrest Audit database between 2011 and 2013. Survival was 49% when the initial rhythm was shockable and 10.5% when the initial rhythm was not shockable.[13]
- Survival to discharge is lower for black patients (25.2%) than for white patients (37.4%) after IHCA.[36] Lower rates of survival to discharge for blacks reflect lower rates of both successful resuscitation (55.8% for blacks versus 67.4% for whites) and postresuscitation survival (45.2% versus 55.5%). The hospital where patients received care explained much of the racial variation in postresuscitation survival (adjusted RR for hospital, 0.92 [95% CI, 0.88–0.96]; adjusted RR for race, 0.99 [95% CI, 0.92–1.06]).
- Survival to hospital discharge after IHCA was lower for males than for females (adjusted OR, 0.90 [95% CI, 0.83–0.99]) in a Swedish registry of 14 933 cases of IHCA from 2007 to 2014.[37]
- Mortality was lower among 348 368 patients with IHCA managed in teaching hospitals (55.3%) than among 376 035 managed in nonteaching hospitals (58.8%), even after adjustment for baseline patient and hospital characteristics (adjusted OR, 0.917 [95% CI, 0.899–0.937]).[38]

OHCA: Children (See Tables 17-1 through 17-3)

- Survival to hospital discharge after EMS-treated nontraumatic cardiac arrest was 13.2% (95% CI, 7.0%–19.4%) for children in the ROC Epistry (ROC Investigators, unpublished data, July 7, 2016) (Table 17-1).
- Survival to hospital discharge was 5.4% for 1197 children ≤1 year old, 18.2% for 484 children 1 to 12 years old, and 20.7% for 376 children 13 to 18 years old in CARES 2017 data (Tables 17-2 and 17-3).
- Mortality was lower in teaching hospitals (OR, 0.57 [95% CI, 0.50–0.66), trauma centers (OR, 0.76 [95% CI, 0.67–0.86]), and urban hospitals (OR, 0.78 [95% CI, 0.63–0.97]) relative to nonteaching, non-trauma, or rural hospitals, respectively, among 42 036 presentations of children 0 to 18 years old for cardiac or respiratory failure in the HCUP's National Emergency Department Sample.[39]

IHCA: Children

- Survival to hospital discharge after pulseless IHCA was 37.2% in 611 children 0 to 18 years old and 22.6% in 214 neonates (0–30 days old) per 2017 GWTG data (GWTG–Resuscitation, unpublished data, 2017) (Table 17-2).
- Survival to hospital discharge for children with IHCA in the ICU was 45% in the Collaborative Pediatric Critical Care Research Network from 2011 to 2013.[28]
- The in-hospital mortality rate was 46% among 29 577 children with IHCA in the Kids' Inpatient Database from 1997 to 2012.[27]

Secular Trends (See Tables 17-2 and 17-3 and Charts 17-2 and 17-3)

- Incidence of EMS-treated OHCA increased from 47 per 100 000 to 66 per 100 000 between 2008 and 2015 in the ROC Epistry (ROC Investigators, unpublished data, July 7, 2016).
- Incidence of pediatric OHCA has declined from 1997 to 2014 in Perth, Western Australia, particularly in children <1 years of age.[18]
- Incidence of pediatric IHCA increased from 0.57 per 1000 discharges in 1997 to 1.01 per 1000 discharges in 2012 based on 29 577 children with IHCA in the Kids' Inpatient Database.[27]
- Age-adjusted death rates for any mention of SCD declined from 138 per 100 000 person-years in 1999 to 98 per 100 000 person-years by 2016 (Chart 17-3).
- Unadjusted survival to hospital discharge after EMS-treated OHCA increased from 10.2% in 2006 to 12.4% in 2015 in the ROC Epistry (ROC Investigators, unpublished data, July 7, 2016) (Table 17-1).
- Survival to hospital discharge for patients hospitalized after OHCA increased from 49.9% (39.8%–60.0%) in 1995 to 54.0% (46.3%–61.8%) in 2013 among 247 684 patients hospitalized in the NIS from 1995 to 2013.[40]
- Survival to hospital discharge in patients with VT/VF OHCA increased from 2000 to 2012 from

46.9% to 60.1%, both in those with ST-segment elevation (59.2%–74.3%) and in those without ST-segment elevation (43.3%–56.8%), based on 407 974 patients from the NIS.[41]

- Survival after IHCA increased between 2000 and 2016 in GWTG data (Chart 17-2).
- The in-hospital mortality rate decreased each year from 69.6% in 2001 to 57.8% in 2009 among 1 190 860 patients hospitalized with a diagnosis of cardiac arrest in the NIS.[42]
- The in-hospital mortality rate declined from 51% in 1997 to 40% in 2012 among 29 577 children with IHCA in the Kids' Inpatient Database.[27]
- Rates of layperson-initiated CPR and layperson use of AEDs have increased over time (Table 17-1).

Complications (See Tables 17-2 through 17-4)

- Survivors of cardiac arrest experience multiple medical problems related to critical illness, including impaired consciousness and cognitive deficits. As many as 18% of survivors of OHCA, 40% of adult survivors of IHCA, and 72% of child survivors of IHCA have moderate to severe functional impairment at hospital discharge (Tables 17-2 through 17-4).
- Functional impairments are associated with reduced function, reduced quality of life, and shortened lifespan.[43,44]
- Functional recovery continues over at least the first 12 months after OHCA in children and over the first 6 to 12 months after OHCA in adults.[45,46]
- Among 366 patients discharged after IHCA in a Veterans Administration hospital between 2014 and 2015, 55 (15%) endorsed suicidal ideation during the first 12 months.[47]
- Among the 2855 patients who were 30-day survivors of OHCA between 2001 and 2012 in a nationwide registry in Denmark, 10.5% had brain damage or were admitted to a nursing home, and 9.7% died during the 1-year follow-up period.[48]
- Serial testing in a cohort of 141 people who survived hospitalization after SCA revealed severe cognitive deficits in 14 (13%), anxiety and depression in 16 (15%), posttraumatic stress symptoms in 29 (28%), and severe fatigue in 55 (52%).[49] Subjective symptoms declined over time after SCA, although 10% to 22% had cognitive impairments at 12 months, with executive functioning being most affected.[50]
- Of 141 individuals who survived hospitalization after SCA, 41 (72%) returned to work by 12 months.[49]
- Of 287 people who survived hospitalization after OHCA, 47% had reduced participation in premorbid activities, and 27% of those who were working before the OHCA were on sick leave at 6 months.[51]
- Among 195 family caregivers of cardiac arrest survivors, anxiety was present in 33 caregivers (25%) and depression in 18 caregivers (14%) at 12 months.[52]

Healthcare Utilization and Cost

- In the Oregon SUDS, the estimated societal burden of SCD in the United States was 2 million years of potential life lost for males and 1.3 million years of potential life lost for females, accounting for 40% to 50% of the years of potential life lost from all cardiac disease.[53]
- Among males, estimated deaths attributable to SCD exceeded all other individual causes of death, including lung cancer, accidents, CLRD, cerebrovascular disease, DM, prostate cancer, and colorectal cancer.[53]

Risk Factors (See Chart 17-4)

Age

- The underlying cause of OHCA varies by age group. Chart 17-4 illustrates the causes of OHCA by age group based on a retrospective cohort of OHCA patients 0 to 35 years of age treated in King County, WA, between 1980 and 2009.[54]

Sex

- In Denmark from 2000 to 2009, incidence of SCD in people aged 1 to 35 years was greater for males (3.6 per 100 000) than for females (1.8 per 100 000; IRR, 2.0 [95% CI, 1.7–2.4]).[55]
- Among 66 cases of arrhythmogenic right ventricular dysplasia detected after SCA or SCD, 65% were males, with a mean±SD age of 29.3±13.8 years; SCA occurred during exertion in 72%, and antecedent cardiac symptoms had been reported by 41%.[56]

Race

- In patients with implanted defibrillators, rate of first ventricular dysrhythmia or death within 4 years was higher among black patients (42%) than whites (34%; adjusted HR, 1.60 [95% CI, 1.18–2.17]).[57]
- A study in New York City, NY, found the age-adjusted incidence of OHCA per 10 000 adults was 10.1 among blacks, 6.5 among Hispanics, and 5.8 among whites.[33]
- The US National Registry of Sudden Death in Athletes (1980–2011) of 2406 SCDs in competitive athletes (mean age, 19 years) revealed a

higher estimated incidence of SCD in black athletes than in white athletes and in males than in females. Of these deaths among athletes, 842 (35%) were adjudicated to have a cardiovascular cause, including HCM (36%), anomalous coronary artery (19%), myocarditis (7%), ARVC (5%), CAD (4%), mitral valve prolapse (4%), aortic rupture (3%), aortic stenosis (2%), DCM (2%), and LQTS (2%).[25]

Socioeconomic Factors

- OHCA rates were higher in census tracts from the lowest socioeconomic quartile relative to the highest socioeconomic quartile (IRR, 1.9 [95% CI, 1.8–2.0]) in 9235 cases from the ROC Epistry (from 2006 to 2007).[58]

HD, Cardiac Risk Factors, and Other Comorbidities

- A large proportion of patients with OHCA have coronary atherosclerosis.[59]
- Approximately 5% to 10% of SCD cases occur in the absence of CAD or structural HD.[60]
- Risk of SCD in prospective cohorts who were initially free of CVD when recruited in 1987 to 1993 was associated with male sex, black race, DM, current smoking, and SBP.[61]
- Prior HD was associated with risk for OHCA in 1275 health maintenance organization enrollees 50 to 79 years of age. Incidence of OHCA was 6.0 per 1000 person-years in subjects with any clinically recognized HD compared with 0.8 per 1000 person-years in subjects without HD. In subgroups with HD, incidence was 13.7 per 1000 person-years in subjects with prior MI and 21.9 per 1000 person-years in subjects with HF.[62]
- A logistic model incorporating age, sex, race, current smoking, SBP, use of antihypertensive medication, DM, serum potassium, serum albumin, HDL-C, eGFR, and QTc interval, derived in 13 677 adults, correctly stratified 10-year risk of SCD in a separate cohort of 4207 adults (C statistic, 0.820 in ARIC and 0.745 in CHS).[61]
- Four lifestyle factors (smoking, exercise, diet, and weight) were associated with SCD in a study of 81 722 females in the Nurses' Health Study who were followed up from 1984 to 2010. RR of SCD (N=321) was 0.54 (95% CI, 0.34–0.86) for females with 1 low-risk factor, 0.41 (95% CI, 0.25–0.65) for those with 2 low-risk factors, 0.33 (95% CI, 0.20–0.54) for 3 low-risk factors, and 0.08 (95% CI, 0.03–0.23) for 4 low-risk factors.[63]
- According to data from the Kids' Inpatient Data Sample from 2000, 2003, and 2006, IHCA occurred in 0.74% of hospitalized children with CVD versus 0.05% of hospitalized children without CVD (OR, 13.8 [95% CI, 12.8–15.0]).[64]
- A meta-analysis of 24 trials of statins in patients with HF, which included a total of 11 463 patients, concluded that statins did not reduce the risk of SCD (RR, 0.92 [95% CI, 0.70–1.21]).[65]
- In a registry of 2119 SCAs in Portland, OR, from 2002 to 2015, prior syncope was present in 6.8% cases, and history of syncope was associated with increased risk of SCA relative to 746 geographically matched control subjects (OR, 2.8 [95% CI, 1.68–4.85]).[66]
- In a cohort of 5211 Finnish people >30 years old in 2000 to 2001 followed up for a median of 13.2 years, high baseline thyroid-stimulating hormone was independently associated with greater risk of SCD (HR, 2.28 [95% CI, 1.13–4.60]).[67]
- In a meta-analysis that included 17 studies with 118 954 subjects, presence of depression or depressive symptoms was associated with increased risk of SCD (HR, 1.62 [95% CI, 1.37–1.92]), and specifically for VT/VF (HR, 1.47 [95% CI, 1.23–1.76]).[68]

Prodromal Symptoms

- Twenty-five percent of those with EMS-treated OHCA have no symptoms before the onset of arrest.[69]
- Abnormal vital signs during the 4 hours preceding IHCA occurred in 59.4% and at least 1 severely abnormal vital sign occurred in 13.4% of 7851 patients in the 2007 to 2010 GWTG data.[70]
- Early warning score systems using both clinical criteria and vital signs can identify hospital patients with a higher risk of IHCA.[71]

ECG Abnormalities

- Among 12 241 subjects from the ARIC study, in which 346 subjects had SCD during a median follow-up of 23.6 years, prolongation of the QT interval at baseline was associated with risk of SCD (HR, 1.49 [95% CI, 1.01–2.18]), and this association was driven specifically by the T-wave onset to T-peak component of the total interval.[72]
- In a cohort of 4176 subjects with no known HD, 687 (16.5%) had early repolarization with terminal J wave, but this pattern had no association with cardiac deaths (0.8%) over 6 years of follow-up compared with matched control subjects.[73]
- Among 11 956 residents of rural Liaoning Province, China, who were ≥35 years old, 1.3% had ERP, with higher prevalence in males (2.6%) than females (0.2%).[74]
- In an Italian public health screening project, 24% of 13 016 students aged 16 to 19 years had at least 1 of the following electrocardiographic abnormalities: ventricular ectopic beats, AV block, Brugada-like ECG pattern, left anterior/posterior

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fascicular block, LVH/RV hypertrophy, long/short QT interval, left atrial enlargement, right atrial enlargement, short PQ interval, and ventricular pre-excitation WPW syndrome.[75]

Genetics and Family History Associated With SCD

- A large proportion of OHCA in the general population results directly from CAD. Risk factors are thus similar to those for CAD.[76]
- Arrhythmic cardiac arrest not attributable to CAD is associated with structural HD in about one-third of cases and primary arrhythmic disorders, often with a genetic basis, in the other two-thirds of cases.[77]
- A family history of cardiac arrest in a first-degree relative is associated with an ≈2-fold increase in risk of cardiac arrest.[78,79]
- Age- and sex-adjusted prevalence of electrocardiographic abnormalities associated with SCD was 0.6% to 1.1% in a sample of 7889 Spanish citizens aged ≥40 years, including Brugada syndrome in 0.13%, QTc <340 ms in 0.18%, and QTc ≥480 ms in 0.42%.[80]
- Exome sequencing in younger (<51 years old) decedents who died of sudden unexplained death or suspected arrhythmic death has revealed likely pathogenic variants in channelopathy-or cardiomyopathy-related genes for 29% to 34% of cases.[81,82] Among children with exertion-related deaths, pathogenic mutations were present in 10 of 11 decedents (91%) 1 to 10 years old and 4 of 21 decedents (19%) 11 to 19 years old.[83]
- Screening of 398 first-degree relatives of 186 unexplained SCA and 212 unexplained SCD probands revealed cardiac abnormalities in 30.2%: LQTS (13%), CPVT (4%), ARVC (4%), and Brugada syndrome (3%).[84]
- In a registry of 109 families of probands with unexplained SCD from 2007 to 2012, screening of 411 relatives revealed a diagnosis in 18% of families: LQTS (15%), Brugada syndrome (3%), and CPVT (1%).[85]
- In a registry of 52 families of probands with unexplained cardiac arrest, screening of 91 relatives revealed a diagnosis in 62% of families: LQTS (21%), Brugada syndrome (17%), CPVT (6%), early repolarization (6%), HCM (6%), ARVC (4%), and short-QT syndrome (2%).[85]
- In a registry of families of probands with unexplained SCD before 45 years of age from 2009 to 2014, screening of 230 people from 64 families revealed a diagnosis in 25% of families: Brugada syndrome (11%), LQTS (7.8%), DCM (3.1%), and HCM (3.1%).[86]

Long-QT Syndrome

- Hereditary LQTS is a genetic channelopathy characterized by prolongation of the QT interval (typically >460 ms) and susceptibility to ventricular tachyarrhythmias that lead to syncope and SCD. Investigators have identified mutations in 15 genes leading to this phenotype (*LQT1* through *LQT15*).[87,88] *LQT1* (*KCNQ1*), *LQT2* (*KCNH2*), and *LQT3* (*SCN5A*) mutations account for the majority (≈80%) of the typed mutations.[89,90]
- The prevalence of LQTS was estimated at 1 per 2000 live births from ECG-guided molecular screening of 44 596 infants (mostly white) born in Italy.[91] A similar prevalence was found among 7961 Japanese schoolchildren screened by use of an ECG-guided molecular screening approach.[92] LQTS has been reported among those of African descent, but its prevalence is not well assessed.[93]
- There is variable penetrance and a sex-time interaction for LQTS symptoms. Therefore, frequency of LQTS mutations without clinically apparent or *forme pleine* LQTS might be much higher. Risk of cardiac events is 21% among males and 14% among females by 12 years of age. Risk of events during adolescence (ages 12–18 years) is equivalent between sexes (≈25% for both sexes). Risk of cardiac events in young adulthood (ages 18–40 years) is 16% among males and 39% among females.[89]
- Individuals can be risk stratified for increased risk of SCD[94] according to their specific long-QT mutation and their response to β-blockers.[95]
- Among 403 patients from the LQTS Registry from birth through age 40 years, multivariate analysis demonstrated that patients with multiple LQTS gene mutations had a 2.3-fold (P=0.015) increased risk for life-threatening cardiac events (comprising aborted cardiac arrest, implantable defibrillator shock, or SCD) compared with patients with a single mutation.[96]
- In 201 cases of sudden infant death syndrome from Norway, molecular screening revealed 19 cases (9.5% [95% CI, 5.8%–14.4%) with likely contributing mutations of genes associated with LQTS (*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *KCNJ2*, *CAV3*).[97]
- LQTS can be associated with a number of childhood genetic syndromes, although most cases are not. The Jervell and Lange-Nielson autosomal recessive syndrome of sensorineural hearing loss and long QT has a prevalence of 1 in 200 000.[98]
- Approximately 5% of sudden infant death syndrome and some cases of intrauterine fetal death could be attributable to LQTS.[97,99,100]

Short-QT Syndrome

Prevalence and Incidence

- Short-QT syndrome is an inherited mendelian condition characterized by shortening of the QT interval (typically QT <320 ms) and predisposition to AF, ventricular tachyarrhythmias, and sudden death. Mutations in 5 ion channel genes have been described (*SQT1–SQT5*).[101]
- Prevalence of a QTc Bazett interval shorter than 320 ms in a population of 41 767 young, predominantly male Swiss conscripts was 0.02%,[102] which was identical to prevalence from a Portugal sudden death registry.[103]
- Prevalence of QT interval ≤320 ms in 18 825 apparently healthy people from the United Kingdom aged 14 to 35 years between 2005 and 2013 was 0.1%.[104] Short QT intervals were associated with male sex and Afro-Caribbean ethnicity.
- Prevalence of QT interval ≤340 ms in 99 380 unique patients aged ≤21 years at Cincinnati Children's Hospital between 1993 and 2013 was 0.05%.[105] Of these children, 15 of 45 (33%) were symptomatic.[105]
- Among 53 patients from the European Short QT Syndrome Registry (75% males, median age 26 years),[106] 89% had a familial or personal history of cardiac arrest. Twenty-four patients received an implantable cardioverter-defibrillator, and 12 received long-term prophylaxis with hydroquinidine. During a median follow-up of 64 months, 2 patients received an appropriate implantable cardioverter-defibrillator shock, and 1 patient experienced syncope. Nonsustained PVT was recorded in 3 patients.
- In an international case series of 15 centers that included 25 patients ≤21 years of age with short-QT syndrome who were followed up for 5.9 years (IQR, 4–7.1 years), 6 patients had aborted sudden death (24%) and 4 (16%) had syncope.[107] Sixteen patients (84%) had a familial or personal history of cardiac arrest. A gene mutation associated with short-QT syndrome was identified in 5 of 21 probands (24%).

Brugada Syndrome

Prevalence and Incidence

- Brugada syndrome is an acquired or inherited channelopathy characterized by persistent ST-segment elevation in the precordial leads (V_1–V_3), right bundle-branch block, and susceptibility to ventricular arrhythmias and SCD.[108] Brugada syndrome is associated with mutations in at least 12 ion channel–related genes.[108,109]
- In a meta-analysis of 24 studies, prevalence was estimated at 0.4% worldwide, with regional prevalence of 0.9%, 0.3%, and 0.2% in Asia, Europe, and North America, respectively.[110] Prevalence is higher in males (0.9%) than females (0.1%).[108,111–113]

Complications

- Cardiac event rates for Brugada syndrome patients followed up prospectively in Northern Europe (31.9 months) and Japan (48.7 months) were similar: 8% to 10% in patients with prior aborted sudden death, 1% to 2% in those with history of syncope, and 0.5% in asymptomatic patients. Predictors of poor outcome include clinical history of syncope or ventricular tachyarrhythmias, family history of sudden death, and a spontaneous ERP on ECG.[111,114,115]
- Among patients with Brugada syndrome, first-degree AV block, syncope, and spontaneous type 1 ST-segment elevation were independently associated with risk of sudden death or implantable cardioverter-defibrillator–appropriate therapies.[116,117]

Catecholaminergic PVT

Prevalence and Incidence

- CPVT is a familial condition characterized by adrenergically induced ventricular arrhythmias associated with syncope and sudden death. Arrhythmias include frequent ectopy, bidirectional VT, and PVT with exercise or catecholaminergic stimulation (such as emotion, or medicines such as isoproterenol). Mutations in genes encoding RYR2 (*CPVT1*) are found in the majority of patients and result in a dominant pattern of inheritance.[118] Mutations in genes encoding CASQ2 (*CPVT2*) are found in a small minority and result in a recessive pattern of inheritance. Mutations have also been described in *KCNJ2* (*CPVT3*), *TRDN*, *ANK2*, and *CALM1*.[118]
- Prevalence of CPVT is not known. Estimates of 1:5000 to 1:10 000 have been proposed, but this could be an underestimate if childhood cases of sudden death are uncounted from the numerator and denominator.[118]

Complications

- Of 101 patients with CPVT, the majority had experienced symptoms before 21 years of age.[119]
- In small series (N=27 to N=101) of patients followed up over a mean of 6.8 to 7.9 years, 27% to 62% experienced cardiac symptoms, and fatal or near-fatal events occurred in 13% to 31%.[119–121]
- Risk factors for cardiac events included younger age at diagnosis and absence of β-blocker therapy. A history of aborted cardiac arrest and

absence of β-blocker therapy were risk factors for fatal or near-fatal events.[119]

- In a cohort of 34 patients with CPVT, 20.6% developed fatal cardiac events during 7.4 years of follow up.[122]

Arrhythmogenic RV Dysplasia/ Cardiomyopathy

Prevalence and Incidence

- Arrhythmogenic RV dysplasia or cardiomyopathy is a form of genetically inherited structural HD that presents with fibrofatty replacement of the myocardium, which increases risk for palpitations, syncope, and sudden death. Twelve ARVC loci have been described (*ARVC1–ARVC12*). Disease-causing genes for 8 of these loci have been identified, the majority of which are in desmosomally related proteins.[123]
- The prevalence of ARVC has not been systematically estimated, but is thought to be between 1 in 1000 and 1 in 5000.[123]
- Of 100 patients in the Johns Hopkins Arrhythmogenic Right Ventricular Dysplasia Registry, 51 were males and 95 were white, with the rest being of black, Hispanic, or Middle Eastern origin. Twenty-two percent of the 87 index cases and 32% of all the identified cases had evidence of the familial form of ARVC.[124]

Complications

- The most common presenting symptoms were palpitations (27%), syncope (26%), and SCD (23%).[124]
- During a median follow-up of 100 patients with arrhythmogenic right ventricular dysplasia for 6 years, 47 patients received an implantable cardioverter-defibrillator, 29 of whom received appropriate implantable cardioverter-defibrillator shocks. At the end of follow-up, 66 patients were alive. Twenty-three patients died at study entry, and 11 died during follow-up (91% of deaths were attributable to SCA).[124] Similarly, the annual mortality rate was 2.3% for 130 patients with ARVC from Paris, France, who were followed up for a mean of 8.1 years.[125]
- In a cohort of 301 patients with ARVC from a single center in Italy, probability of a first life-threatening arrhythmic event was 14% at 5 years, 23% at 10 years, and 30% at 15 years.[126]

Hypertrophic Cardiomyopathy

(Please refer to Chapter 20, Cardiomyopathy and Heart Failure, for statistics regarding the general epidemiology of HCM.)

Complications

- Over a mean follow-up of 8±7 years, 6% of 744 HCM patients experienced SCD.[127]
- Among 1866 sudden deaths in athletes between 1980 and 2006, HCM was the most common cause of cardiovascular sudden death (in 251 cases, or 36% of the 690 deaths that could be reliably attributed to a cardiovascular cause).[128]
- The risk of sudden death increases with increasing maximum LV wall thickness,[129,130] and the risk for those with wall thickness ≥30 mm is 18.2 per 1000 patient-years (95% CI, 7.3–37.6),[130] or approximately twice that of those with maximal wall thickness <30 mm.[129–131] Of note, an association between maximum wall thickness and sudden death has not been found in every HCM population.[130]
- Nonsustained VT is a risk factor for sudden death,[132,133] particularly in younger patients. Nonsustained VT in those ≤30 years of age is associated with a 4.35-greater odds of sudden death (95% CI, 1.5–12.3).[133]
- A history of syncope is also a risk factor for sudden death in HCM,[134] particularly if the syncope was recent before the initial evaluation and not attributable to a neurally mediated event.[135]
- The presence of LV outflow tract obstruction with pressure gradients ≥30 mm Hg appears to increase the risk of sudden death by ≈2-fold.[136,137] The presence of LV outflow tract obstruction has a low positive predictive value (7%–8%) but a high negative predictive value (92%–95%) for predicting sudden death.[136,138]
- The rate of malignant ventricular arrhythmias detected by implantable cardioverter-defibrillators appears to be similar between HCM patients with a family history of sudden death in ≥1 first-degree relative and those with at least 1 of the risk factors described above.[139]
- The risk of sudden death increases with the number of risk factors.[140]

Early Repolarization Syndrome

Prevalence and Incidence

- There is no single electrocardiographic definition or set of criteria for ERP. Studies have used a range of criteria including ST elevation, terminal QRS slurring, terminal QRS notching, J-point elevation, J waves, and other variations. Although the Brugada ECG pattern is considered an early repolarization variant, it is generally not included in epidemiology assessments of ERP or early repolarization syndrome.[141]
- Because of the high variation in early repolarization definitions and heterogeneity in published

outcomes, systematic screening for ERP has not been recommended.[142]

- A syndrome in which ≥1-mm positive deflections (sometimes referred to as J waves) occurred in the S wave of ≥2 consecutive inferior or lateral leads was significantly more common among patients with idiopathic VF than among control subjects.[142,143]
- ERP is observed in 4% to 19% of the population (more commonly in young males and in athletes) and conventionally has been considered a benign finding.[141–145]
- In CARDIA, 18.6% of 5069 participants had early repolarization restricted to the inferior and lateral leads at baseline; by year 20, only 4.8% exhibited an ERP.[144] Younger age, black race, male sex, longer exercise duration and QRS duration, and lower BMI, heart rate, QT index, and Cornell voltage were associated with the presence of baseline early repolarization. Persistence of the electrocardiographic pattern from baseline to year 20 was associated with black race (OR, 2.62 [95% CI, 1.61–4.25]), BMI (OR, 0.62 per 1 SD [95% CI, 0.40–0.94]), serum triglyceride levels (OR, 0.66 per 1 SD [95% CI, 0.45–0.98]), and QRS duration (OR, 1.68 per 1 SD [95% CI, 1.37–2.06]) at baseline.[144]

Complications

- Shocks from an automatic implantable cardioverter-defibrillator occur more often and earlier in survivors of idiopathic VF with inferolateral early repolarization syndrome.[146,147]
- In an analysis of the Social Insurance Institution's Coronary Disease Study in Finland, J-point elevation was identified in 5.8% of 10 864 people.[144] Those with inferior lead J-point elevation more often were male and more often were smokers; had a lower resting heart rate, lower BMI, lower BP, shorter QTc, and longer QRS duration; and were more likely to have electrocardiographic evidence of CAD. Those with lateral J-point elevation were more likely to have LVH. Before and after multivariable adjustment, subjects with J-point elevation ≥1 mm in the inferior leads (N=384) had a higher risk of cardiac death (adjusted RR, 1.28 [95% CI, 1.04–1.59]) and arrhythmic death (adjusted RR, 1.43 [95% CI, 1.06–1.94]); however, these patients did not have a significantly higher rate of all-cause mortality. Before and after multivariable adjustment, subjects with J-point elevation >2 mm (N=36) had an increased risk of cardiac death (adjusted RR, 2.98 [95% CI, 1.85–4.92]), arrhythmic death (adjusted RR, 3.94 [95% CI, 1.96–7.90]), and death of any cause (adjusted RR, 1.54 [95% CI, 1.06–2.24]).
- Evidence from families with a high penetrance of the early repolarization syndrome associated with a high risk of sudden death suggests that the syndrome can be inherited in an autosomal dominant fashion.[148] A meta-analysis of GWASs performed in population-based cohorts failed to identify any genetic variants.[149]

Genome-Wide Association Studies

- GWASs on cases of arrhythmic death attempt to identify previously unidentified genetic variants and biological pathways associated with potentially lethal ventricular arrhythmias and risk of sudden death. Limitations of these studies are the small number of samples available for analysis and the heterogeneity of case definition. The number of loci uniquely associated with SCD is much smaller than for other complex diseases. In addition, studies do not consistently identify the same variants. A pooled analysis of case-control and cohort GWASs identified a rare (1.4% minor allele frequency) novel marker at the *BAZ2B* locus (bromodomain adjacent zinc finger domain 2B) that was associated with a risk of arrhythmic death (OR, 1.9 [95% CI, 1.6–2.3]).[149]

Premature Ventricular Contractions

- In a study of 1139 older adults in the CHS without HF or systolic dysfunction studied by Holter monitor (median duration, 22.2 hours), 0.011% of all heartbeats were PVCs, and 5.5% of participants had nonsustained VT. Over follow-up, the highest quartile of ambulatory ECG PVC burden was associated with an adjusted odds of decreased LVEF (OR, 1.13 [95% CI, 1.05–1.21]) and incident HF (HR, 1.06 [95% CI, 1.02–1.09]) and death (HR, 1.04 [95% CI, 1.02–1.06]).[150] Although PVC ablation has been shown to improve cardiomyopathy, the association with death may be complex, representing both a potential cause and a noncausal marker for coronary or structural HD.

Monomorphic VT

Prevalence and Incidence

- Monomorphic VT can be reentrant or focal. Reentrant monomorphic VT is generally caused by scar, usually in the setting of prior MI, and is considered malignant and increases the risk of SCD. Focal RMVT is the most common form of idiopathic VT and is generally not considered a risk factor for SCD. RMVT and paroxysmal exercise-induced VT are often grouped together for the purposes of risk stratification because they generally do not increase risk of SCD.

- The overall prevalence of reentrant monomorphic VT is not known, because VT can precede SCD and therefore not be ascertained. It is more prevalent in diseases more likely to have scar, including prior MI, cardiomyopathy and HF, infiltrative diseases, myocarditis, and ARVC.
- In 634 patients with implantable cardioverter-defibrillators who had structural HD (including both primary and secondary prevention patients) followed up for a mean 11±3 months, 81% of potentially clinically relevant ventricular tachyarrhythmias were attributable to VT amenable to antitachycardia pacing (which implies a stable circuit and therefore monomorphic VT).[151] Because therapy might have been delivered before spontaneous resolution occurred, the proportion of these VT episodes with definite clinical relevance is not known.
- Among 2099 subjects (mean age 52 years; 52.2% male) without known CVD, exercise-induced nonsustained VT occurred in 3.7% and was not independently associated with total mortality.[152]
- RMVT most commonly arises from the RV outflow tract. The incidence or prevalence of RMVT is not known, but it is a relatively common diagnosis in cardiac electrophysiology referral practices. RMVT occurs almost exclusively in young to middle-aged patients without structural HD. It has been perceived to be more common in athletes, which might be because of a higher likelihood of exercise-triggered manifestation than in the general population.[153]

Complications

- Although the prognosis of those with VT or frequent PVCs in the absence of structural HD is good,[154,155] a potentially reversible cardiomyopathy can develop in patients with very frequent PVCs,[156,157] and some cases of sudden death attributable to short-coupled PVCs have been described.[158,159]

Polymorphic VT

Prevalence and Incidence

- Among patients who developed SCD during ambulatory cardiac monitoring, PVT was detected in 30% to 43%.[160–162]
- In the setting of AMI, the prevalence of PVT was 4.4%.[163]

Complications

- The presentation of PVT can range from a brief, asymptomatic, self-terminating episode to recurrent syncope or SCD.[160–162,164]
- In the setting of AMI, PVT is associated with increased mortality (17.8%).[163]
- PVT resulting in cardiac arrest outside of the hospital has a 28% survival rate.[165]

Risk Factors

- PVT in the setting of a normal QT interval is most frequently seen in the context of acute ischemia or MI.[166]

Torsade de Pointes

Prevalence and Incidence

- Among 14 756 patients exposed to QT-prolonging drugs in 36 studies, 6.3% developed QT prolongation, and 0.33% developed TdP.[167]
- A prospective, active surveillance, Berlin-based registry of 51 hospitals observed that the annual incidence of symptomatic drug-induced QT prolongation in adults was 2.5 per million males and 4.0 per million females. The authors reported 42 potentially associated drugs, including metoclopramide, amiodarone, melperone, citalopram, and levomethadone. The mean age of patients with QT prolongation/TdP was 57±20 years, and the majority of the cases occurred in females (66%) and out of the hospital (60%).[168]
- The prevalence of drug-induced prolongation of QT interval and TdP is 2 to 3 times higher in females than in males.[169,170] Other risk factors include hypokalemia, hypomagnesemia, and bradycardia.[171]

Complications

- In a cohort of 459 614 Medicaid and Medicaid-Medicare enrollees aged 30 to 75 years who were taking antipsychotic medications, the incidence of sudden death was 3.4 per 1000 person-years, and the incidence of ventricular arrhythmia was 35.1 per 1000 person-years.[172]

Risk Factors

- TdP is usually related to administration of QT-interval–prolonging drugs.[173] An up-to-date list of drugs with the potential to cause TdP is available at a website maintained by the University of Arizona Center for Education and Research on Therapeutics.[174]
- Specific risk factors for drug-induced TdP include prolonged QT interval, female sex, advanced age, bradycardia, hypokalemia, hypomagnesemia, LV systolic dysfunction, and conditions that lead to elevated plasma concentrations of causative drugs, such as kidney disease, liver disease, drug interactions, or some combination of these.[170,173,175]

- Drug-induced TdP rarely occurs in patients without concomitant risk factors. An analysis of 144 published articles describing TdP associated with noncardiac drugs revealed that 100% of the patients had at least 1 risk factor, and 71% had at least 2 risk factors.[170]
- Both common and rare genetic variants have been shown to increase the propensity for drug-induced QT-interval prolongation.[176,177]

Prevention

- Appropriate monitoring when a QT-interval–prolonging drug is administered is essential. Also, prompt withdrawal of the offending agent should be initiated.[173]

Awareness and Treatment

- Median annual CPR training rate for US counties was 2.39% (25th–75th percentiles, 0.88%–5.31%) and ranged from 0.00% to >4.07% (median, 6.81%), based on training data from the AHA, the American Red Cross, and the Health & Safety Institute, the largest providers of CPR training in the United States.[178] Training rates were lower in rural areas, counties with high proportions of black or Hispanic residents, and counties with lower median household income.
- Prevalence of reported current training in CPR was 18% and prevalence of having CPR training at some point was 65% in a survey of 9022 people in the United States in 2015.[179] The prevalence of CPR training was lower in Hispanic/Latino people, older people, people with less formal education, and lower-income groups.
- Those with prior CPR training include 90% of citizens in Norway,[180] 68% of citizens in Victoria, Australia,[181] 61.1% of laypeople in the United Kingdom,[182] and 49% of people in the Republic of Korea,[183] according to surveys.
- Laypeople with knowledge of AEDs include 69.3% of people in the United Kingdom, 66% in Philadelphia, PA, and 32.6% in the Republic of Korea.[182–184] A total of 58% of Philadelphia respondents[184] but only 2.1% of United Kingdom respondents[182] reported that they would actually use an AED during a cardiac arrest.
- Laypeople in the United States initiated CPR in 34.4% of OHCAs recorded in the 2005 to 2014 CARES dataset and in 39.4% of OHCAs in CARES 2017 data[11] (Table 17-1).
- Layperson CPR rates in Asian countries range from 10.5% to 40.9%.[185]
- Laypeople in the United States are less likely to initiate CPR for people with OHCA in low-income black neighborhoods (OR, 0.49 [95% CI, 0.41–0.58])[186] or in predominantly Hispanic neighborhoods (OR, 0.62 [95% CI, 0.44–0.89]) than in high-income white neighborhoods.[187]
- Laypeople from Hispanic and Latino neighborhoods in Denver, CO, report that barriers to learning or providing CPR include lack of recognition of cardiac arrest events and lack of understanding about what a cardiac arrest is and how CPR can save a life, as well as fear of becoming involved with law enforcement.[188]
- A survey of 5456 households in Beijing, China, Shanghai, China, and Bangalore, India, revealed that 26%, 15%, and 3% of respondents, respectively, were trained in CPR.[189]

Global Burden

- International comparisons of cardiac arrest epidemiology must take into account differences in case ascertainment. OHCA usually is identified through EMS systems, and regional and cultural differences in use of EMS affect results.[190]
- A systematic review of international epidemiology of OHCA from 1991 to 2007 included 30 studies from Europe, 24 from North America, 7 from Asia, and 6 from Australia.[191] Estimated incidence per 100 000 population of EMS-assessed OHCA was 86.4 in Europe, 98.1 in North America, 52.5 in Asia, and 112.9 in Australia. Estimated incidence per 100 000 population of EMS-treated OHCA was 40.6 in Europe, 47.3 in North America, 45.9 in Asia, and 51.1 in Australia. The proportion of cases with VF was highest in Europe (35.2%) and lowest in Asia (11.2%).
- A prospective data collection concerning 10 682 OHCA cases from 27 European countries in October 2014 found an incidence of 84 per 100 000 people, with CPR attempted in 19 to 104 cases per 100 000 people.[192] Return of pulse occurred in 28.6% (range for countries, 9%–50%), with 10.3% (range, 1.1%–30.8%) of people on whom CPR was attempted surviving to hospital discharge or 30 days.
- Western Australia reports an age- and sex-adjusted incidence of 65.9 EMS-attended cardiac arrests per 100 000 population, with resuscitation attempted in 43%.[193] Survival to hospital discharge was 8.7%. Among children (<18 years old), crude incidence was 5.6 per 100 000.[18]
- Hospitals in Beijing, China, reported IHCA incidence of 17.5 events per 1000 admissions.[194]

Future Research

- The absence of standards for monitoring and reporting the incidence and outcomes of cardiac arrest remains a barrier to population research in the United States.[6] Cardiac arrest is a syndrome that results from many disease processes, and diagnosis codes are often assigned to those diseases rather than to cardiac arrest. Consequently, incidence of cardiac arrest is underestimated from administrative data. Finally, regional and cultural differences in use of EMS systems could affect ascertainment of OHCA in current registries. Regimenting and increasing the rigor of reporting of cardiac arrest will improve the understanding of the epidemiology of this syndrome.

Table 17-1. Trends in Layperson Response and Outcomes for EMS-Treated OHCA[10]

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Survival to hospital discharge, %												
ROC	10.2	10.1	11.9	10.3	11.1	11.3	12.4	11.9	12.7	12.4	…	…
CARES	…	…	…	…	…	10.5	10	10.6	10.8	10.6	10.8	10.5
Survival if first rhythm shockable, %												
ROC	25.9	29	33.6	27.8	30.1	30.9	34.1	32.7	33.5	30.2	…	…
CARES	…	…	…	…	…	…	…	…	29.3	29.1	29.5	29.3
First rhythm shockable, %												
ROC	23.7	21.7	21.9	20.9	20.8	21.4	21.7	20.2	20.8	21.3	…	…
CARES	…	…	…	…	…	23.2	23.1	23.2	20.4	20.1	19.8	18.4
Layperson-initiated CPR, %												
ROC	36.5	37.9	37.4	39.1	38.6	38.6	42.8	43	44.5	43.6	…	…
CARES	…	…	…	…	…	38	37.8	40.4	40.4	40.6	40.7	39.4
Layperson use of AED, %												
ROC	3.2	3.3	3.9	4.5	4	3.9	5.1	6	6.6	6.7	…	…
CARES	…	…	…	…	…	4.4	4	4.6	4.9	5.4	5.7	6.0
AED shock by layperson, %												
ROC	2	1.6	1.8	1.8	2	1.8	2	2.2	2.2	2.3	…	…
CARES	…	…	…	…	…	1.7	1.6	1.6	1.6	1.7	1.7	1.6

AED indicates automated external defibrillator; CARES, Cardiac Arrest Registry to Enhance Survival; CPR, cardiopulmonary resuscitation; ellipses (…), data not available; EMS, emergency medical services, OHCA, out-of-hospital cardiac arrest; and ROC, Resuscitation Outcomes Consortium.

Source: Data reported by ROC (ROC Investigators, unpublished data, July 7, 2016) and CARES.[10]

Table 17-2. Characteristics of and Outcomes for OHCA and IHCA

	OHCA		IHCA	
	Adults	Children	Adults	Children
Survival to hospital discharge	10.4	11.1	25.6	48.9
Good functional status at hospital discharge	8.4	9.9	22.0	16.8
VF/VT/shockable	18.7	8.0	15.3	9.9
PEA	…	…	53.1	48.8
Asystole	…	…	23.9	25.8
Unknown	…	…	7.7	15.5
Public setting	18.8	14.6	…	…
Home	69.5	85.3	…	…
Nursing home	11.7	0.1	…	…
Arrest in ICU, operating room, or ED	…	…	53.5	87.8
Noncritical care area	…	…	46.5	12.2

Values are percentages. ED indicates emergency department; ellipses (…), data not available; ICU, intensive care unit; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electrical activity; VF, ventricular fibrillation; and VT, ventricular tachycardia.

OHCA data are from CARES (Cardiac Arrest Registry to Enhance Survival)[10] 2017, based on 76 040 emergency medical services (EMS)–treated OHCA adult cases and 2057 EMS-treated OHCA child cases. IHCA data are from Get With The Guidelines 2017, based on 26 178 adult IHCAs in 311 hospitals and 897 child IHCAs in 92 hospitals.

Table 17-3. Outcomes of EMS-Treated Nontraumatic OHCA in Children: CARES Registry 2017

Age Groups (n)	Survival to Hospital Admission	Survival to Hospital Discharge	Survival With Good Neurological Function (CPC 1 or 2)	In-Hospital Mortality*
<1 y (1197)	19.1	5.4	4.7	71.6
1–12 y (484)	34.9	18.2	15.7	47.9
13–18 y (376)	42.3	20.7	18.9	50.9

Values are percentages. CARES indicates Cardiac Arrest Registry to Enhance Survival; CPC, Cerebral Performance Category; EMS, emergency medical services; and OHCA, out-of-hospital cardiac arrest.

*Percentage of patients admitted to hospital who die before hospital discharge.

Data derived from CARES.[10]

Table 17-4. Outcomes of EMS-Treated Nontraumatic OHCA in Adults (Age ≥18 Years), CARES Registry 2017

Presenting Characteristics (N)	Survival to Hospital Admission	Survival to Hospital Discharge	Survival With Good Neurological Function (CPC 1 or 2)	In-Hospital Mortality*
All presentations (73 910)	28.2	10.4	8.4	63.0
Home/residence (51 344)	26.5	8.7	6.9	67.1
Nursing home (8655)	18.4	4.1	2.0	77.9
Public setting (13 911)	40.3	20.6	17.8	48.8
Unwitnessed (37 397)	18.3	4.6	3.3	75.0
Bystander witnessed (27 296)	37.4	15.9	13.2	57.4
EMS provider witnessed (9217)	40.9	18.0	14.6	56.1
Shockable presenting rhythm (13 792)	48.6	29.1	25.7	40.2
Nonshockable presenting rhythm (60 112)	23.5	6.1	4.4	73.8
Layperson CPR (29 034)	28.3	11.7	9.8	58.6
No layperson CPR (35 657)	24.7	7.4	5.6	70.1

Values are percentages. CARES indicates Cardiac Arrest Registry to Enhance Survival; CPC, Cerebral Performance Index; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; and OHCA, out-of-hospital cardiac arrest.

*Percentage of patients admitted to hospital who die before hospital discharge.

Modified from CARES.[10]

Table 17-5. Sudden Cardiac Arrest (*ICD-10* Codes 146.0, 146.1, 146.9, 149.0)

Population Group	Number of Deaths as Underlying Cause, All Ages	Number of Deaths as Any-Mention Cause, All Ages
Both sexes	17 661	366 494
Males	9354	187 671
Females	8307	178 823
NH white males	7153	135 832
NH white females	6236	127 696
NH black males	1529	24 748
NH black females	1500	25 957
Hispanic males	400	17 700
Hispanic females	313	16 590
NH Asian/Pacific Islander males	210	7233
NH Asian/Pacific Islander females	221	6924
NH American Indian/Alaska Natives	70	2402

ICD-10 indicates *International Classification of Diseases, 10th Revision*; and NH, non-Hispanic.

Data derived from 2016 Centers for Disease Control and Prevention WONDER (Wide-ranging Online Data for Epidemiologic Research) database. Accessed April 17, 2018.[30]

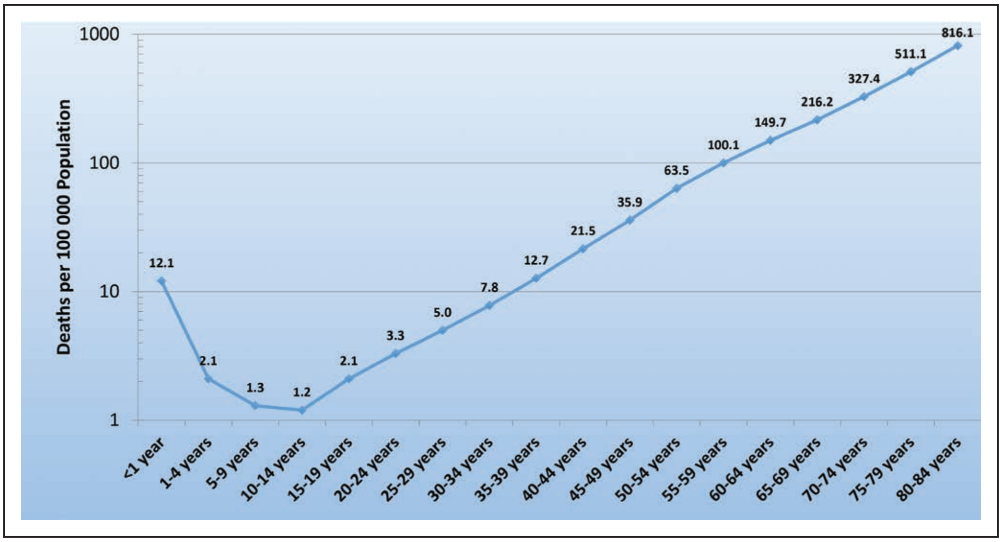

Chart 17-1. **Age-specific death rates for any mention of sudden cardiac death by age, 2016.**
Data derived from Centers for Disease Control and Prevention WONDER (Wide-ranging Online Data for Epidemiologic Research) database. Accessed June 7, 2018.[30]

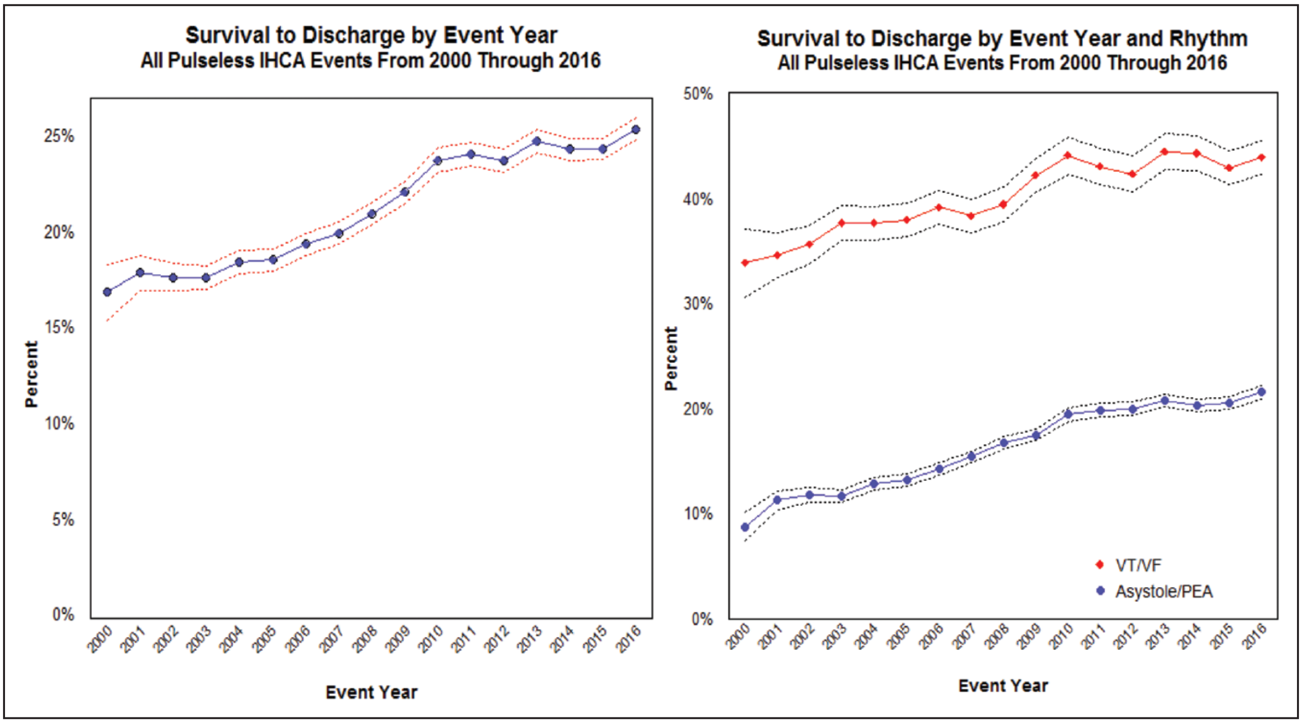

Chart 17-2. **Temporal trends in survival to hospital discharge after pulseless IHCA in GWTG–Resuscitation from 2000 to 2016.**
GWTG indicates Get With The Guidelines; IHCA, in-hospital cardiac arrest; PEA, pulseless electrical activity; VF, ventricular fibrillation; and VT, ventricular tachycardia.
Source: GWTG–Resuscitation; unpublished data, 2017.

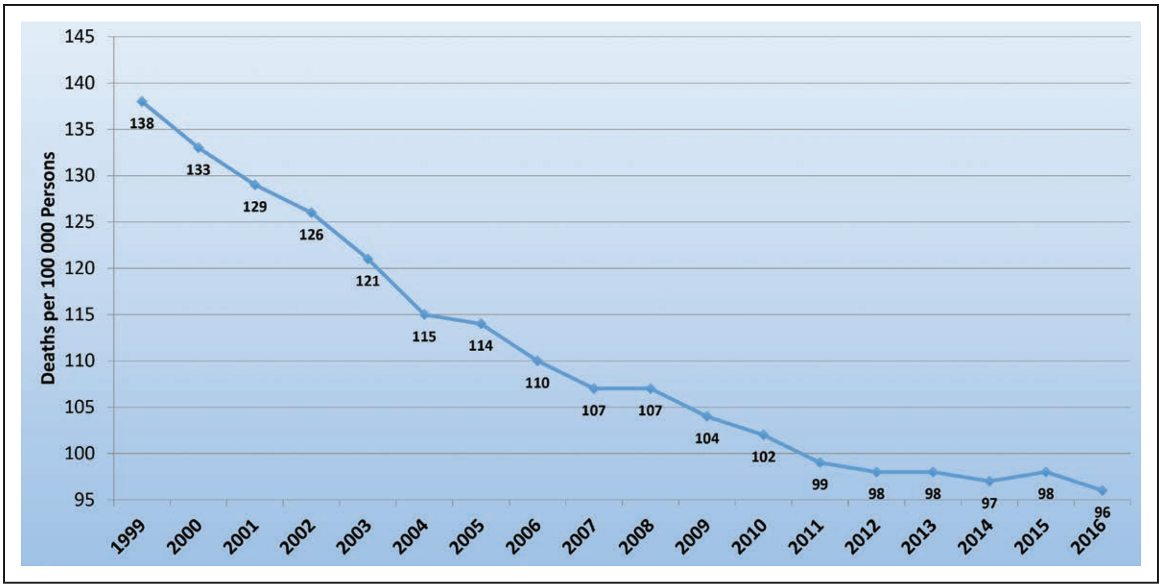

Chart 17-3. Age-adjusted death rates for any mention of sudden cardiac death, 1999 to 2016.
Data derived from Centers for Disease Control and Prevention WONDER (Wide-ranging Online Data for Epidemiologic Research) database. Accessed June 7, 2018.[30]

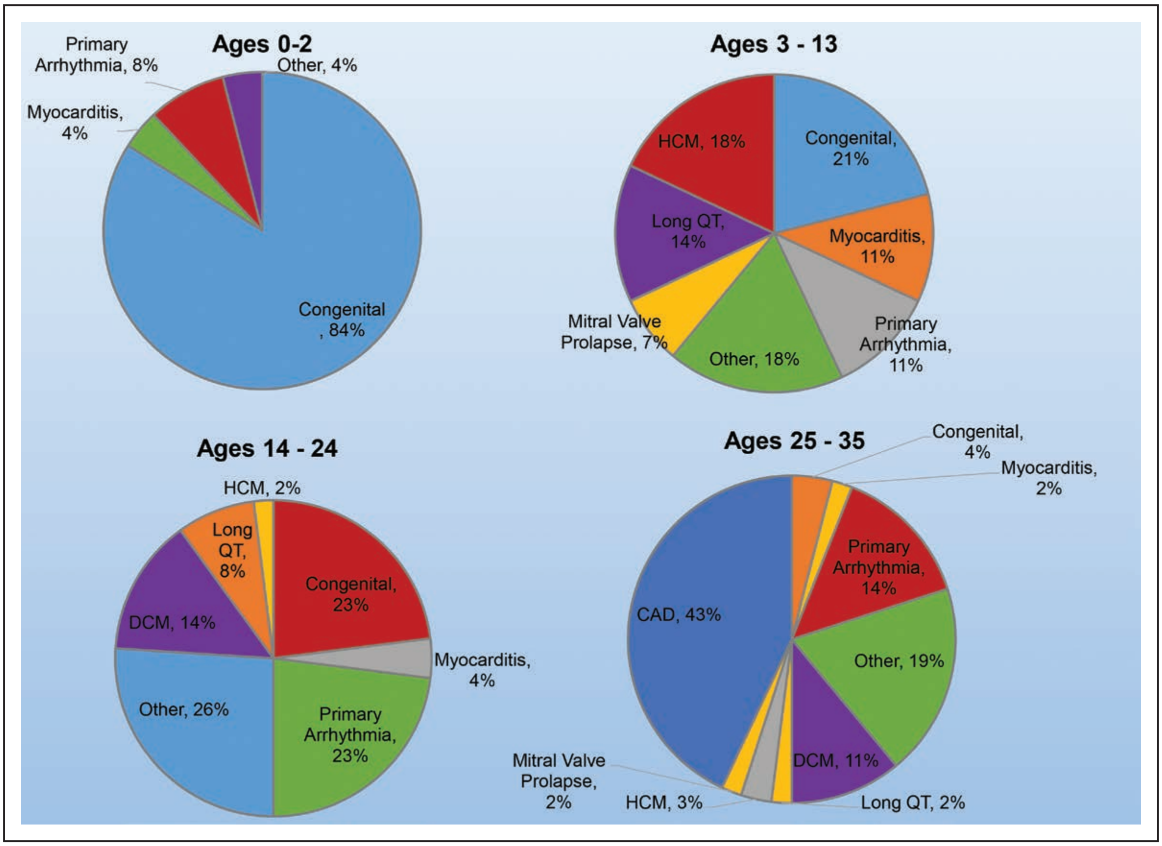

Chart 17-4. Detailed causes of cardiac arrest by age group in children and young adults in King County, WA (1980–2009).
CAD indicates coronary artery disease; DCM, dilated cardiomyopathy; and HCM, hypertrophic cardiomyopathy. "Other" corresponds to all other causes. Reprinted from Meyer et al.[54] Copyright © 2012, American Heart Association, Inc.

REFERENCES

1. Jacobs I, Nadkarni V; and the ILCOR Task Force on Cardiac Arrest and Cardiopulmonary Resuscitation Outcomes. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). *Circulation*. 2004;110:3385–3397. doi: 10.1161/01.CIR.0000147236.85306.15
2. Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, Bossaert LL, Brett SJ, Chamberlain D, de Caen AR, Deakin CD, Finn JC, Gräsner JT, Hazinski MF, Iwami T, Koster RW, Lim SH, Huei-Ming Ma M, McNally BF, Morley PT, Morrison LJ, Monsieurs KG, Montgomery W, Nichol G, Okada K, Eng Hock Ong M, Travers AH, Nolan JP; for the Utstein Collaborators. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry templates for out-of-hospital cardiac arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation [published correction appears in Circulation. 2015;132:e168–e169. *Circulation*. 2015;132:1286–1300. doi: 10.1161/CIR.0000000000000144
3. Claesson A, Djarv T, Nordberg P, Ringh M, Hollenberg J, Axelsson C, Ravn-Fischer A, Stromsoe A. Medical versus non medical etiology in out-of-hospital cardiac arrest-Changes in outcome in relation to the revised Utstein template. *Resuscitation*. 2017;110:48–55. doi: 10.1016/j.resuscitation.2016.10.019
4. Peterson DF, Siebert DM, Kucera KL, et al. Etiology of sudden cardiac arrest and death in US competitive athletes: a 2-year prospective surveillance study [published online April 9, 2018]. *Clin J Sport Med*. doi: 10.1097/JSM.0000000000000598
5. US population data (population clock). United States Census Bureau website. http://www.census.gov. Accessed June 8, 2018.
6. Graham R, McCoy MA, Schultz AM, eds. Committee on the Treatment of Cardia Arrest: Current Status and Future Directions; Board on Health Sciences Policy; Institute of Medicine. *Strategies to Improve Cardiac Arrest Survival: A Time to Act*. Washington, DC: National Academy of Sciences; June 2015.
7. Kurz MC, Donnelly JP, Wang HE. Variations in survival after cardiac arrest among academic medical center-affiliated hospitals. *PLoS One*. 2017;12:e0178793. doi: 10.1371/journal.pone.0178793
8. HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality, Rockville, MD. https://hcupnet.ahrq.gov/. Accessed September 11, 2018.
9. Hawkes C, Booth S, Ji C, Brace-McDonnell SJ, Whittington A, Mapstone J, Cooke MW, Deakin CD, Gale CP, Fothergill R, Nolan JP, Rees N, Soar J, Siriwardena AN, Brown TP, Perkins GD; OHCAO collaborators. Epidemiology and outcomes from out-of-hospital cardiac arrests in England. *Resuscitation*. 2017;110:133–140. doi: 10.1016/j.resuscitation.2016.10.030
10. Cardiac Arrest Registry to Enhance Survival. https://mycares.net. Accessed April 17, 2017.
11. Shavelle DM, Bosson N, Thomas JL, Kaji AH, Sung G, French WJ, Niemann JT. Outcomes of ST elevation myocardial infarction complicated by out-of-hospital cardiac arrest (from the Los Angeles County Regional System). *Am J Cardiol*. 2017;120:729–733. doi: 10.1016/j.amjcard.2017.06.010
12. Merchant RM, Yang L, Becker LB, Berg RA, Nadkarni V, Nichol G, Carr BG, Mitra N, Bradley SM, Abella BS, Groeneveld PW; American Heart Association Get With The Guidelines-Resuscitation Investigators. Incidence of treated cardiac arrest in hospitalized patients in the United States. *Crit Care Med*. 2011;39:2401-2406. doi: 10.1097/CCM.0b013e3182257459
13. Nolan JP, Soar J, Smith GB, Gwinnutt C, Parrott F, Power S, Harrison DA, Nixon E, Rowan K; National Cardiac Arrest Audit. Incidence and outcome of in-hospital cardiac arrest in the United Kingdom National Cardiac Arrest Audit. *Resuscitation*. 2014;85:987–992. doi: 10.1016/j.resuscitation.2014.04.002
14. Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, Ahn C, Iwai S, Jain D, Sule S, Ahmed A, Cooper HA, Frishman WH, Bhatt DL, Panza JA, Fonarow GC. Regional variation in the incidence and outcomes of in-hospital cardiac arrest in the United States. *Circulation*. 2015;131:1415–1425. doi: 10.1161/CIRCULATIONAHA.114.014542
15. Mallikethi-Reddy S, Briasoulis A, Akintoye E, Jagadeesh K, Brook RD, Rubenfire M, Afonso L, Grines CL. Incidence and survival after in-hospital cardiopulmonary resuscitation in nonelderly adults: US experience, 2007 to 2012. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003194. doi: 10.1161/CIRCOUTCOMES.116.003194
16. Bradley SM, Kaboli P, Kamphuis LA, Chan PS, Iwashyna TJ, Nallamothu BK. Temporal trends and hospital-level variation of inhospital cardiac arrest incidence and outcomes in the Veterans Health Administration. *Am Heart J*. 2017;193:117–123. doi: 10.1016/j.ahj.2017.05.018
17. Fink EL, Prince DK, Kaltman JR, Atkins DL, Austin M, Warden C, Hutchison J, Daya M, Goldberg S, Herren H, Tijssen JA, Christenson J, Vaillancourt C, Miller R, Schmicker RH, Callaway CW; Resuscitation Outcomes Consortium. Unchanged pediatric out-of-hospital cardiac arrest incidence and survival rates with regional variation in North America. *Resuscitation*. 2016;107:121–128. doi: 10.1016/j.resuscitation.2016.07.244
18. Inoue M, Tohira H, Williams T, Bailey P, Borland M, McKenzie N, Brink D, Finn J. Incidence, characteristics and survival outcomes of out-of-hospital cardiac arrest in children and adolescents between 1997 and 2014 in Perth, Western Australia. *Emerg Med Australas*. 2017;29:69–76. doi: 10.1111/1742-6723.12657
19. Roberts WO, Stovitz SD. Incidence of sudden cardiac death in Minnesota high school athletes 1993-2012 screened with a standardized pre-participation evaluation. *J Am Coll Cardiol*. 2013;62:1298–1301. doi: 10.1016/j.jacc.2013.05.080
20. Harmon KG, Asif IM, Klossner D, Drezner JA. Incidence of sudden cardiac death in National Collegiate Athletic Association athletes. *Circulation*. 2011;123:1594–1600. doi: 10.1161/CIRCULATIONAHA.110.004622
21. Kim JH, Malhotra R, Chiampas G, d'Hemecourt P, Troyanos C, Cianca J, Smith RN, Wang TJ, Roberts WO, Thompson PD, Baggish AL; Race Associated Cardiac Arrest Event Registry (RACER) Study Group. Cardiac arrest during long-distance running races. *N Engl J Med*. 2012;366:130–140. doi: 10.1056/NEJMoa1106468
22. Jayaraman R, Reinier K, Nair S, Aro AL, Uy-Evanado A, Rusinaru C, Stecker EC, Gunson K, Jui J, Chugh SS. Risk factors of sudden cardiac death in the young: multiple-year community-wide assessment. *Circulation*. 2018;137:1561–1570. doi: 10.1161/CIRCULATIONAHA.117.031262
23. Harmon KG, Asif IM, Maleszewski JJ, Owens DS, Prutkin JM, Salerno JC, Zigman ML, Ellenbogen R, Rao AL, Ackerman MJ,Drezner JA. Incidence and etiology of sudden cardiac arrest and death in high school athletes in the United States. *Mayo Clin Proc*. 2016;91:1493–1502. doi: 10.1016/j.mayocp.2016.07.021
24. Landry CH, Allan KS, Connelly KA, Cunningham K, Morrison LJ, Dorian P; Rescu Investigators. Sudden cardiac arrest during participation in competitive sports. *N Engl J Med*. 2017;377:1943–1953. doi: 10.1056/NEJMoa1615710
25. Maron BJ, Haas TS, Ahluwalia A, Murphy CJ, Garberich RF. Demographics and epidemiology of sudden deaths in young competitive athletes: from the United States National Registry. *Am J Med*. 2016;129:1170–1177. doi: 10.1016/j.amjmed.2016.02.031
26. Harmon KG, Drezner JA, Maleszewski JJ, Lopez-Anderson M, Owens D, Prutkin JM, Asif IM, Klossner D, Ackerman MJ. Pathogeneses of sudden cardiac death in National Collegiate Athletic Association athletes. *Circ Arrhythm Electrophysiol*. 2014;7:198–204. doi: 10.1161/CIRCEP.113.001376
27. Martinez PA, Totapally BR. The epidemiology and outcomes of pediatric in-hospital cardiopulmonary arrest in the United States during 1997 to 2012. *Resuscitation*. 2016;105:177–181. doi: 10.1016/j.resuscitation.2016.06.010
28. Berg RA, Nadkarni VM, Clark AE, Moler F, Meert K, Harrison RE, Newth CJ, Sutton RM, Wessel DL, Berger JT, Carcillo J, Dalton H, Heidemann S, Shanley TP, Zuppa AF, Doctor A, Tamburro RF, Jenkins TL, Dean JM, Holubkov R, Pollack MM; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Incidence and outcomes of cardiopulmonary resuscitation in PICUs. *Crit Care Med*. 2016;44:798–808. doi: 10.1097/CCM.0000000000001484
29. Alten JA, Klugman D, Raymond TT, Cooper DS, Donohue JE, Zhang W, Pasquali SK, Gaies MG. Epidemiology and outcomes of cardiac arrest in pediatric cardiac ICUs. *Pediatr Crit Care Med*. 2017;18:935–943. doi: 10.1097/PCC.0000000000001273

30. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death, 1999–2016. CDC WONDER Online Database [database online]. Released December 2017. Atlanta, GA: Centers for Disease Control and Prevention. http://wonder.cdc.gov/mcd-icd10.html Accessed September 11, 2018 9:57:28 PM.
31. El-Assaad I, Al-Kindi SG, Aziz PF. Trends of out-of-hospital sudden cardiac death among children and young adults. *Pediatrics*. 2017;140:e20171438. doi: 10.1542/peds.2017-1438
32. Girotra S, van Diepen S, Nallamothu BK, Carrel M, Vellano K, Anderson ML, McNally B, Abella BS, Sasson C, Chan PS; in collaboration with CARES Surveillance Group and the HeartRescue Project. Regional variation in out-of-hospital cardiac arrest survival in the United States. *Circulation*. 2016;133:2159–2168. doi: 10.1161/CIRCULATIONAHA.115.018175
33. Galea S, Blaney S, Nandi A, Silverman R, Vlahov D, Foltin G, Kusick M, Tunik M, Richmond N. Explaining racial disparities in incidence of and survival from out-of-hospital cardiac arrest. *Am J Epidemiol*. 2007;166:534–543. doi: 10.1093/aje/kwm102
34. Albaeni A, Beydoun MA, Beydoun HA, Akinyele B, RaghavaKurup L, Chandra-Strobos N, Eid SM. Regional variation in outcomes of hospitalized patients having out-of-hospital cardiac arrest. *Am J Cardiol*. 2017;120:421–427. doi: 10.1016/j.amjcard.2017.04.045
35. Andrew E, Nehme Z, Wolfe R, Bernard S, Smith K. Long-term survival following out-of-hospital cardiac arrest. *Heart*. 2017;103:1104–1110. doi: 10.1136/heartjnl-2016-310485
36. Chan PS, Nichol G, Krumholz HM, Spertus JA, Jones PG, Peterson ED, Rathore SS, Nallamothu BK; American Heart Association National Registry of Cardiopulmonary Resuscitation (NRCPR) Investigators. Racial differences in survival after in-hospital cardiac arrest. *JAMA*. 2009;302:1195–1201. doi: 10.1001/jama.2009.1340
37. Al-Dury N, Rawshani A, Israelsson J, Strömsöe A, Aune S, Agerström J, Karlsson T, Ravn-Fischer A, Herlitz J. Characteristics and outcome among 14,933 adult cases of in-hospital cardiac arrest: a nationwide study with the emphasis on gender and age. *Am J Emerg Med*. 2017;35:1839–1844. doi: 10.1016/j.ajem.2017.06.012
38. Dolmatova EV, Moazzami K, Klapholz M, Kothari N, Feurdean M, Waller AH. Impact of hospital teaching status on mortality, length of stay and cost among patients with cardiac arrest in the United States. *Am J Cardiol*. 2016;118:668–672. doi: 10.1016/j.amjcard.2016.05.062
39. Hansen M, Fleischman R, Meckler G, Newgard CD. The association between hospital type and mortality among critically ill children in US EDs. *Resuscitation*. 2013;84:488–491. doi: 10.1016/j.resuscitation.2016.07.032
40. Eid SM, Abougergi MS, Albaeni A, Chandra-Strobos N. Survival, expenditure and disposition in patients following out-of-hospital cardiac arrest: 1995-2013. *Resuscitation*. 2017;113:13–20. doi: 10.1016/j.resuscitation.2016.12.027
41. Patel N, Patel NJ, Macon CJ, Thakkar B, Desai M, Rengifo-Moreno P, Alfonso CE, Myerburg RJ, Bhatt DL, Cohen MG. Trends and outcomes of coronary angiography and percutaneous coronary intervention after out-of-hospital cardiac arrest associated with ventricular fibrillation or pulseless ventricular tachycardia. *JAMA Cardiol*. 2016;1:890–899. doi: 10.1001/jamacardio.2016.2860
42. Fugate JE, Brinjikji W, Mandrekar JN, Cloft HJ, White RD, Wijdicks EF, Rabinstein AA. Post-cardiac arrest mortality is declining: a study of the US National Inpatient Sample 2001 to 2009. *Circulation*. 2012;126:546–550. doi: 10.1161/CIRCULATIONAHA.111.088807
43. Geri G, Dumas F, Bonnetain F, Bougouin W, Champigneulle B, Arnaout M, Carli P, Marijon E, Varenne O, Mira JP, Empana JP, Cariou A. Predictors of long-term functional outcome and health-related quality of life after out-of-hospital cardiac arrest. *Resuscitation*. 2017;113:77–82. doi: 10.1016/j.resuscitation.2017.01.028
44. Elmer J, Rittenberger JC, Coppler PJ, Guyette FX, Doshi AA, Callaway CW; Pittsburgh Post-Cardiac Arrest Service. Long-term survival benefit from treatment at a specialty center after cardiac arrest. *Resuscitation*. 2016;108:48–53. doi: 10.1016/j.resuscitation.2016.09.008
45. Silverstein FS, Slomine BS, Christensen J, Holubkov R, Page K, Dean JM, Moler FW; Therapeutic Hypothermia to Improve Survival After Cardiac Arrest Trial Group. Functional outcome trajectories after out-of-hospital pediatric cardiac arrest. *Crit Care Med*. 2016;44:e1165–e1174. doi: 10.1097/CCM.0000000000002003
46. Tong JT, Eyngorn I, Mlynash M, Albers GW, Hirsch KG. Functional neurologic outcomes change over the first 6 months after cardiac arrest. *Crit Care Med*. 2016;44:e1202–e1207. doi: 10.1097/CCM.0000000000001963
47. Bucy RA, Hanisko KA, Kamphuis LA, Nallamothu BK, Iwashyna TJ, Pfeiffer PN. Suicide risk management protocol in post-cardiac arrest survivors: development, feasibility, and outcomes. *Ann Am Thorac Soc*. 2017;14:363–367. doi: 10.1513/AnnalsATS.201609-694BC
48. Kragholm K, Wissenberg M, Mortensen RN, Hansen SM, Malta Hansen C, Thorsteinsson K, Rajan S, Lippert F, Folke F, Gislason G, Køber L, Fonager K, Jensen SE, Gerds TA, Torp-Pedersen C, Rasmussen BS. Bystander efforts and 1-year outcomes in out-of-hospital cardiac arrest. *N Engl J Med*. 2017;376:1737–1747. doi: 10.1056/NEJMoa1601891
49. Moulaert VRM, van Heugten CM, Gorgels TPM, Wade DT, Verbunt JA. Long-term outcome after survival of a cardiac arrest: a prospective longitudinal cohort study. *Neurorehabil Neural Repair*. 2017;31:530–539. doi: 10.1177/1545968317697032
50. Steinbusch CVM, van Heugten CM, Rasquin SMC, Verbunt JA, Moulaert VRM. Cognitive impairments and subjective cognitive complaints after survival of cardiac arrest: a prospective longitudinal cohort study. *Resuscitation*. 2017;120:132–137. doi: 10.1016/j.resuscitation.2017.08.007
51. Lilja G, Nielsen N, Bro-Jeppesen J, Dunford H, Friberg H, Hofgren C, Horn J, Insorsi A, Kjaergaard J, Nilsson F, Pelosi P, Winters T, Wise MP, Cronberg T. Return to work and participation in society after out-of-hospital cardiac arrest. *Circ Cardiovasc Qual Outcomes*. 2018;11:e003566. doi: 10.1161/CIRCOUTCOMES.117.003566
52. van Wijnen HG, Rasquin SM, van Heugten CM, Verbunt JA, Moulaert VR. The impact of cardiac arrest on the long-term wellbeing and caregiver burden of family caregivers: a prospective cohort study. *Clin Rehabil*. 2017;31:1267–1275. doi: 10.1177/0269215516686155
53. Stecker EC, Reinier K, Marijon E, Narayanan K, Teodorescu C, Uy-Evanado A, Gunson K, Jui J, Chugh SS. Public health burden of sudden cardiac death in the United States. *Circ Arrhythm Electrophysiol*. 2014;7:212–217. doi: 10.1161/CIRCEP.113.001034
54. Meyer L, Stubbs B, Fahrenbruch C, Maeda C, Harmon K, Eisenberg M, Drezner J. Incidence, causes, and survival trends from cardiovascular-related sudden cardiac arrest in children and young adults 0 to 35 years of age: a 30-year review. *Circulation*. 2012;126:1363–1372. doi: 10.1161/CIRCULATIONAHA.111.076810
55. Winkel BG, Risgaard B, Bjune T, Jabbari R, Lynge TH, Glinge C, Bundgaard H, Haunsø S, Tfelt-Hansen J. Gender differences in sudden cardiac death in the young: a nationwide study. *BMC Cardiovasc Disord*. 2017;17:19. doi: 10.1186/s12872-016-0446-5
56. Gupta R, Tichnell C, Murray B, Rizzo S, Te Riele A, Tandri H, Judge DP, Thiene G, Basso C, Calkins H, James CA. Comparison of features of fatal versus nonfatal cardiac arrest in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Am J Cardiol*. 2017;120:111–117. doi: 10.1016/j.amjcard.2017.03.251
57. Sabbag A, Goldenberg I, Moss AJ, McNitt S, Glikson M, Biton Y, Jackson L, Polonsky B, Zareba W, Kutyifa V. Predictors and risk of ventricular tachyarrhythmias or death in black and white cardiac patients: a MADIT-CRT Trial substudy. *JACC Clin Electrophysiol*. 2016;2:448–455. doi: 10.1016/j.jacep.2016.03.003
58. Reinier K, Thomas E, Andrusiek DL, Aufderheide TP, Brooks SC, Callaway CW, Pepe PE, Rea TD, Schmicker RH, Vaillancourt C, Chugh SS; Resuscitation Outcomes Consortium Investigators. Socioeconomic status and incidence of sudden cardiac arrest. *CMAJ*. 2011;183:1705–1712. doi: 10.1503/cmaj.101512
59. Chelly J, Mongardon N, Dumas F, Varenne O, Spaulding C, Vignaux O, Carli P, Charpentier J, Pène F, Chiche JD, Mira JP, Cariou A. Benefit of an early and systematic imaging procedure after cardiac arrest: insights from the PROCAT (Parisian Region Out of Hospital Cardiac Arrest) registry. *Resuscitation*. 2012;83:1444–1450. doi: 10.1016/j.resuscitation.2012.08.321
60. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *Circulation*. 2006;114:e385–e484. doi: 10.1161/CIRCULATIONAHA.106.178233
61. Deo R, Norby FL, Katz R, Sotoodehnia N, Adabag S, DeFilippi CR, Kestenbaum B, Chen LY, Heckbert SR, Folsom AR, Kronmal RA, Konety S, Patton KK, Siscovick D, Shlipak MG, Alonso A. Development and validation of a sudden cardiac death prediction

model for the general population. *Circulation*. 2016;134:806–816. doi: 10.1161/CIRCULATIONAHA.116.023042
62. Rea TD, Pearce RM, Raghunathan TE, Lemaitre RN, Sotoodehnia N, Jouven X, Siscovick DS. Incidence of out-of-hospital cardiac arrest. *Am J Cardiol*. 2004;93:1455–1460. doi: 10.1016/j.amjcard.2004.03.002
63. Chiuve SE, Fung TT, Rexrode KM, Spiegelman D, Manson JE, Stampfer MJ, Albert CM. Adherence to a low-risk, healthy lifestyle and risk of sudden cardiac death among women. *JAMA*. 2011;306:62–69. doi: 10.1001/jama.2011.907
64. Lowry AW, Knudson JD, Cabrera AG, Graves DE, Morales DL, Rossano JW. Cardiopulmonary resuscitation in hospitalized children with cardiovascular disease: estimated prevalence and outcomes from the Kids' Inpatient Database. *Pediatr Crit Care Med*. 2013;14:248–255. doi: 10.1097/PCC.0b013e3182713329
65. Al-Gobari M, Le HH, Fall M, Gueyffier F, Burnand B. No benefits of statins for sudden cardiac death prevention in patients with heart failure and reduced ejection fraction: a meta-analysis of randomized controlled trials. *PLoS One*. 2017;12:e0171168. doi: 10.1371/journal.pone.0171168
66. Aro AL, Rusinaru C, Uy-Evanado A, Reinier K, Phan D, Gunson K, Jui J, Chugh SS. Syncope and risk of sudden cardiac arrest in coronary artery disease. *Int J Cardiol*. 2017;231:26–30. doi: 10.1016/j.ijcard.2016.12.021
67. Langén VL, Niiranen TJ, Puukka P, Lehtonen AO, Hernesniemi JA, Sundvall J, Salomaa V, Jula AM. Thyroid-stimulating hormone and risk of sudden cardiac death, total mortality and cardiovascular morbidity. *Clin Endocrinol (Oxf)*. 2018;88:105–113. doi: 10.1111/cen.13472
68. Shi S, Liu T, Liang J, Hu D, Yang B. Depression and risk of sudden cardiac death and arrhythmias: a meta-analysis. *Psychosom Med*. 2017;79:153–161. doi: 10.1097/PSY.0000000000000382
69. Müller D, Agrawal R, Arntz HR. How sudden is sudden cardiac death? *Circulation*. 2006;114:1146–1150. doi: 10.1161/CIRCULATIONAHA.106.616318
70. Andersen LW, Kim WY, Chase M, Berg KM, Mortensen SJ, Moskowitz A, Novack V, Cocchi MN, Donnino MW; American Heart Association's Get With the Guidelines–Resuscitation Investigators. The prevalence and significance of abnormal vital signs prior to in-hospital cardiac arrest. *Resuscitation*. 2016;98:112–117. doi: 10.1016/j.resuscitation.2015.08.016
71. Smith GB, Prytherch DR, Jarvis S, Kovacs C, Meredith P, Schmidt PE, Briggs J. A comparison of the ability of the physiologic components of medical emergency team criteria and the U.K. National Early Warning Score to discriminate patients at risk of a range of adverse clinical outcomes. *Crit Care Med*. 2016;44:2171–2181. doi: 10.1097/CCM.0000000000002000
72. O'Neal WT, Singleton MJ, Roberts JD, Tereshchenko LG, Sotoodehnia N, Chen LY, Marcus GM, Soliman EZ. Association between QT-interval components and sudden cardiac death: the ARIC study (Atherosclerosis Risk in Communities). *Circ Arrhythm Electrophysiol*. 2017;10:e005485. doi: 10.1161/CIRCEP.117.005485
73. Lanza GA, Argirò A, Mollo R, De Vita A, Spera F, Golino M, Rota E, Filice M, Crea F. Six-year outcome of subjects without overt heart disease with an early repolarization/J wave electrocardiographic pattern. *Am J Cardiol*. 2017;120:2073–2077. doi: 10.1016/j.amjcard.2017.08.028
74. Sun GZ, Ye N, Chen YT, Zhou Y, Li Z, Sun YX. Early repolarization pattern in the general population: prevalence and associated factors. *Int J Cardiol*. 2017;230:614–618. doi: 10.1016/j.ijcard.2016.12.045
75. De Lazzari C, Genuini I, Gatto MC, Cinque A, Mancone M, D'Ambrosi A, Silvetti E, Fusto A, Pisanelli DM, Fedele F. Screening high school students in Italy for sudden cardiac death prevention by using a telecardiology device: a retrospective observational study. *Cardiol Young*. 2017;27:74–81. doi: 10.1017/S1047951116000147
76. Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. *Circulation*. 2012;125:620–637. doi: 10.1161/CIRCULATIONAHA.111.023838
77. Krahn AD, Healey JS, Chauhan V, Birnie DH, Simpson CS, Champagne J, Gardner M, Sanatani S, Exner DV, Klein GJ, Yee R, Skanes AC, Gula LJ, Gollob MH. Systematic assessment of patients with unexplained cardiac arrest: Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER) [published correction appears in *Circulation*. 2010;121:e460]. *Circulation*. 2009;120:278–285. doi: 10.1161/CIRCULATIONAHA.109.853143
78. Hookana E, Junttila MJ, Kaikkonen KS, Ukkola O, Kesäniemi YA, Kortelainen ML, Huikuri HV. Comparison of family history of sudden cardiac death in nonischemic and ischemic heart disease. *Circ Arrhythm Electrophysiol*. 2012;5:757–761. doi: 10.1161/CIRCEP.112.971465
79. Kaikkonen KS, Kortelainen ML, Linna E, Huikuri HV. Family history and the risk of sudden cardiac death as a manifestation of an acute coronary event. *Circulation*. 2006;114:1462–1467. doi: 10.1161/CIRCULATIONAHA.106.624593
80. Awamleh Garcia P, Alonso Martin JJ, Graupner Abad C, Jiménez Hernández RM, Curcio Ruigómez A, Talavera Calle P, Cristóbal Varela C, Serrano Antolín J, Muñiz J, Gómez Doblas JJ, Roig E; Investigators of the OFRECE study. Prevalence of electrocardiographic patterns associated with sudden cardiac death in the Spanish population aged 40 years or older. results of the OFRECE Study. *Rev Esp Cardiol (Engl Ed)*. 2017;70:801–807. doi: 10.1016/j.rec.2016.11.039
81. Christiansen SL, Hertz CL, Ferrero-Miliani L, Dahl M, Weeke PE, LuCamp, Ottesen GL, Frank-Hansen R, Bundgaard H, Morling N. Genetic investigation of 100 heart genes in sudden unexplained death victims in a forensic setting. *Eur J Hum Genet*. 2016;24:1797–1802. doi: 10.1038/ejhg.2016.118
82. Nunn LM, Lopes LR, Syrris P, Murphy C, Plagnol V, Firman E, Dalageorgou C, Zorio E, Domingo D, Murday V, Findlay I, Duncan A, Carr-White G, Robert L, Bueser T, Langman C, Fynn SP, Goddard M, White A, Bundgaard H, Ferrero-Miliani L, Wheeldon N, Suvarna SK, O'Beirne A, Lowe MD, McKenna WJ, Elliott PM, Lambiase PD. Diagnostic yield of molecular autopsy in patients with sudden arrhythmic death syndrome using targeted exome sequencing. *Europace*. 2016;18:888–896. doi: 10.1093/europace/euv285
83. Anderson JH, Tester DJ, Will ML, Ackerman MJ. Whole-exome molecular autopsy after exertion-related sudden unexplained death in the young. *Circ Cardiovasc Genet*. 2016;9:259–265. doi: 10.1161/CIRCGENETICS.115.001370
84. Steinberg C, Padfield GJ, Champagne J, Sanatani S, Angaran P, Andrade JG, Roberts JD, Healey JS, Chauhan VS, Birnie DH, Janzen M, Gerull B, Klein GJ, Leather R, Simpson CS, Seifer C, Talajic M, Gardner M, Krahn AD. Cardiac abnormalities in first-degree relatives of unexplained cardiac arrest victims: a report from the Cardiac Arrest Survivors With Preserved Ejection Fraction Registry. *Circ Arrhythm Electrophysiol*. 2016;9:e004274. doi: 10.1161/CIRCEP.115.004274
85. Kumar S, Peters S, Thompson T, Morgan N, Maccicoca I, Trainer A, Zentner D, Kalman JM, Winship I, Vohra JK. Familial cardiological and targeted genetic evaluation: low yield in sudden unexplained death and high yield in unexplained cardiac arrest syndromes. *Heart Rhythm*. 2013;10:1653–1660. doi: 10.1016/j.hrthm.2013.08.022
86. Quenin P, Kyndt F, Mabo P, Mansourati J, Babuty D, Thollet A, Guyomarch B, Redon R, Barc J, Schott JJ, Sacher F, Probst V, Gourraud JB. Clinical yield of familial screening after sudden death in young subjects: the French experience. *Circ Arrhythm Electrophysiol*. 2017;10:e005236. doi: 10.1161/CIRCEP.117.005236.
87. Bezzina CR, Lahrouchi N, Priori SG. Genetics of sudden cardiac death. *Circ Res*. 2015;116:1919–1936. doi: 10.1161/CIRCRESAHA.116.304030
88. Nakano Y, Shimizu W. Genetics of long-QT syndrome. *J Hum Genet*. 2016;61:51–55. doi: 10.1038/jhg.2015.74
89. Goldenberg I, Zareba W, Moss AJ. Long QT syndrome. *Curr Probl Cardiol*. 2008;33:629–694. doi: 10.1016/j.cpcardiol.2008.07.002
90. Wedekind H, Burde D, Zumhagen S, Debus V, Burkhardtsmaier G, Mönnig G, Breithardt G, Schulze-Bahr E. QT interval prolongation and risk for cardiac events in genotyped LQTS-index children. *Eur J Pediatr*. 2009;168:1107–1115. doi: 10.1007/s00431-008-0896-6
91. Schwartz PJ, Stramba-Badiale M, Crotti L, Pedrazzini M, Besana A, Bosi G, Gabbarini F, Goulene K, Insolia R, Mannarino S, Mosca F, Nespoli L, Rimini A, Rosati E, Salice P, Spazzolini C. Prevalence of the congenital long-QT syndrome. *Circulation*. 2009;120:1761–1767. doi: 10.1161/CIRCULATIONAHA.109.863209
92. Hayashi K, Fujino N, Uchiyama K, Ino H, Sakata K, Konno T, Masuta E, Funada A, Sakamoto Y, Tsubokawa T, Nakashima K, Liu L, Higashida H, Hiramaru Y, Shimizu M, Yamagishi M. Long QT syndrome and associated gene mutation carriers in Japanese children: results from ECG screening examinations. *Clin Sci (Lond)*. 2009;117:415–424. doi: 10.1042/CS20080528
93. Fugate T 2nd, Moss AJ, Jons C, McNitt S, Mullally J, Ouellet G, Goldenberg I, Zareba W, Robinson JL; for the U.S. portion of International Long QT Syndrome Registry Investigators. Long QT syndrome in African-Americans. *Ann Noninvasive Electrocardiol*. 2010;15:73–76. doi: 10.1111/j.1542-474X.2009.00342.x
94. Jons C, O-Uchi J, Moss AJ, Reumann M, Rice JJ, Goldenberg I, Zareba W, Wilde AA, Shimizu W, Kanters JK, McNitt S, Hofman N, Robinson JL, Lopes CM. Use of mutant-specific ion channel characteristics for risk stratification of long QT syndrome patients. *Sci Transl Med*. 2011;3:76ra28. doi: 10.1126/scitranslmed.3001551

95. Barsheshet A, Goldenberg I, O-Uchi J, Moss AJ, Jons C, Shimizu W, Wilde AA, McNitt S, Peterson DR, Zareba W, Robinson JL, Ackerman MJ, Cypress M, Gray DA, Hofman N, Kanters JK, Kaufman ES, Platonov PG, Qi M, Towbin JA, Vincent GM, Lopes CM. Mutations in cytoplasmic loops of the KCNQ1 channel and the risk of life-threatening events: implications for mutation-specific response to β-blocker therapy in type 1 long-QT syndrome. *Circulation*. 2012;125:1988–1996. doi: 10.1161/CIRCULATIONAHA.111.048041
96. Mullally J, Goldenberg I, Moss AJ, Lopes CM, Ackerman MJ, Zareba W, McNitt S, Robinson JL, Benhorin J, Kaufman ES, Towbin JA, Barsheshet A. Risk of life-threatening cardiac events among patients with long QT syndrome and multiple mutations. *Heart Rhythm*. 2013;10:378–382. doi: 10.1016/j.hrthm.2012.11.006
97. Arnestad M, Crotti L, Rognum TO, Insolia R, Pedrazzini M, Ferrandi C, Vege A, Wang DW, Rhodes TE, George AL Jr, Schwartz PJ. Prevalence of long-QT syndrome gene variants in sudden infant death syndrome. *Circulation*. 2007;115:361–367. doi: 10.1161/CIRCULATIONAHA.106.658021
98. Chiang CE, Roden DM. The long QT syndromes: genetic basis and clinical implications. *J Am Coll Cardiol*. 2000;36:1–12.
99. Crotti L, Tester DJ, White WM, Bartos DC, Insolia R, Besana A, Kunic JD, Will ML, Velasco EJ, Bair JJ, Ghidoni A, Cetin I, Van Dyke DL, Wick MJ, Brost B, Delisle BP, Facchinetti F, George AL, Schwartz PJ, Ackerman MJ. Long QT syndrome-associated mutations in intrauterine fetal death. *JAMA*. 2013;309:1473–1482. doi: 10.1001/jama.2013.3219
100. Tester DJ, Wong LCH, Chanana P, Jaye A, Evans JM, FitzPatrick DR, Evans MJ, Fleming P, Jeffrey I, Cohen MC, Tfelt-Hansen J, Simpson MA, Behr ER, Ackerman MJ. Cardiac genetic predisposition in sudden infant death syndrome. *J Am Coll Cardiol*. 2018;71:1217–1227. doi: 10.1016/j.jacc.2018.01.030
101. Cross B, Homoud M, Link M, Foote C, Garlitski AC, Weinstock J, Estes NA 3rd. The short QT syndrome. *J Interv Card Electrophysiol*. 2011;31:25–31. doi: 10.1007/s10840-011-9566-0
102. Kobza R, Roos M, Niggli B, Abächerli R, Lupi GA, Frey F, Schmid JJ, Erne P. Prevalence of long and short QT in a young population of 41,767 predominantly male Swiss conscripts. *Heart Rhythm*. 2009;6:652–657. doi: 10.1016/j.hrthm.2009.01.009
103. Providência R, Karim N, Srinivasan N, Honarbakhsh S, Vidigal Ferreira MJ, Gonçalves L, Marijon E, Lambiase PD. Impact of QTc formulae in the prevalence of short corrected QT interval and impact on probability and diagnosis of short QT syndrome. *Heart*. 2018;104:502–508. doi: 10.1136/heartjnl-2017-311673
104. Dhutia H, Malhotra A, Parpia S, Gabus V, Finocchiaro G, Mellor G, Merghani A, Millar L, Narain R, Sheikh N, Behr ER, Papadakis M, Sharma S. The prevalence and significance of a short QT interval in 18,825 low-risk individuals including athletes. *Br J Sports Med*. 2016;50:124–129. doi: 10.1136/bjsports-2015-094827
105. Guerrier K, Kwiatkowski D, Czosek RJ, Spar DS, Anderson JB, Knilans TK. Short QT interval prevalence and clinical outcomes in a pediatric population. *Circ Arrhythm Electrophysiol*. 2015;8:1460–1464. doi: 10.1161/CIRCEP.115.003256
106. Giustetto C, Schimpf R, Mazzanti A, Scrocco C, Maury P, Anttonen O, Probst V, Blanc JJ, Sbragia P, Dalmasso P, Borggrefe M, Gaita F. Long-term follow-up of patients with short QT syndrome. *J Am Coll Cardiol*. 2011;58:587–595. doi: 10.1016/j.jacc.2011.03.038
107. Villafañe J, Atallah J, Gollob MH, Maury P, Wolpert C, Gebauer R, Watanabe H, Horie M, Anttonen O, Kannankeril P, Faulknier B, Bleiz J, Makiyama T, Shimizu W, Hamilton RM, Young ML. Long-term follow-up of a pediatric cohort with short QT syndrome. *J Am Coll Cardiol*. 2013;61:1183–1191. doi: 10.1016/j.jacc.2012.12.025
108. Benito B, Brugada J, Brugada R, Brugada P. Brugada syndrome [published correction appears in *Rev Esp Cardiol*. 2010;63:620]. *Rev Esp Cardiol*. 2009;62:1297–1315.
109. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP; Heart Rhythm Society (HRS); European Heart Rhythm Association (EHRA). HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) [published correction appears in *Europace*. 2012;14:277]. *Europace*. 2011;13:1077–1109. doi: 10.1093/europace/eur245
110. Quan XQ, Li S, Liu R, Zheng K, Wu XF, Tang Q. A meta-analytic review of prevalence for Brugada ECG patterns and the risk for death. *Medicine (Baltimore)*. 2016;95:e5643. doi: 10.1097/MD.0000000000005643
111. Baron RC, Thacker SB, Gorelkin L, Vernon AA, Taylor WR, Choi K. Sudden death among Southeast Asian refugees: an unexplained nocturnal phenomenon. *JAMA*. 1983;250:2947–2951.
112. Gilbert J, Gold RL, Haffajee CI, Alpert JS. Sudden cardiac death in a southeast Asian immigrant: clinical, electrophysiologic, and biopsy characteristics. *Pacing Clin Electrophysiol*. 1986;9(pt 1):912–914.
113. Hermida JS, Lemoine JL, Aoun FB, Jarry G, Rey JL, Quiret JC. Prevalence of the Brugada syndrome in an apparently healthy population. *Am J Cardiol*. 2000;86:91–94.
114. Miyasaka Y, Tsuji H, Yamada K, Tokunaga S, Saito D, Imuro Y, Matsumoto N, Iwasaka T. Prevalence and mortality of the Brugada-type electrocardiogram in one city in Japan. *J Am Coll Cardiol*. 2001;38:771–774.
115. Kamakura S, Ohe T, Nakazawa K, Aizawa Y, Shimizu A, Horie M, Ogawa S, Okumura K, Tsuchihashi K, Sugi K, Makita N, Hagiwara N, Inoue H, Atarashi H, Aihara N, Shimizu W, Kurita T, Suyama K, Noda T, Satomi K, Okamura H, Tomoike H; Brugada Syndrome Investigators in Japan. Long-term prognosis of probands with Brugada-pattern ST-elevation in leads V1-V3. *Circ Arrhythm Electrophysiol*. 2009;2:495–503. doi: 10.1161/CIRCEP.108.816892
116. Maury P, Rollin A, Sacher F, Gourraud JB, Raczka F, Pasquié JL, Duparc A, Mondoly P, Cardin C, Delay M, Derval N, Chatel S, Bongard V, Sadron M, Denis A, Davy JM, Hocini M, Jaïs P, Jesel L, Haïssaguerre M, Probst V. Prevalence and prognostic role of various conduction disturbances in patients with the Brugada syndrome. *Am J Cardiol*. 2013;112:1384–1389. doi: 10.1016/j.amjcard.2013.06.033
117. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, Babuty D, Sacher F, Giustetto C, Schulze-Bahr E, Borggrefe M, Haissaguerre M, Mabo P, Le Marec H, Wolpert C, Wilde AA. Long-term prognosis of patients diagnosed with Brugada syndrome: results from the FINGER Brugada Syndrome Registry. *Circulation*. 2010;121:635–643. doi: 10.1161/CIRCULATIONAHA.109.887026
118. Lieve KV, Wilde AA. Inherited ion channel diseases: a brief review. *Europace*. 2015;17(suppl 2):ii1–ii6. doi: 10.1093/europace/euv105
119. Hayashi M, Denjoy I, Extramiana F, Maltret A, Buisson NR, Lupoglazoff JM, Klug D, Hayashi M, Takatsuki S, Villain E, Kamblock J, Messali A, Guicheney P, Lunardi J, Leenhardt A. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2009;119:2426–2434. doi: 10.1161/CIRCULATIONAHA.108.829267
120. Sumitomo N, Harada K, Nagashima M, Yasuda T, Nakamura Y, Aragaki Y, Saito A, Kurosaki K, Jouo K, Koujiro M, Konishi S, Matsuoka S, Oono T, Hayakawa S, Miura M, Ushinohama H, Shibata T, Niimura I. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. *Heart*. 2003;89:66–70.
121. Sy RW, Gollob MH, Klein GJ, Yee R, Skanes AC, Gula LJ, Leong-Sit P, Gow RM, Green MS, Birnie DH, Krahn AD. Arrhythmia characterization and long-term outcomes in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm*. 2011;8:864–871. doi: 10.1016/j.hrthm.2011.01.048
122. Kawata H, Ohno S, Aiba T, Sakaguchi H, Miyazaki A, Sumitomo N, Kamakura T, Nakajima I, Inoue YY, Miyamoto K, Okamura H, Noda T, Kusano K, Kamakura S, Miyamoto Y, Shiraishi I, Horie M, Shimizu W. Catecholaminergic polymorphic ventricular tachycardia (CPVT) associated with ryanodine receptor (RyR2) gene mutations: long-term prognosis after initiation of medical treatment. *Circ J*. 2016;80:1907–1915. doi: 10.1253/circj.CJ-16-0250
123. Hamilton RM. Arrhythmogenic right ventricular cardiomyopathy. *Pacing Clin Electrophysiol*. 2009;32(suppl 2):S44–S51. doi: 10.1111/j.1540-8159.2009.02384.x
124. Dalal D, Nasir K, Bomma C, Prakasa K, Tandri H, Piccini J, Roguin A, Tichnell C, James C, Russell SD, Judge DP, Abraham T, Spevak PJ, Bluemke DA, Calkins H. Arrhythmogenic right ventricular dysplasia: a United States experience. *Circulation*. 2005;112:3823–3832. doi: 10.1161/CIRCULATIONAHA.105.542266
125. Hulot JS, Jouven X, Empana JP, Frank R, Fontaine G. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circulation*. 2004;110:1879–1884. doi: 10.1161/01.CIR.0000143375.93288.82
126. Mazzanti A, Ng K, Faragli A, Maragna R, Chiodaroli E, Orphanou N, Monteforte N, Memmi M, Gambelli P, Novelli V, Bloise R, Catalano O, Moro G, Tibollo V, Morini M, Bellazzi R, Napolitano C, Bagnardi V, Priori

SG. Arrhythmogenic right ventricular cardiomyopathy: clinical course and predictors of arrhythmic risk. *J Am Coll Cardiol*. 2016;68:2540–2550. doi: 10.1016/j.jacc.2016.09.951
127. Maron BJ, Olivotto I, Spirito P, Casey SA, Bellone P, Gohman TE, Graham KJ, Burton DA, Cecchi F. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. *Circulation*. 2000;102:858–864.
128. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980-2006. *Circulation*. 2009;119:1085–1092. doi: 10.1161/CIRCULATIONAHA.108.804617
129. Elliott PM, Gimeno Blanes JR, Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. *Lancet*. 2001;357:420–424. doi: 10.1016/S0140-6736(00)04005-8
130. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. *N Engl J Med*. 2000;342:1778–1785. doi: 10.1056/NEJM200006153422403
131. Blomström-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ, Campbell WB, Haines DE, Kuck KH, Lerman BB, Miller DD, Shaeffer CW, Stevenson WG, Tomaselli GF. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias). *Circulation*. 2003;108:1871–1909. doi: 10.1161/01.CIR.0000091380.04100.84
132. Adabag AS, Casey SA, Kuskowski MA, Zenovich AG, Maron BJ. Spectrum and prognostic significance of arrhythmias on ambulatory Holter electrocardiogram in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2005;45:697–704. doi: 10.1016/j.jacc.2004.11.043
133. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. *J Am Coll Cardiol*. 2003;42:873–879.
134. Kofflard MJ, Ten Cate FJ, van der Lee C, van Domburg RT. Hypertrophic cardiomyopathy in a large community-based population: clinical outcome and identification of risk factors for sudden cardiac death and clinical deterioration. *J Am Coll Cardiol*. 2003;41:987–993.
135. Spirito P, Autore C, Rapezzi C, Bernabò P, Badagliacca R, Maron MS, Bongioanni S, Coccolo F, Estes NA, Barillà CS, Biagini E, Quarta G, Conte MR, Bruzzi P, Maron BJ. Syncope and risk of sudden death in hypertrophic cardiomyopathy. *Circulation*. 2009;119:1703–1710. doi: 10.1161/CIRCULATIONAHA.108.798314
136. Elliott PM, Gimeno JR, Tomé MT, Shah J, Ward D, Thaman R, Mogensen J, McKenna WJ. Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy. *Eur Heart J*. 2006;27:1933–1941. doi: 10.1093/eurheartj/ehl041
137. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med*. 2003;348:295–303. doi: 10.1056/NEJMoa021332
138. Efthimiadis GK, Parcharidou DG, Giannakoulas G, Pagourelias ED, Charalampidis P, Savvopoulos G, Ziakas A, Karvounis H, Styliadis IH, Parcharidis GE. Left ventricular outflow tract obstruction as a risk factor for sudden cardiac death in hypertrophic cardiomyopathy. *Am J Cardiol*. 2009;104:695–699. doi: 10.1016/j.amjcard.2009.04.039
139. Bos JM, Maron BJ, Ackerman MJ, Haas TS, Sorajja P, Nishimura RA, Gersh BJ, Ommen SR. Role of family history of sudden death in risk stratification and prevention of sudden death with implantable defibrillators in hypertrophic cardiomyopathy. *Am J Cardiol*. 2010;106:1481–1486. doi: 10.1016/j.amjcard.2010.06.077
140. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, Mahon NG, McKenna WJ. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. *J Am Coll Cardiol*. 2000;36:2212–2218.
141. Patton KK, Ellinor PT, Ezekowitz M, Kowey P, Lubitz SA, Perez M, Piccini J, Turakhia M, Wang P, Viskin S; on behalf of the American Heart Association Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology and Council on Functional Genomics and Translational Biology. Electrocardiographic early repolarization: a scientific statement from the American Heart Association. *Circulation*. 2016;133:1520–1529. doi: 10.1161/CIR.0000000000000388
142. Haïssaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquié JL, Nogami A, Babuty D, Yli-Mayry S, De Chillou C, Scanu P, Mabo P, Matsuo S, Probst V, Le Scouarnec S, Defaye P, Schlaepfer J, Rostock T, Lacroix D, Lamaison D, Lavergne T, Aizawa Y, Englund A, Anselme F, O'Neill M, Hocini M, Lim KT, Knecht S, Veenhuyzen GD, Bordachar P, Chauvin M, Jais P, Coureau G, Chene G, Klein GJ, Clémenty J. Sudden cardiac arrest associated with early repolarization. *N Engl J Med*. 2008;358:2016–2023. doi: 10.1056/NEJMoa071968
143. Rosso R, Kogan E, Belhassen B, Rozovski U, Scheinman MM, Zeltser D, Halkin A, Steinvil A, Heller K, Glikson M, Katz A, Viskin S. J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance. *J Am Coll Cardiol*. 2008;52:1231–1238. doi: 10.1016/j.jacc.2008.07.010
144. Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med*. 2009;361:2529–2537. doi: 10.1056/NEJMoa0907589
145. Walsh JA 3rd, Ilkhanoff L, Soliman EZ, Prineas R, Liu K, Ning H, Lloyd-Jones DM. Natural history of the early repolarization pattern in a biracial cohort: CARDIA (Coronary Artery Risk Development in Young Adults) Study. *J Am Coll Cardiol*. 2013;61:863–869. doi: 10.1016/j.jacc.2012.11.053
146. Kamakura T, Kawata H, Nakajima I, Yamada Y, Miyamoto K, Okamura H, Noda T, Satomi K, Aiba T, Takaki H, Aihara N, Kamakura S, Kimura T, Shimizu W. Significance of non-type 1 anterior early repolarization in patients with inferolateral early repolarization syndrome. *J Am Coll Cardiol*. 2013;62:1610–1618. doi: 10.1016/j.jacc.2013.05.081
147. Siebermair J, Sinner MF, Beckmann BM, Laubender RP, Martens E, Sattler S, Fichtner S, Estner HL, Kääb S, Wakili R. Early repolarization pattern is the strongest predictor of arrhythmia recurrence in patients with idiopathic ventricular fibrillation: results from a single centre long-term follow-up over 20 years. *Europace*. 2016;18:718–725. doi: 10.1093/europace/euv301
148. Gourraud JB, Le Scouarnec S, Sacher F, Chatel S, Derval N, Portero V, Chavernac P, Sandoval JE, Mabo P, Redon R, Schott JJ, Le Marec H, Haïssaguerre M, Probst V. Identification of large families in early repolarization syndrome. *J Am Coll Cardiol*. 2013;61:164–172. doi: 10.1016/j.jacc.2012.09.040
149. Sinner MF, Porthan K, Noseworthy PA, Havulinna AS, Tikkanen JT, Müller-Nurasyid M, Peloso G, Ulivi S, Beckmann BM, Brockhaus AC, Cooper RR, Gasparini P, Hengstenberg C, Hwang SJ, Iorio A, Junttila MJ, Klopp N, Kähönen M, Laaksonen MA, Lehtimäki T, Lichtner P, Lyytikäinen LP, Martens E, Meisinger C, Meitinger T, Merchant FM, Nieminen MS, Peters A, Pietilä A, Perz S, Oikarinen L, Raitakari O, Reinhard W, Silander K, Thorand B, Wichmann HE, Sinagra G, Viikari J, O'Donnell CJ, Ellinor PT, Huikuri HV, Kääb S, Newton-Cheh C, Salomaa V. A meta-analysis of genome-wide association studies of the electrocardiographic early repolarization pattern. *Heart Rhythm*. 2012;9:1627–1634. doi: 10.1016/j.hrthm.2012.06.008
150. Dukes JW, Dewland TA, Vittinghoff E, Mandyam MC, Heckbert SR, Siscovick DS, Stein PK, Psaty BM, Sotoodehnia N, Gottdiener JS, Marcus GM. Ventricular ectopy as a predictor of heart failure and death. *J Am Coll Cardiol*. 2015;66:101–109. doi: 10.1016/j.jacc.2015.04.062
151. Wathen MS, DeGroot PJ, Sweeney MO, Stark AJ, Otterness MF, Adkisson WO, Canby RC, Khalighi K, Machado C, Rubenstein DS, Volosin KJ; PainFREE Rx II Investigators. Prospective randomized multicenter trial of empirical antitachycardia pacing versus shocks for spontaneous rapid ventricular tachycardia in patients with implantable cardioverter-defibrillators: Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx II) trial results. *Circulation*. 2004;110:2591–2596. doi: 10.1161/01.CIR.0000145610.64014.E4
152. Marine JE, Shetty V, Chow GV, Wright JG, Gerstenblith G, Najjar SS, Lakatta EG, Fleg JL. Prevalence and prognostic significance of exercise-induced nonsustained ventricular tachycardia in asymptomatic volunteers: BLSA (Baltimore Longitudinal Study of Aging). *J Am Coll Cardiol*. 2013;62:595–600. doi: 10.1016/j.jacc.2013.05.026
153. Belhassen B, Viskin S. Idiopathic ventricular tachycardia and fibrillation. *J Cardiovasc Electrophysiol*. 1993;4:356–368.
154. Lemery R, Brugada P, Bella PD, Dugernier T, van den Dool A, Wellens HJ. Nonischemic ventricular tachycardia: clinical course and long-term follow-up in patients without clinically overt heart disease. *Circulation*. 1989;79:990–999.
155. Sacher F, Tedrow UB, Field ME, Raymond JM, Koplan BA, Epstein LM, Stevenson WG. Ventricular tachycardia ablation: evolution of patients and procedures over 8 years. *Circ Arrhythm Electrophysiol*. 2008;1:153–161. doi: 10.1161/CIRCEP.108.769471

156. Baman TS, Lange DC, Ilg KJ, Gupta SK, Liu TY, Alguire C, Armstrong W, Good E, Chugh A, Jongnarangsin K, Pelosi F Jr, Crawford T, Ebinger M, Oral H, Morady F, Bogun F. Relationship between burden of premature ventricular complexes and left ventricular function. *Heart Rhythm*. 2010;7:865–869. doi: 10.1016/j.hrthm.2010.03.036
157. Yarlagadda RK, Iwai S, Stein KM, Markowitz SM, Shah BK, Cheung JW, Tan V, Lerman BB, Mittal S. Reversal of cardiomyopathy in patients with repetitive monomorphic ventricular ectopy originating from the right ventricular outflow tract. *Circulation*. 2005;112:1092–1097. doi: 10.1161/CIRCULATIONAHA.105.546432
158. Noda T, Shimizu W, Taguchi A, Aiba T, Satomi K, Suyama K, Kurita T, Aihara N, Kamakura S. Malignant entity of idiopathic ventricular fibrillation and polymorphic ventricular tachycardia initiated by premature extrasystoles originating from the right ventricular outflow tract. *J Am Coll Cardiol*. 2005;46:1288–1294. doi: 10.1016/j.jacc.2005.05.077
159. Viskin S, Rosso R, Rogowski O, Belhassen B. The "short-coupled" variant of right ventricular outflow ventricular tachycardia: a not-so-benign form of benign ventricular tachycardia? *J Cardiovasc Electrophysiol*. 2005;16:912–916. doi: 10.1111/j.1540-8167.2005.50040.x
160. Panidis IP, Morganroth J. Sudden death in hospitalized patients: cardiac rhythm disturbances detected by ambulatory electrocardiographic monitoring. *J Am Coll Cardiol*. 1983;2:798–805.
161. Lewis BH, Antman EM, Graboys TB. Detailed analysis of 24 hour ambulatory electrocardiographic recordings during ventricular fibrillation or torsade de pointes. *J Am Coll Cardiol*. 1983;2:426–436.
162. Gang UJ, Jøns C, Jørgensen RM, Abildstrøm SZ, Haarbo J, Messier MD, Huikuri HV, Thomsen PE; CARISMA Investigators. Heart rhythm at the time of death documented by an implantable loop recorder. *Europace*. 2010;12:254–260. doi: 10.1093/europace/eup383
163. Hai JJ, Un KC, Wong CK, Wong KL, Zhang ZY, Chan PH, Lau CP, Siu CW, Tse HF. Prognostic implications of early monomorphic and non-monomorphic tachyarrhythmias in patients discharged with acute coronary syndrome. *Heart Rhythm*. 2018;15:822–829. doi: 10.1016/j.hrthm.2018.02.016
164. Passman R, Kadish A. Polymorphic ventricular tachycardia, long Q-T syndrome, and torsades de pointes. *Med Clin North Am*. 2001;85:321–341.
165. Brady WJ, DeBehnke DJ, Laundrie D. Prevalence, therapeutic response, and outcome of ventricular tachycardia in the out-of-hospital setting: a comparison of monomorphic ventricular tachycardia, polymorphic ventricular tachycardia, and torsades de pointes. *Acad Emerg Med*. 1999;6:609–617.
166. Choudhuri I, Pinninti M, Marwali MR, Sra J, Akhtar M. Polymorphic ventricular tachycardia, part I: structural heart disease and acquired causes. *Curr Probl Cardiol*. 2013;38:463–496. doi: 10.1016/j.cpcardiol.2013.07.001
167. Arunachalam K, Lakshmanan S, Maan A, Kumar N, Dominic P. Impact of drug induced long QT syndrome: a systematic review. *J Clin Med Res*. 2018;10:384–390. doi: 10.14740/jocmr3338w
168. Sarganas G, Garbe E, Klimpel A, Hering RC, Bronder E, Haverkamp W. Epidemiology of symptomatic drug-induced long QT syndrome and Torsade de Pointes in Germany. *Europace*. 2014;16:101–108. doi: 10.1093/europace/eut214
169. Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. *JAMA*. 1993;270:2590–2597.
170. Zeltser D, Justo D, Halkin A, Prokhorov V, Heller K, Viskin S. Torsade de pointes due to noncardiac drugs: most patients have easily identifiable risk factors. *Medicine (Baltimore)*. 2003;82:282–290. doi: 10.1097/01.md.0000085057.63483.9b
171. Kannankeril P, Roden DM, Darbar D. Drug-induced long QT syndrome. *Pharmacol Rev*. 2010;62:760–781. doi: 10.1124/pr.110.003723
172. Leonard CE, Freeman CP, Newcomb CW, Bilker WB, Kimmel SE, Strom BL, Hennessy S. Antipsychotics and the risks of sudden cardiac death and all-cause death: cohort studies in Medicaid and dually-eligible Medicaid-Medicare beneficiaries of five states. *J Clin Exp Cardiolog*. 2013;(suppl 10):1–9. doi: 10.4172/2155-9880.S10-006
173. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, Philippides GJ, Roden DM, Zareba W; on behalf of the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology; Council on Cardiovascular Nursing; American College of Cardiology Foundation. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation [published correction appears in *Circulation*. 2010;122:e440]. *Circulation*. 2010;121:1047–1060. doi: 10.1161/CIRCULATIONAHA.109.192704
174. QTDrugs list. Credible Meds website. Arizona Center for Education and Research on Therapeutics. https://crediblemeds.org/healthcare-providers/. Accessed September 11, 2018.
175. Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. *Am Heart J*. 2007;153:891–899. doi: 10.1016/j.ahj.2007.01.040
176. Jamshidi Y, Nolte IM, Dalageorgou C, Zheng D, Johnson T, Bastiaenen R, Ruddy S, Talbott D, Norris KJ, Snieder H, George AL, Marshall V, Shakir S, Kannankeril PJ, Munroe PB, Camm AJ, Jeffery S, Roden DM, Behr ER. Common variation in the NOS1AP gene is associated with drug-induced QT prolongation and ventricular arrhythmia. *J Am Coll Cardiol*. 2012;60:841–850. doi: 10.1016/j.jacc.2012.03.031
177. Ramirez AH, Shaffer CM, Delaney JT, Sexton DP, Levy SE, Rieder MJ, Nickerson DA, George AL Jr, Roden DM. Novel rare variants in congenital cardiac arrhythmia genes are frequent in drug-induced torsades de pointes. *Pharmacogenomics J*. 2013;13:325–329. doi: 10.1038/tpj.2012.14
178. Anderson ML, Cox M, Al-Khatib SM, Nichol G, Thomas KL, Chan PS, Saha-Chaudhuri P, Fosbol EL, Eigel B, Clendenen B, Peterson ED. Rates of cardiopulmonary resuscitation training in the United States. *JAMA Intern Med*. 2014;174:194–201. doi: 10.1001/jamainternmed.2013.11320
179. Blewer AL IS, Leary M, Dutwin D, McNally B, Anderson ML, Morrison LJ, Aufderheide TA, Daya M, Idris A, Callaway CW, Kudenchuk PJ, Vilke GM, Abella BS. Cardiopulmonary resuscitation training disparities in the United States. *Journal of Am Heart Assoc*. 2017;6:e006124. doi: 10.1161/JAHA.117.006124
180. Bakke HK, Steinvik T, Angell J, Wisborg T. A nationwide survey of first aid training and encounters in Norway. *BMC Emerg Med*. 2017;17:6. doi: 10.1186/s12873-017-0116-7
181. Bray JE, Smith K, Case R, Cartledge S, Straney L, Finn J. Public cardiopulmonary resuscitation training rates and awareness of hands-only cardiopulmonary resuscitation: a cross-sectional survey of Victorians. *Emerg Med Australas*. 2017;29:158–164. doi: 10.1111/1742-6723.12720
182. Brooks B, Chan S, Lander P, Adamson R, Hodgetts GA, Deakin CD. Public knowledge and confidence in the use of public access defibrillation. *Heart*. 2015;101:967–971. doi: 10.1136/heartjnl-2015-307624
183. Lee MJ, Hwang SO, Cha KC, Cho GC, Yang HJ, Rho TH. Influence of nationwide policy on citizens' awareness and willingness to perform bystander cardiopulmonary resuscitation. *Resuscitation*. 2013;84:889–894. doi: 10.1016/j.resuscitation.2013.01.009
184. Gonzalez M, Leary M, Blewer AL, Cinousis M, Sheak K, Ward M, Merchant RM, Becker LB, Abella BS. Public knowledge of automatic external defibrillators in a large U.S. urban community. *Resuscitation*. 2015;92:101–106. doi: 10.1016/j.resuscitation.2015.04.022
185. Ong ME, Shin SD, De Souza NN, Tanaka H, Nishiuchi T, Song KJ, Ko PC, Leong BS, Khunkhlai N, Naroo GY, Sarah AK, Ng YY, Li WY, Ma MH; PAROS Clinical Research Network. Outcomes for out-of-hospital cardiac arrests across 7 countries in Asia: the Pan Asian Resuscitation Outcomes Study (PAROS) [published correction appears in *Resuscitation*. 2016;98:125–126]. *Resuscitation*. 2015;96:100–108. doi: 10.1016/j.resuscitation.2015.07.026
186. Sasson C, Magid DJ, Chan P, Root ED, McNally BF, Kellermann AL, Haukoos JS; CARES Surveillance Group. Association of neighborhood characteristics with bystander-initiated CPR. *N Engl J Med*. 2012;367:1607–1615. doi: 10.1056/NEJMoa1110700
187. Moon S, Bobrow BJ, Vadeboncoeur TF, Kortuem W, Kisakye M, Sasson C, Stolz U, Spaite DW. Disparities in bystander CPR provision and survival from out-of-hospital cardiac arrest according to neighborhood ethnicity. *Am J Emerg Med*. 2014;32:1041–1045. doi: 10.1016/j.ajem.2014.06.019
188. Sasson C, Haukoos JS, Ben-Youssef L, Ramirez L, Bull S, Eigel B, Magid DJ, Padilla R. Barriers to calling 911 and learning and performing cardiopulmonary resuscitation for residents of primarily Latino, high-risk neighborhoods in Denver, Colorado. *Ann Emerg Med*. 2015;65:545–552.e2. doi: 10.1016/j.annemergmed.2014.10.028
189. Duber HC, McNellan CR, Wollum A, Phillips B, Allen K, Brown JC, Bryant M, Guptam RB, Li Y, Majumdar P, Roth GA, Thomson B, Wilson S, Woldeab A, Zhou M, Ng M. Public knowledge of cardiovascular disease and response to acute cardiac events in three cities in China and India. *Heart*. 2018;104:67–72. doi: 10.1136/heartjnl-2017-311388
190. Nishiyama C, Brown SP, May S, Iwami T, Koster RW, Beesems SG, Kuisma M, Salo A, Jacobs I, Finn J, Sterz F, Nürnberger A, Smith K, Morrison L, Olasveengen TM, Callaway CW, Shin SD, Gräsner JT, Daya M, Ma MH, Herlitz J, Strömsöe A, Aufderheide TP, Masterson S, Wang H, Christenson

J, Stiell I, Davis D, Huszti E, Nichol G. Apples to apples or apples to oranges? International variation in reporting of process and outcome of care for out-of-hospital cardiac arrest. *Resuscitation*. 2014;85:1599–1609. doi: 10.1016/j.resuscitation.2014.06.031

191. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. *Resuscitation*. 2010;81:1479–1487. doi: 10.1016/j.resuscitation.2010.08.006
192. Gräsner JT, Lefering R, Koster RW, Masterson S, Böttiger BW, Herlitz J, Wnent J, Tjelmeland IB, Ortiz FR, Maurer H, Baubin M, Mols P, Hadžibegović I, Ioannides M, Škulec R, Wissenberg M, Salo A, Hubert H, Nikolaou NI, Lóczi G, Svavarsdóttir H, Semeraro F, Wright PJ, Clarens C, Pijls R, Cebula G, Correia VG, Cimpoesu D, Raffay V, Trenkler S, Markota A, Strömsöe A, Burkart R, Perkins GD, Bossaert LL; EuReCa ONE Collaborators. EuReCa ONE-27 Nations, ONE Europe, ONE Registry: a prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. *Resuscitation*. 2016;105:188–195. doi: 10.1016/j.resuscitation.2016.06.004
193. Bray JE, Di Palma S, Jacobs I, Straney L, Finn J. Trends in the incidence of presumed cardiac out-of-hospital cardiac arrest in Perth, Western Australia, 1997-2010. *Resuscitation*. 2014;85:757–761. doi: 10.1016/j.resuscitation.2014.02.017
194. Shao F, Li CS, Liang LR, Qin J, Ding N, Fu Y, Yang K, Zhang GQ, Zhao L, Zhao B, Zhu ZZ, Yang LP, Yu DM, Song ZJ, Yang QL. Incidence and outcome of adult in-hospital cardiac arrest in Beijing, China. *Resuscitation*. 2016;102:51–56. doi: 10.1016/j.resuscitation.2016.02.002

18. SUBCLINICAL ATHEROSCLEROSIS

See Charts 18-1 through 18-4

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Multiple complementary imaging modalities allow detection and quantification of atherosclerosis through its stages and in multiple different vascular beds. Early identification of subclinical atherosclerosis can guide preventive care, including lifestyle modifications and medical treatment (eg, aspirin, antihypertensive therapy, lipid-lowering therapy) to prevent clinical manifestations of atherosclerosis such as MI, stroke, or PAD. Although several invasive and noninvasive imaging modalities can be used for imaging atherosclerosis, 2 modalities, CT of the chest for evaluation of CAC and B-mode ultrasound of the neck for evaluation of carotid artery IMT, have been used in large studies with outcomes data and can help define the burden of atherosclerosis in individuals before they develop symptoms or clinical events such as heart attack or stroke. Data on cardiovascular outcomes are beginning to emerge for additional modalities that measure anatomic and functional measures of subclinical disease, including brachial artery reactivity testing, aortic and carotid MRI, and tonometric methods of measuring vascular compliance or microvascular reactivity. Further research could help to define the role of these techniques in cardiovascular risk assessment. Some guidelines have recommended that assessing for subclinical atherosclerosis, especially by CAC, might be appropriate as a decision aid in people at intermediate risk for ASCVD (eg, 10-year estimated risk of 10%–20%) but not for lower-risk general population screening or for people with preexisting CHD or most other high-risk conditions.[1,2]

Abbreviations Used in Chapter 18

ABI	ankle-brachial index
ACC	American College of Cardiology
AF	atrial fibrillation
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities Study
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
CAC	coronary artery calcification
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CKD	chronic kidney disease
CI	confidence interval
CONFIRM	Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry
CRP	C-reactive protein
CT	computed tomography
CVD	cardiovascular disease
DBP	diastolic blood pressure
DM	diabetes mellitus
EF	ejection fraction
ESRD	end-stage renal disease
FHS	Framingham Heart Study
FMD	flow-mediated dilation
FRS	Framingham Risk Score
HBP	high blood pressure
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HR	hazard ratio
IMT	intima-media thickness
JHS	Jackson Heart Study
JUPITER	Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin
LDL-C	low-density lipoprotein cholesterol
LV	left ventricular
LVH	left ventricular hypertrophy
MACE	major adverse cardiovascular event(s)
MASALA	Mediators of Atherosclerosis in South Asians Living in America
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
MRI	magnetic resonance imaging
NHLBI	National Heart, Lung, and Blood Institute
NNT_5	5-year number needed to treat
PAD	peripheral artery disease
PWV	pulse wave velocity
QALY	quality-adjusted life-year
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
TC	total cholesterol
TIA	transient ischemic attack
TIPS	The Indian Polycap Study
WC	waist circumference

According to the 2018 ACC/AHA cholesterol management guideline, in intermediate-risk or selected borderline-risk adults, if the decision about statin therapy remains uncertain after 10-year risk calculation and after accounting for risk enhancers, it is reasonable to use a CAC score in the decision to withhold, postpone, or initiate statin therapy.[3] A large-scale randomized trial showed that coronary calcium scanning, compared with no scanning, led to improved risk factor control without increasing downstream medical costs.[4] In addition, a cost-effectiveness analysis based on MESA[5] data reported that CAC testing and statin treatment for those with CAC >0 was cost-effective (<$50 000 per QALY) in intermediate-risk scenarios even when considering less favorable statin assumptions ($1.00 per pill).

Coronary Artery Calcification

Background

- CAC is a measure of the burden of atherosclerosis in the heart arteries and is measured by CT. Other components of the atherosclerotic plaque, including fatty (eg, cholesterol-rich components) and fibrotic components, often accompany CAC and can be present even in the absence of CAC.

- The presence of any CAC, which indicates that at least some atherosclerotic plaque is present, is defined by an Agatston score >0. Clinically significant plaque, frequently an indication for more aggressive risk factor management, is often defined by an Agatston score ≥100 or a score ≥75th percentile for one's age and sex; however, although they predict short- to intermediate-term risk, absolute CAC cutoffs offer more prognostic information across all age groups in both males andfemales.[6]

Prevalence
(See Charts 18-1 through 18-3)

- The NHLBI's FHS reported CAC measured in 3238 white adults in age groups ranging from <45 to ≥75 years of age.[6a]
  - Overall, 32.0% of females and 52.9% of males had prevalent CAC.
  - Among participants at intermediate risk according to FRS, 58% of females and 67% of males had prevalent CAC.
- The NHLBI's CARDIA study measured CAC in 3043 black and white adults 33 to 45 years of age (at the CARDIA year 15 examination).[7]
  - Overall, 15.0% of males, 5.1% of females, 5.5% of those 33 to 39 years of age, and 13.3% of those 40 to 45 years of age had prevalent CAC. Overall, 1.6% of participants had an Agatston score that exceeded 100.
- Chart 18-1 shows the prevalence of CAC by ethnicity and sex in adults 33 to 45 years of age. The prevalence of CAC was lower in black versus white males but was similar in black versus white females at these ages.[7]
- The NHLBI's JHS assessed outcomes with presence of elevated CAC (>100) in 4416 African American participants (mean age 54 years; 64% females) followed up for 6 years.[8]
- CAC >100 was noted in 14% of those without any metabolic syndrome or DM, 26% of those with metabolic syndrome, and 41% of those with DM.
- The NHLBI's MESA measured CAC in 6814 participants 45 to 84 years of age (mean 63), including white (n=2619), black (n=1898), Hispanic (n=1494), and Chinese (n=803) males and females.[9]
  - The overall prevalence of CAC in these 4 ethnic groups was 70.4%, 52.1%, 56.5%, and 59.2%, respectively.
  - Chart 18-2 shows the prevalence of CAC by sex and ethnicity in US adults 45 to 84 years of age in MESA.
  - The prevalence and 75th percentile levels of CAC were highest in white males and lowest in black and Hispanic females. Significant ethnic differences persisted after adjustment for risk factors, with the RR of coronary calcium being 22% less in blacks, 15% less in Hispanics, and 8% less in Chinese than in whites.
- In a comparison of MESA with the MASALA study, which is a community-based cohort of South Asians in the United States and on average 5 years younger than MESA, the age-adjusted prevalence of CAC was similar among white (68.8%) and South Asian (67.9%) males, with these groups having a greater prevalence of CAC than Chinese (57.8%), African American (51.2%), and Hispanic (57.9%) males. In contrast, the age-adjusted prevalence of CAC was lower in South Asian females (36.8%) than in white females (42.6%) and females of other races/ethnicities.[10]
- Further illustrating the variability of CAC based on population and habits, a forager-horticulturalist population of 705 individuals living in the Bolivian Amazon had the lowest reported levels of CAC of any population recorded to date.[11] Overall in the population (mean age 58 years; 50% females), 85% of individuals were free from any CAC, and even in individuals >75 years of age, 65% remained free of CAC. These unique data indicate that coronary atherosclerosis can be typically be avoided by maintaining a low lifetime burden of CAD risk factors.[11]
- To date, sparse research exists on the prevalence of subclinical atherosclerosis, including CAC, in rural areas of the United States.[12] A study reported the distribution of CAC scores among 1607 (mean age 56 years; 56% females) community-dwelling asymptomatic individuals from central Appalachia. Overall, 44% had a CAC score of 0, whereas the prevalence of those with mild (1–99), moderate (100–399), and severe (≥400) CAC was 29%, 15%, and 11%, respectively.[12]
- The prevalence of CAC varies widely according to baseline risk profile. In recent studies from MESA, the prevalence of CAC in those with no lipid abnormalities was 42% versus 50% in those with 3 lipid abnormalities,[13] and 32% of people in MESA with no known traditional CVD risk factors had presence of CAC versus 65% of those with 3 risk factors.[14]
- The 10-year trends in CAC among individuals without clinical CVD in MESA were assessed[15] (Chart 18-3). After adjustment for age, sex, ethnicity, and type of CT scanner, the proportion of participants with no CAC decreased over time from 40.7% to 32.6% (*P*=0.007), and the proportions

increased from 29.9% to 37.0% (*P*=0.01) for those with a CAC score ranging from 1 to 99 and from 14.7% to 17.7% (*P*=0.14) for those with a CAC score of 100 to 399, whereas the proportion with a CAC score ≥400 decreased from 9.1% to 7.2% (*P*=0.11). Trends in CAC among the 4 racial/ethnic groups revealed a significant trend toward increased prevalence of CAC in African Americans but not in any other group. Among African Americans, the CAC prevalence ratio (year 10 versus baseline) was 1.27 (*P*<0.001 for test for trend). Adjustment for risk factors made no notable difference in CAC trends in any ethnic group.[15]

CAC and Incidence of Cardiovascular Events (See Chart 18-4)

- In a landmark study, the NHLBI's MESA reported on the association of CAC scores with first CHD events over a median follow-up of 3.9 years among a population-based sample of 6722 individuals (39% white, 27% black, 22% Hispanic, and 12% Chinese).[16]
  - Chart 18-4 shows the HRs associated with CAC scores of 1 to 100, 101 to 300, and >300 compared with those without CAC (score=0), after adjustment for standard risk factors. People with CAC scores of 1 to 100 had ≈4 times greater risk and those with CAC scores >100 were 7 to 10 times more likely to experience a coronary event than those without CAC.
  - CAC provided similar predictive value for coronary events in whites, Chinese, blacks, and Hispanics (HRs ranging from 1.15–1.39 for each doubling of coronary calcium).
- In a more recent MESA analysis with 12-year follow-up, machine learning was used to assess predictors of cardiovascular events. Among 735 variables from imaging and noninvasive tests, questionnaires, and biomarker panels, CAC emerged as the strongest predictor of CHD and ASCVD events.[17]
- In MESA, CAC was noted to be highly predictive of CHD event risk across in both young and elderly MESA participants in a follow-up that extended to 8.5 years, which suggests that once CAC is known, chronological age has less importance. Compared with a CAC score of 0, CAC >100 was associated with an increased multivariable-adjusted CHD event risk in the younger individuals (45–54 years old), with an HR of 12.4 (95% CI, 5.1–30.0). The respective risk was similar even in the very elderly (75–84 years of age), with an HR of 12.1 (95% CI, 2.9–50.2).[18]
- In a study of healthy adults 60 to 72 years of age who were free of clinical CAD, predictors of the progression of CAC were assessed. Predictors tested included age, sex, race/ethnicity, smoking status, BMI, family history of CAD, CRP, several measures of DM, insulin levels, BP, and lipids. Insulin resistance, in addition to the traditional cardiac risk factors, independently predicts progression of CAC.[19] Clinically, however, it is not recommended to conduct serial scanning of CAC to measure effects of therapeutic interventions.
- It is noteworthy, as demonstrated in MESA in 5878 participants with a median of 5.8 years of follow-up, that the addition of CAC to standard risk factors resulted in significant improvement of classification of risk for incident CHD events, placing 77% of people in the highest or lowest risk categories compared with 69% based on risk factors alone. An additional 23% of those who experienced events were reclassified as high risk, and 13% with events were reclassified as low risk.[20] The contribution of CAC to risk prediction has also been observed in other cohorts, including both the Heinz Nixdorf Recall Study[21] and the Rotterdam Study.[22]
- The prospective Dallas Heart Study reported the prognostic value of CAC scores in a relatively younger cohort (44.4±9.0 years of age). Among the 2084 participants who were followed up for a median of 9 years, compared with individuals with CAC=0, those with CAC scores of 10 to 100 and >100 were associated with an HR (95% CI) of 3.43 (1.36–8.56) and 5.64 (2.28–13.97) for CHD events, respectively. The addition of CAC to the traditional risk factor model resulted in significant improvement in the C statistic (Δ=0.03; *P*=0.003), as well as a net correct reclassification of 22%.[23]
- In the Heinz Nixdorf Recall Study of 4180 individuals,[21] CAC independently predicted stroke during a mean follow-up of 7.9 years. Cox proportional hazards regressions were used to examine CAC as a predictor of stroke in addition to established vascular risk factors (age, sex, SBP, LDL-C, HDL-C, DM, smoking, and AF). Study participants who had a stroke had significantly higher CAC values at baseline than the remaining participants (median 104.8 [quartile 1, 14.0; quartile 3, 482.2] versus 11.2 [quartile 1, 0; quartile 3, 106.2]; *P*<0.001). In a multivariable Cox regression, log10(CAC+1) was a stroke predictor (HR, 1.52 [95% CI, 1.19–1.92]; *P*=0.001) independent of traditional risk factors in low- and intermediate-risk individuals.[21]
- A meta-analysis[24] also highlighted the utility of CAC testing in the diabetic population. In this meta-analysis, 8 studies were included (n=6521; 802 events; mean follow-up 5.2 years). The RR for

all-cause mortality or cardiovascular events or both comparing a total CAC score ≥10 with a score <10 was 5.47 (95% CI, 2.59–11.53; I^2=82.4%, *P*<0.001). For people with a CAC score <10, the posttest probability of the composite outcome was ≈1.8%, which represents a 6.8-fold reduction from the pretest probability. This suggests that low or absent CAC could facilitate risk stratification by enabling the identification of people at low risk within this high-risk population.[24]

- CAC also appears to have predictive value for cardiac events beyond stroke and MI. In the Rotterdam Study, CAC independently predicted incident HF during a median follow-up of 6.8 years. After adjustment for risk factors, those with severe CAC (>400) had a 4.1-fold higher risk (95% CI, 1.7–10.1) of HF than those with CAC scores of 0 to 10.[25] In addition, CAC substantially improved the risk classification (net reclassification index, 34.0%). A recent MESA analysis examining prediction of HF with preserved EF found that CAC >300 was a significant independent predictor in females (HR, 2.82 [95% CI, 1.32–6.00]) but not in males (HR, 0.91 [95% CI, 0.46–1.82]).[26]
- In MESA, during a median follow-up of 8.5 years, after accounting for risk factors, higher CAC scores were associated with increased risk for AF (CAC=0: HR, 1.0 [referent]; CAC=1–100: HR, 1.4 [95% CI, 1.01–2.0]; CAC=101–300: HR, 1.6 [95% CI, 1.1–2.4]; CAC >300: HR, 2.1 [95% CI, 1.4–2.9]). The addition of CAC to a risk score yielded relative integrated discrimination improvement of 0.10 (95% CI, 0.061–0.15).[27]
- A MESA analysis also showed that a higher CAC burden was associated with non-CVD outcomes. During a median follow-up of 10.2 years, accounting for demographics and traditional risk factors, participants with severe CAC (>400) were at an increased risk of cancer (HR, 1.53 [95% CI, 1.18–1.99]), CKD (HR, 1.70 [95% CI, 1.21–2.39]), pneumonia (HR, 1.97 [95% CI, 1.37–2.82]), chronic obstructive pulmonary disease (HR, 2.71 [95% CI, 1.60–4.57]), and hip fracture (HR, 4.29 [95% CI, 1.47–12.50]) compared with those with CAC=0.[28]
- In a meta-analysis of 13 studies assessing the relationship of CAC with adverse cardiovascular outcomes that included 71 595 asymptomatic individuals, 29 312 (41%) did not have any evidence of CAC.[29] In a mean follow-up of 4.3 years, 154 of 29 312 individuals without CAC (0.47%) experienced a cardiovascular event compared with 1749 of 42 283 individuals with CAC (4.14%). The cumulative RR was 0.15 (95% CI, 0.11–0.21; *P*<0.001). These findings were confirmed in MESA, which reported a rate of 0.52% for CHD events during a median of 4.1 years of follow-up among people with no detectable CAC.[30]
- The value of CAC=0 has been confirmed in various high-risk groups. For example, in MESA, 38% of those with DM had CAC=0, and the annualized CHD and CVD event rates were 0.4% and 0.8%, respectively.[31] A publication[14] from MESA demonstrated a low hard CHD event rate per 1000 years during a median follow-up of 7.1 years across the entire spectrum of baseline FRS (0%–6%: 0.9; 6%–10%: 1.1; 10%–20%: 1.9; >20%: 2.5). Among high-risk individuals considered for various polypill criteria in MESA, based on age and risk factors, the prevalence of CAC=0 ranged from 39% to 59%, and the respective rate of CHD events varied from 1.2 to 1.9 events per 1000 person-years during a median follow-up of 7.6 years.[32]
- A recent meta-analysis that pooled data from 3 studies evaluated 13 262 asymptomatic individuals (mean age 60 years, 50% males) without apparent CVD. During a mean follow-up of 7.2 years, the pooled RR of incident stroke with CAC >0 was 2.95 (95% CI, 2.18–4.01; *P*<0.001) compared with CAC=0. Furthermore, there was an increasing risk with higher CAC score (0.12% per year for CAC=0, 0.26% per year for CAC 1–99, 0.41% per year for CAC 100–399, and 0.70% per year for CAC ≥400).[33]

CAC Progression and Risk

- Data from 6778 people in MESA showed annual CAC progression averaged 25±65 Agatston units, and among those without CAC at baseline, a 5-U annual change in CAC was associated with HRs of 1.4 and 1.5 for total and hard CHD events, respectively. Among those with CAC >0 at baseline, HRs per 100-U annual change in CAC were 1.2 and 1.3, respectively, and for those with annual progression ≥300 versus no progression, HRs were 3.8 and 6.3, respectively.[34] Progression of CAC in MESA was greater in those with metabolic syndrome and DM than in those with neither condition, and progression of CAC in each of these conditions was associated with a greater future risk of CHD events.[35]
- Furthermore, in MESA, CAC progression was associated with incident AF. Presence of any CAC progression (>0 per year) in the 5-year follow-up was associated with 1.55-fold higher risk for AF (95% CI, 1.10–2.19). The risk of AF increased with higher levels of CAC progression: (1–100 per year: HR, 1.47 [95% CI, 1.03–2.09]; 101–300 per year: HR, 1.92 [95% CI, 1.15–3.20]; >300 per year: HR, 3.23 [95% CI, 1.48–7.05]).[27]

- In MESA, greater adherence to a healthy lifestyle, based on a healthy lifestyle score, was associated with slower progression of CAC and lower mortality rates relative to those with the most unhealthy lifestyle.[36]

Carotid IMT

Background

- Carotid IMT measures the thickness of 2 layers (the intima and media) of the wall of the carotid arteries, the largest conduits of blood going to the brain. Carotid IMT is thought to be an even earlier manifestation of atherosclerosis than CAC, because thickening precedes the development of frank atherosclerotic plaque. Carotid IMT methods are still being refined, so it is important to know which part of the artery was measured (common carotid, internal carotid, or bulb) and whether near and far walls were both measured. Additionally, measurement can be reported as the average thickness or maximum thickness, although the average is more commonly reported.
- Unlike CAC, everyone has some thickness to the layers of their arteries, but people who develop atherosclerosis have greater thickness. Additionally, the thickness is expected to increase with age and for males. Thus, high-risk levels of thickening might be considered as those in the highest quartile or quintile for one's age and sex, or ≥1 mm. Ultrasound of the carotid arteries can also detect plaques and determine the degree of narrowing of the artery they might cause. Although this is commonly used to diagnose plaque in the carotid arteries in people who have had strokes or who have bruits (sounds of turbulence in the artery), current primary prevention guidelines do not recommend screening of asymptomatic people using either the presence of atherosclerotic plaque or carotid IMT to quantify atherosclerosis or predict risk.[37,38]

Prevalence and Association With Incident Cardiovascular Events

- In the Bogalusa Heart Study,[39] carotid IMT was measured in 518 black and white males and females at a mean age of 32±3 years. These males and females were healthy but overweight.
  - Males had significantly higher carotid IMT in all segments than females, and blacks had higher common carotid and carotid bulb IMTs than whites.
  - Even at this young age, after adjustment for age, race, and sex, carotid IMT was associated significantly and positively with WC, SBP, DBP, and LDL-C. Carotid IMT was inversely correlated with HDL-C levels. Participants with greater numbers of adverse risk factors (0, 1, 2, 3, or more) had stepwise increases in mean carotid IMT levels.
- In a subsequent analysis, the Bogalusa investigators examined the association of risk factors measured since childhood with carotid IMT measured in these young adults.[40] Higher BMI and LDL-C levels measured at 4 to 7 years of age were associated with increased risk for being >75th percentile for carotid IMT in young adulthood. Higher SBP and LDL-C and lower HDL-C in young adulthood were also associated with having high carotid IMT.
- A similar pattern of association between risk factors at a younger age and carotid IMT in adulthood have also been demonstrated in a large Finnish cohort study.[41] These data highlight the importance of adverse risk factor levels in early childhood and young adulthood in the early development of atherosclerosis.
- Updates from an individual-participant meta-analysis involving 15 population-based cohorts worldwide that included 60 211 individuals (46 788 whites, 7200 blacks, 3816 Asians, and 2407 Hispanics) demonstrated differing associations between risk factors and burden of carotid IMT according to racial/ethnic groups.[42] Specifically, association between age and carotid IMT was weaker in blacks and Hispanics, SBP was more strongly associated with carotid IMT in Asians, and HDL-C and smoking were associated less with carotid IMT in blacks.
- Among both females and males in MESA, blacks had the highest common carotid IMT, but they were similar to whites and Hispanics in internal carotid IMT. Chinese participants had the lowest carotid IMT, in particular in the internal carotid, of the 4 ethnic groups.[43]
- The CHS reported follow-up of 4476 males and females ≥65 years of age (mean age 72 years) who were free of CVD at baseline.[44] Mean maximal common carotid IMT was 1.03±0.20 mm, and mean internal carotid IMT was 1.37±0.55 mm. After a mean follow-up of 6.2 years, those with maximal combined carotid IMT in the highest quintile had a 4- to 5-fold greater risk for incident heart attack or stroke than those in the bottom quintile. After adjustment for other risk factors, there was still a 2- to 3-fold greater risk for the top versus the bottom quintile.
- In MESA, during a median follow-up of 3.3 years, an IMT rate of change of 0.5 mm per year was associated with an HR of 1.23 (95% CI, 1.02–1.48) for incident stroke. The upper quartile of

IMT rate of change had an HR of 2.18 (95% CI, 1.07–4.46) compared with the lower 3 quartiles combined.[45]

- Despite this evidence, conflicting data have been reported on the contribution of carotid IMT to risk prediction. A recent study from a consortium of 14 population-based cohorts consisting of 45 828 individuals followed up for a median of 11 years demonstrated little additive value of common carotid IMT to FRS for purposes of discrimination and reclassification as far as incident MI and stroke were concerned. The C statistics of the model with FRS alone (0.757 [95% CI, 0.749–0.764]) and with addition of common carotid IMT (0.759 [95% CI, 0.752–0.766]) were similar. The net reclassification improvement with the addition of common carotid IMT was small (0.8% [95% CI, 0.1%–1.6%]). In those at intermediate risk, the net reclassification improvement was 3.6% among all individuals (95% CI, 2.7%–4.6%).[46]
- Interestingly, the ability of carotid IMT to predict incident CVD events might also depend on how the data are modeled. In MESA, the use of an age-, sex-, and race-adjusted carotid IMT score that combined data from both the internal and common carotid artery resulted in a significant improvement in the net reclassification improvement of 4.9% (*P*=0.024), with a particularly higher impact in individuals with an intermediate FRS, in whom the net reclassification improvement was 11.5%.[47]
- Among 13 590 participants in the ARIC study aged 45 to 64 years, each 1-SD increase in carotid IMT was associated with incident HF (HR, 1.20 [95% CI, 1.16–1.25) in a 20-year follow-up after accounting for major CVD risk factors and CHD. Similar associations were also noted across all race and sex groups.[48] This relationship was found to be much stronger among those without established DM.[48]
- A recent study[49] from 3 population-based cohorts (ARIC, N=13 907; MESA, N=6640; and the Rotterdam Study, N=5220) demonstrated that both a higher carotid IMT and presence of carotid plaque were independently associated with an increased risk of incident AF. In this study, a 1-SD increase in carotid IMT and presence of carotid plaque were associated with a meta-analyzed HR (95% CI) of 1.12 (1.08–1.16) and 1.30 (1.19–1.42), respectively.[49]
- A study from a consortium of population-based cohorts reported no added value of measurement of mean common carotid IMT in individuals with HBP for improving cardiovascular risk prediction. For those at intermediate risk, the addition of mean common carotid IMT to an existing cardiovascular risk score resulted in a small but statistically significant improvement in risk prediction.[50]
- In a recent study, however, carotid plaque burden measured via 3-dimensional carotid ultrasound showed promise in improving CVD risk prediction. The prospective BioImage Study enrolled 5808 asymptomatic US adults (mean age 69 years; 56.5% females). Carotid plaque areas from both carotid arteries were summed as the carotid plaque burden. The primary end point was the composite of MACE (cardiovascular death, MI, and ischemic stroke). After adjustment for risk factors, the HRs for MACE were 1.45 (95% CI, 0.67–3.14) and 2.36 (95% CI, 1.13–4.92) with increasing carotid plaque burden tertile. Net reclassification improved significantly with carotid plaque burden (0.23).[51]
- Two large, population-based prospective studies have aimed to elucidate the association of carotid ultrasound findings with outcomes with shared pathogenesis of atherosclerosis.[52,53] Among 13 197 individuals aged 45 to 64 years (26% blacks, 56% females) followed up for a median of 22.7 years, mean carotid IMT in the fourth quartile (≥0.81 mm) versus first quartile (<0.62) was significantly associated with ESRD.[52,53]
- Investigators from the FHS demonstrated that additional information obtained from carotid ultrasound regarding the degree of carotid stenotic burden was predictive of cerebral microbleeds detected on brain MRI, which are recognized as a marker of stroke and dementia, in 1243 participants (56.9±8.8 years old; 53% females). Carotid stenosis ≥25% was associated with a 2.2-fold (95% CI, 1.10–4.40) increased risk of cerebral microbleed, whereas no association was noted with carotid IMT.[52]

CAC and Carotid IMT

- In the NHLBI's MESA, a study of white, black, Chinese, and Hispanic adults 45 to 84 years of age, carotid IMT and CAC were found to be commonly associated, but patterns of association differed somewhat by sex and race.[43]
  - — Common and internal carotid IMT were greater in females and males who had CAC than in those who did not, regardless of ethnicity.
  - — Overall, CAC prevalence and scores were associated with carotid IMT, but associations were somewhat weaker in blacks than in other ethnic groups.
  - — In general, blacks had the thickest carotid IMT of all 4 ethnic groups, regardless of the presence of CAC.

- Common carotid IMT differed little by race/ethnicity in females with any CAC, but among females with no CAC, IMT was higher among blacks (0.86 mm) than in the other 3 groups (0.76–0.80 mm).
- In a more recent analysis from MESA, the investigators reported on follow-up of 6779 males and females in 4 ethnic groups over 9.5 years and compared the predictive utility of carotid IMT, carotid plaque, and CAC (presence and burden).[54]
  - CAC presence was a stronger predictor of incident CVD and CHD than carotid ultrasound measures.
  - Mean IMT ≥75th percentile (for age, sex, and race) alone did not predict events. Compared with traditional risk factors, C statistics for CVD (C=0.756) and CHD (C=0.752) increased the most by the addition of CAC presence (CVD, 0.776; CHD, 0.784; *P*<0.001), followed by carotid plaque presence (CVD, C=0.760; CHD, C=0.757; *P*<0.05).
  - Compared with risk factors (C=0.782), carotid plaque presence (C=0.787; *P*=0.045) but not CAC (C=0.785; *P*=0.438) improved prediction of stroke/TIA.
- Investigators from the NHLBI's CARDIA and MESA studies examined the burden and progression of subclinical atherosclerosis among adults <50 years of age. Ten-year and lifetime risks for CVD were estimated for each participant, and the participants were stratified into 3 groups: (1) those with low 10-year (<10%) and low lifetime (<39%) predicted risk for CVD; (2) those with low 10-year (<10%) but high lifetime (≥39%) predicted risk; and (3) those with high 10-year risk (>10%). The latter group had the highest burden and greatest progression of subclinical atherosclerosis. Given the young age of those studied, ≈90% of participants were at low 10-year risk, but of these, half had high predicted lifetime risk. Compared with those with low short-term/low lifetime predicted risks, those with low short-term/high lifetime predicted risk had significantly greater burden and progression of CAC and significantly greater burden of carotid IMT, even at these younger ages. These data confirm the importance of early exposure to risk factors for the onset and progression of subclinical atherosclerosis.[55]

Carotid IMT Progression and Risk

To date, few studies have comprehensively studied the impact of carotid IMT progression on CVD outcomes. Data from a comprehensive meta-analysis of individual participant data demonstrated that common carotid artery IMT progression in people with DM ranged between −0.09 and 0.04 mm per year in a follow-up of 3.6 years; however, this change was not associated with cardiovascular outcomes. The HR for a 1-SD increase in common carotid artery IMT progression was 0.99 (95% CI, 0.91–1.08).[56]

CT Angiography

- CT angiography is widely used to aid in the diagnosis of CAD in symptomatic individuals because of its ability to detect and possibly quantitate overall plaque burden and certain characteristics of plaques that might make them prone to rupture, such as positive remodeling, low attenuation, and spotty calcifications.[57]
- Compared with the established value of CAC scanning for risk reclassification in asymptomatic patients, there are limited data regarding the utility of CT angiography in asymptomatic people. In a recent study from the CONFIRM registry, CT angiography data on the presence, extent, and severity of CAD improved risk prediction over traditional risk factors. However, no additional prognostic value was added by coronary CT angiography data for the prediction of all-cause death once traditional risk factors and CAC scores were included in the model.[58] In another analysis of the CONFIRM data, it was noted that coronary CT angiography only provided incremental prognostic utility for prediction of mortality and nonfatal MI for asymptomatic individuals with moderately high CAC scores, but not for those with lower or higher CAC scores.[59]
- Because of this limited impact on the prediction of outcomes in asymptomatic individuals, current guidelines do not recommend its use as a screening tool for assessment of cardiovascular risk in asymptomatic individuals.[2]

Measures of Vascular Function and Incident CVD Events

Background

- Measures of arterial tonometry (stiffness) are based on the concept that pulse pressure has been shown to be an important risk factor for CVD. Arterial tonometry offers the ability to directly and noninvasively measure central PWV in the thoracic and abdominal aorta.
- Brachial FMD is a marker for nitric oxide release from the endothelium that can be measured by ultrasound. Impaired FMD is an early marker of CVD.
- Recommendations have not been specific, however, as to which, if any, measures of vascular

function might be useful for CVD risk stratification in selected patient subgroups. Because of the absence of significant prospective data relating these measures to outcomes, the latest guidelines do not recommend measuring either FMD or arterial stiffness for cardiovascular risk assessment in asymptomatic adults.[2]

Arterial Tonometry and CVD

- The Rotterdam Study measured arterial stiffness in 2835 elderly participants (mean age 71 years).[60] They found that as aortic PWV increased, the RR of CHD was 1.72 (second versus first tertile) and 2.45 (third versus first tertile). Results remained robust even after accounting for carotid IMT, ABI, and pulse pressure.
- A study from Denmark of 1678 individuals aged 40 to 70 years found that each 1-SD increment in aortic PWV (3.4 m/s) increased CVD risk by 16% to 20%.[61]
- The FHS measured several indices of arterial stiffness, including PWV, wave reflection, and central pulse pressure.[62] They found that not only was higher PWV associated with a 48% increased risk of incident CVD events, but PWV additionally improved CVD risk prediction (integrated discrimination improvement of 0.7%, $P<0.05$).
- An analysis from the JHS suggested peripheral arterial tonometry to be associated with LVH. A total of 440 African American participants (mean age 59±10 years, 60% females) underwent both peripheral arterial tonometry and cardiac MRI evaluations between 2007 and 2013. Age- and sex-adjusted Pearson correlation analysis suggested that natural log-transformed LV mass index measured by MRI was negatively correlated with reactive hyperemia index (coefficient −0.114; $P=0.02$) after accounting for age, sex, BMI, DM, hypertension, ratio of TC and HDL-C, smoking, and history of CVD.[63]

FMD and CVD

- A recent meta-analysis assessed the relation of FMD with CVD events. Thirteen studies involving 11 516 individuals without established CVD, with a mean duration of 2 to 7.2 years and adjusted for age, sex, and risk factors, reported a multivariate RR of 0.93 (95% CI, 0.90–0.96) per 1% increase in brachial FMD.[64]

Comparison of Measures

- In MESA, a comparison of 6 risk markers—CAC, ABI, high-sensitivity CRP, carotid IMT, brachial FMD, and family history of CHD—and their clinical utility over FRS was evaluated in 1330 intermediate-risk individuals. After 7.6 years of follow-up, CAC, ABI, high-sensitivity CRP, and family history were independently associated with incident CHD in multivariable analyses (HRs of 2.6, 0.79, 1.28, and 2.18, respectively), but carotid IMT and brachial FMD were not. CAC provided the highest incremental improvement over the FRS (0.784 for both CAC and FRS versus 0.623 for FRS alone), as well as the greatest net reclassification improvement (0.659).[65]
- Additionally, in MESA, the values of 12 negative markers (CAC score of 0, carotid IMT <25th percentile, absence of carotid plaque, brachial FMD >5% change, ABI >0.9 and <1.3, high-sensitivity CRP <2 mg/L, homocysteine <10 µmol/L, N-terminal pro-BNP <100 pg/mL, no microalbuminuria, no family history of CHD [any/premature], absence of metabolic syndrome, and healthy lifestyle) were compared for all and hard CHD and all CVD events over the 10-year follow-up. After accounting for CVD risk factor, absence of CAC had the strongest negative predictive value, with an adjusted mean diagnostic likelihood ratio of 0.41 (SD, 0.12) for all CHD and 0.54 (SD, 0.12) for CVD, followed by carotid IMT <25th percentile (diagnostic likelihood ratio, 0.65 [SD, 0.04] and 0.75 [SD, 0.04], respectively).[66]
- Similar findings were also noted in the Rotterdam Study, in which among 12 CHD risk markers, improvements in FRS predictions were most statistically and clinically significant with the addition of CAC scores.[67]

Utility for Risk Stratification for Treatment

- CAC has been examined in multiple studies for its potential to identify those most likely and not likely to benefit from pharmacological treatment for the primary prevention of CVD.
- A total of 950 participants from MESA who met JUPITER clinical trial entry criteria (risk factors plus LDL-C <130 mg/dL and high-sensitivity CRP ≥2 mg/L) were identified and stratified according to CAC scores of 0, 1 to 100, or >100; CHD event rates were calculated, and the NNT_5 was calculated by applying the benefit found in JUPITER to the event rates found in each of these groups. For CHD, the predicted NNT_5 was 549 for those with CAC of 0, 94 for scores of 1 to 100, and 24 for scores >100.[68]
- In a similar fashion, 2 studies extrapolated the NNT_5 for LDL-C lowering by statins, applying the 30% RR reduction associated with a 1 mmol/L (39 mg/dL) reduction in LDL-C from a Cochrane meta-analysis of statin therapy in primary

prevention across the spectrum of lipid abnormalities (LDL-C ≥130 mg/dL, HDL-C <40 mg/dL for males or <50 mg/dL for females, and triglycerides ≥150 mg/dL), as well as across 10-year FRS categories (0%–6%, 6%–10%, 10%–20%, and >20%). The estimated NNT_5 for preventing 1 CVD event across dyslipidemia categories in this MESA cohort ranged from 23 to 30 in those with CAC ≥100.[13] The NNT_5 was 30 in participants with no lipid abnormality and CAC >100, whereas it was 154 in those with 3 lipid abnormalities and CAC of 0.[13] A very high NNT_5 of 186 and 222, respectively, was estimated to prevent 1 CHD event in the absence of CAC among those with 10-year FRS of 11% to 20% and >20%. The respective estimated NNT_5 was as low as 36 and 50 with the presence of a very high CAC score (>300) among those with 10-year FRS of 0% to 6% and 6% to 10%, respectively.[13] These collective data show the utility of CAC in identifying those most likely to benefit from statin treatment across the spectrum of risk profiles with an appropriate NNT_5.

- Similarly, CAC testing also identified appropriate candidates who might derive the highest benefit with aspirin therapy. In MESA, individuals with CAC ≥100 had an estimated net benefit with aspirin regardless of their traditional risk status; the estimated NNT_5 was 173 for individuals classified as having <10% FRS and 92 for individuals with ≥10% FRS, and the estimated 5-year number needed to harm was 442 for a major bleed.[69] Conversely, individuals with zero CAC had unfavorable estimates (estimated NNT_5 of 2036 for individuals with <10% FRS and 808 for individuals with ≥10% FRS; estimated 5-year number needed to harm of 442 for a major bleed). Sex-specific and age-stratified analyses showed similar results.
- A study from MESA also examined the role of CAC testing to define the target population to treat with a polypill.[32] The NNT_5 to prevent 1 event was estimated by applying the expected 62% CHD event reduction associated with the use of the polypill (based on TIPS). The estimated NNT_5 to prevent 1 CHD event ranged from 170 to 269 for patients with CAC=0, from 58 to 79 for those with CAC scores from 1 to 100, and from 25 to 27 for those with CAC scores >100,[32] which enabled significant reductions in the population considered for treatment with more selective use of the polypill and, as a result, avoidance of treatment of those who were unlikely to benefit.
- Within the scope of the 2013 ACC/AHA guidelines, data from MESA demonstrated that among those for whom statins were recommended, 41% had CAC=0 and had 5.2 ASCVD events per 1000 person-years. Among 589 participants (12%) considered for moderate-intensity statin treatment, 338 (57%) had CAC=0, with an ASCVD event rate of 1.5 per 1000 person-years. Of participants eligible (recommended or considered) for statins, 44% (1316 of 2966) had CAC=0 at baseline and an observed 10-year ASCVD event rate of 4.2 per 1000 person-years. The study results highlighted that among the intermediate-risk range of 5% to 20%, nearly half (48%) had CAC=0, and their 10-year ASCVD risk was below the threshold recommended for statin therapy (4.5%).[70] These findings were recently confirmed in the JHS. Among 2812 African American individuals aged 40 to 75 years without prevalent ASCVD followed up for a median of 10 years, participants who were statin eligible by ACC/AHA guidelines experienced a 10-year ASCVD event rate of 8.1 per 1000 person-years. However, in the absence of CAC, the 10-year observed ASCVD risk was below the threshold of statin recommendation set by the guidelines, at 3.1 per 1000 person-years.[71]

Family History and Genetics

- There is evidence for genetic control of subclinical atherosclerosis, with several loci identified that associate with CAC and carotid artery IMT.[72–75] On the basis of the identified genes and variants, there are considerable shared genetic components to subclinical disease and other risk factors (such as blood lipids) and incident disease.

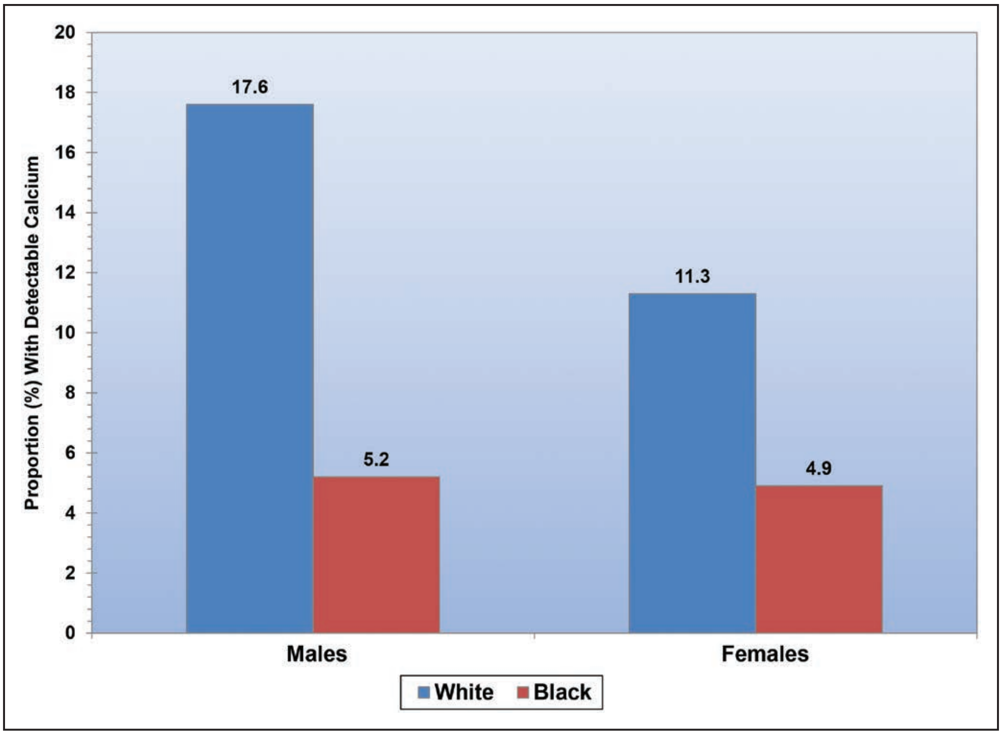

Chart 18-1. Prevalence (%) of detectable coronary calcium in the CARDIA study: US adults 33 to 45 years of age (2000–2001).
$P<0.0001$ across race-sex groups.
CARDIA indicates Coronary Artery Risk Development in Young Adults.
Data derived from Loria et al.[7]

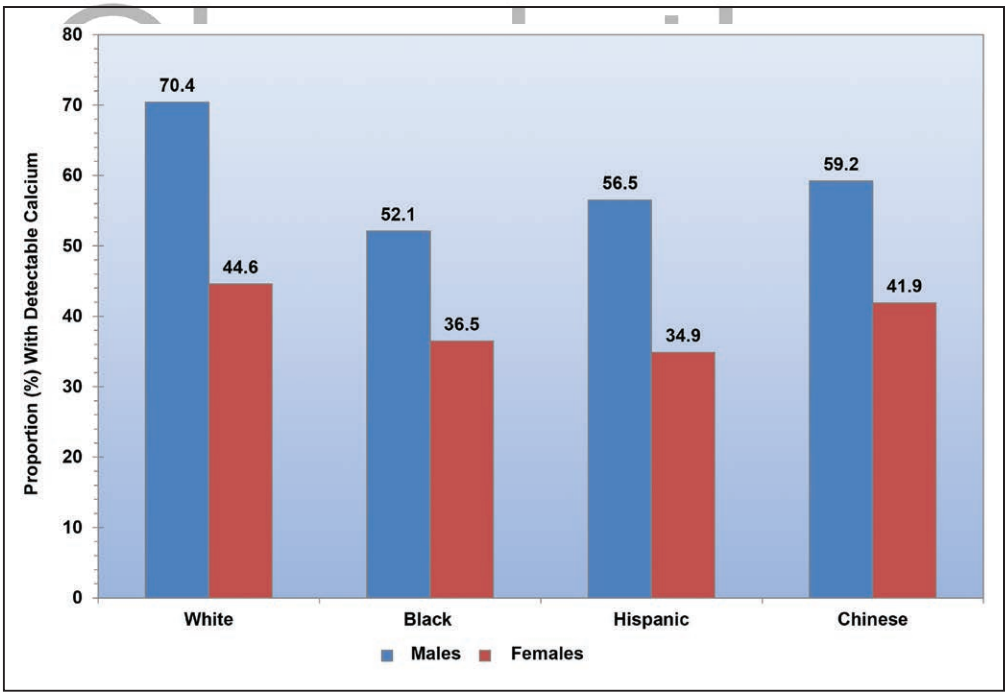

Chart 18-2. Prevalence (%) of detectable coronary calcium in MESA: US adults 45 to 84 years of age.
$P<0.0001$ across ethnic groups in both males and females.
MESA indicates Multi-Ethnic Study of Atherosclerosis.
Data derived from Bild et al.[9]

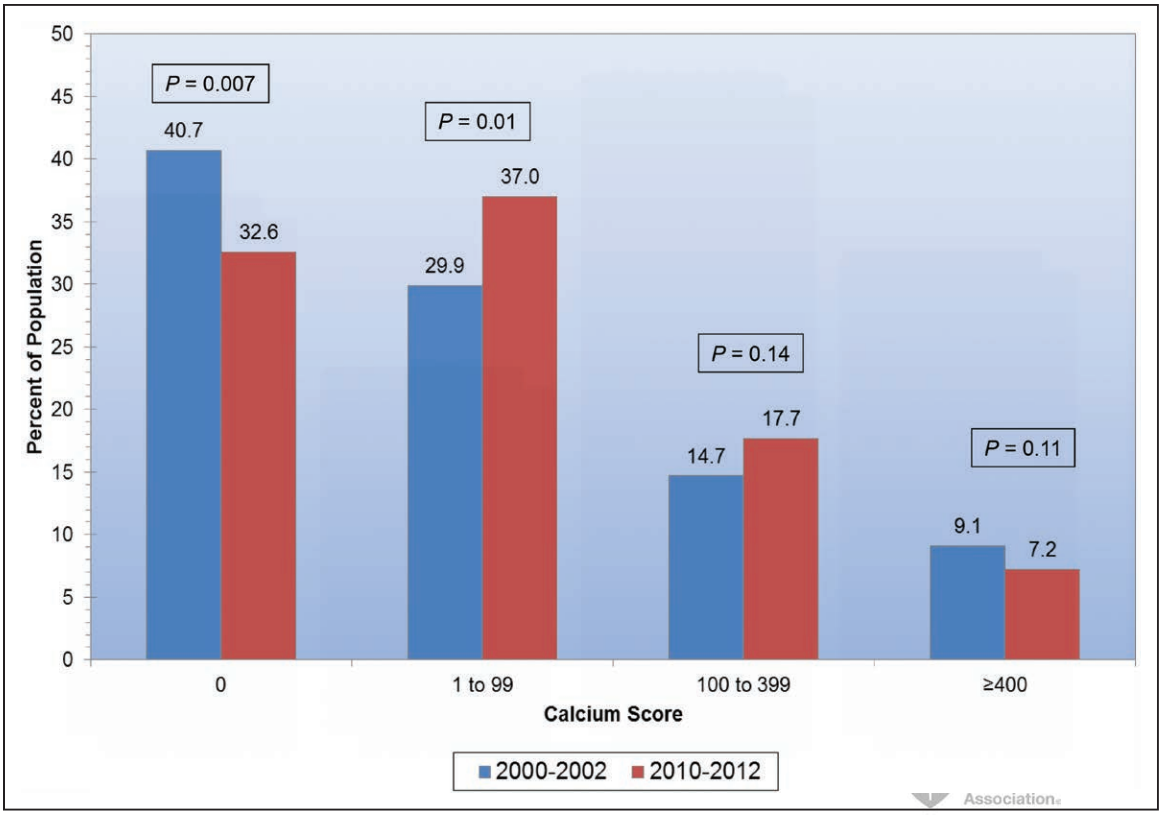

Chart 18-3. Ten-year trends in coronary artery calcification in individuals without clinical cardiovascular disease in MESA.
MESA indicates Multi-Ethnic Study of Atherosclerosis.
Adapted from Bild et al.[15]

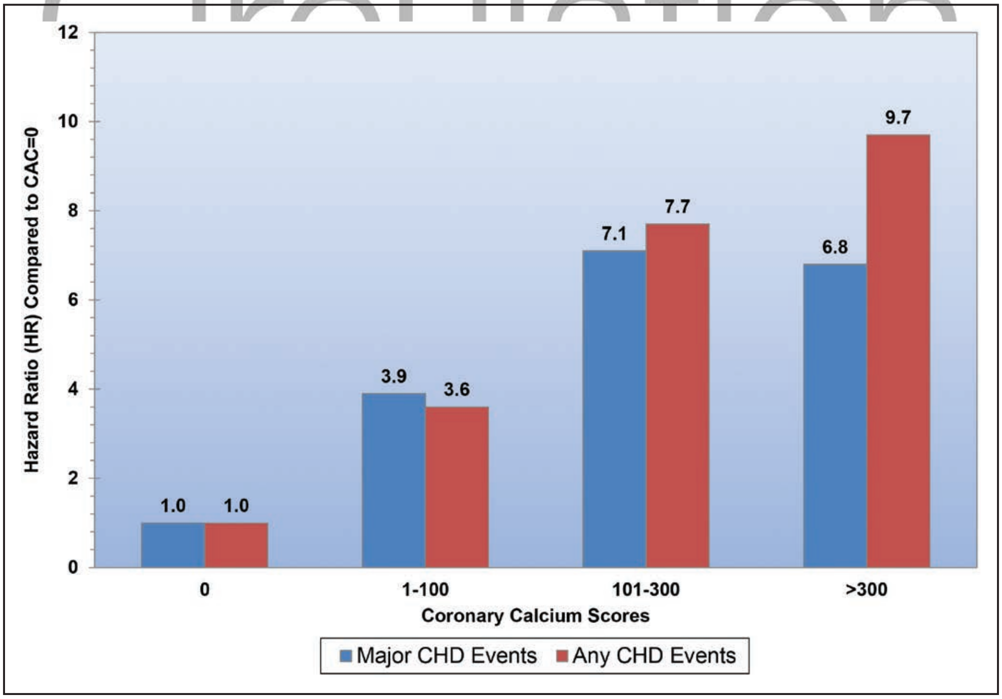

Chart 18-4. HRs for CHD events associated with CAC scores: US adults 45 to 84 years of age (reference group, CAC=0).
All HRs P<0.0001. Major CHD events included myocardial infarction and death attributable to CHD; any CHD events included major CHD events plus definite angina or definite or probable angina followed by revascularization.
CAC indicates coronary artery calcification; CHD, coronary heart disease; and HR, hazard ratio.
Data derived from Detrano et al.[16]

REFERENCES

1. Budoff MJ, Achenbach S, Blumenthal RS, Carr JJ, Goldin JG, Greenland P, Guerci AD, Lima JA, Rader DJ, Rubin GD, Shaw LJ, Wiegers SE. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation*. 2006;114:1761–1791. doi: 10.1161/CIRCULATIONAHA.106.178458
2. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC Jr, Taylor AJ, Weintraub WS, Wenger NK. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2010;122:e584–e636. doi: 10.1161/CIR.0b013e3182051b4c
3. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2018; doi: 10.1161/CIR.0000000000000625
4. Rozanski A, Gransar H, Shaw LJ, Kim J, Miranda-Peats L, Wong ND, Rana JS, Orakzai R, Hayes SW, Friedman JD, Thomson LE, Polk D, Min J, Budoff MJ, Berman DS. Impact of coronary artery calcium scanning on coronary risk factors and downstream testing: the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) prospective randomized trial. *J Am Coll Cardiol*. 2011;57:1622–1632. doi: 10.1016/j.jacc.2011.01.019
5. Pletcher MJ, Pignone M, Earnshaw S, McDade C, Phillips KA, Auer R, Zablotska L, Greenland P. Using the coronary artery calcium score to guide statin therapy: a cost-effectiveness analysis. *Circ Cardiovasc Qual Outcomes*. 2014;7:276–284. doi: 10.1161/CIRCOUTCOMES.113.000799
6. Budoff MJ, Nasir K, McClelland RL, Detrano R, Wong N, Blumenthal RS, Kondos G, Kronmal RA. Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles: MESA (Multi-Ethnic Study of Atherosclerosis) [published correction appears in *J Am Coll Cardiol*. 2009;53:1474]. *J Am Coll Cardiol*. 2009;53:345–352. doi: 10.1016/j.jacc.2008.07.072

6a. Hoffmann U, Massaro JM, Fox CS, Manders E, O'Donnell CJ. Defining normal distributions of coronary artery calcium in women and men (from the Framingham Heart Study). *Am J Cardiol*. 2008;102:1136–1141. doi: 10.1016/j.amjcard.2008.06.038

7. Loria CM, Liu K, Lewis CE, Hulley SB, Sidney S, Schreiner PJ, Williams OD, Bild DE, Detrano R. Early adult risk factor levels and subsequent coronary artery calcification: the CARDIA Study. *J Am Coll Cardiol*. 2007;49:2013–2020. doi: 10.1016/j.jacc.2007.03.009
8. Xanthakis V, Sung JH, Samdarshi TE, Hill AN, Musani SK, Sims M, Ghraibeh KA, Liebson PR, Taylor HA, Vasan RS, Fox ER. Relations between subclinical disease markers and type 2 diabetes, metabolic syndrome, and incident cardiovascular disease: the Jackson Heart Study. *Diabetes Care*. 2015;38:1082–1088. doi: 10.2337/dc14-2460
9. Bild DE, Detrano R, Peterson D, Guerci A, Liu K, Shahar E, Ouyang P, Jackson S, Saad MF. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2005;111:1313–1320. doi: 10.1161/01.CIR.0000157730.94423.4B
10. Kanaya AM, Kandula NR, Ewing SK, Herrington D, Liu K, Blaha MJ, Srivastava S, Dave SS, Budoff MJ. Comparing coronary artery calcium among U.S. South Asians with four racial/ethnic groups: the MASALA and MESA studies [published correction appears in *Atherosclerosis*. 2014;235:36–37]. *Atherosclerosis*. 2014;234:102–107. doi: 10.1016/j.atherosclerosis.2014.02.017
11. Kaplan H, Thompson RC, Trumble BC, Wann LS, Allam AH, Beheim B, Frohlich B, Sutherland ML, Sutherland JD, Stieglitz J, Rodriguez DE, Michalik DE, Rowan CJ, Lombardi GP, Bedi R, Garcia AR, Min JK, Narula J, Finch CE, Gurven M, Thomas GS. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. *Lancet*. 2017;389:1730–1739. doi: 10.1016/S0140-6736(17)30752-3
12. Mamudu HM, Paul TK, Wang L, Veeranki SP, Panchal HB, Alamian A, Sarnosky K, Budoff M. The effects of multiple coronary artery disease risk factors on subclinical atherosclerosis in a rural population in the United States. *Prev Med*. 2016;88:140–146. doi: 10.1016/j.ypmed.2016.04.003
13. Martin SS, Blaha MJ, Blankstein R, Agatston A, Rivera JJ, Virani SS, Ouyang P, Jones SR, Blumenthal RS, Budoff MJ, Nasir K. Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the Multi-Ethnic Study of Atherosclerosis. *Circulation*. 2014;129:77–86. doi: 10.1161/CIRCULATIONAHA.113.003625
14. Silverman MG, Blaha MJ, Krumholz HM, Budoff MJ, Blankstein R, Sibley CT, Agatston A, Blumenthal RS, Nasir K. Impact of coronary artery calcium on coronary heart disease events in individuals at the extremes of traditional risk factor burden: the Multi-Ethnic Study of Atherosclerosis. *Eur Heart J*. 2014;35:2232–2241. doi: 10.1093/eurheartj/eht508
15. Bild DE, McClelland R, Kaufman JD, Blumenthal R, Burke GL, Carr JJ, Post WS, Register TC, Shea S, Szklo M. Ten-year trends in coronary calcification in individuals without clinical cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis [published correction appears in *PLoS One*. 2014;9:e103666]. *PLoS One*. 2014;9:e94916. doi: 10.1371/journal.pone.0094916
16. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O'Leary DH, Tracy R, Watson K, Wong ND, Kronmal RA. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med*. 2008;358:1336–1345. doi: 10.1056/NEJMoa072100
17. Ambale-Venkatesh B, Yang X, Wu CO, Liu K, Hundley WG, McClelland R, Gomes AS, Folsom AR, Shea S, Guallar E, Bluemke DA, Lima JAC. Cardiovascular event prediction by machine learning: the Multi-Ethnic Study of Atherosclerosis. *Circ Res*. 2017;121:1092–1101. doi: 10.1161/CIRCRESAHA.117.311312
18. Tota-Maharaj R, Blaha MJ, Blankstein R, Silverman MG, Eng J, Shaw LJ, Blumenthal RS, Budoff MJ, Nasir K. Association of coronary artery calcium and coronary heart disease events in young and elderly participants in the Multi-Ethnic Study of Atherosclerosis: a secondary analysis of a prospective, population-based cohort. *Mayo Clin Proc*. 2014;89:1350–1359. doi: 10.1016/j.mayocp.2014.05.017
19. Lee KK, Fortmann SP, Fair JM, Iribarren C, Rubin GD, Varady A, Go AS, Quertermous T, Hlatky MA. Insulin resistance independently predicts the progression of coronary artery calcification. *Am Heart J*. 2009;157:939–945. doi: 10.1016/j.ahj.2009.02.006
20. Polonsky TS, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, Greenland P. Coronary artery calcium score and risk classification for coronary heart disease prediction. *JAMA*. 2010;303:1610–1616. doi: 10.1001/jama.2010.461
21. Hermann DM, Gronewold J, Lehmann N, Moebus S, Jöckel KH, Bauer M, Erbel R; on behalf of the Heinz Nixdorf Recall Study Investigative Group. Coronary artery calcification is an independent stroke predictor in the general population. *Stroke*. 2013;44:1008–1013. doi: 10.1161/STROKEAHA.111.678078
22. Elias-Smale SE, Proença RV, Koller MT, Kavousi M, van Rooij FJ, Hunink MG, Steyerberg EW, Hofman A, Oudkerk M, Witteman JC. Coronary calcium score improves classification of coronary heart disease risk in the elderly: the Rotterdam study. *J Am Coll Cardiol*. 2010;56:1407–1414. doi: 10.1016/j.jacc.2010.06.029
23. Paixao AR, Ayers CR, El Sabbagh A, Sanghavi M, Berry JD, Rohatgi A, Kumbhani DJ, McGuire DK, Das SR, de Lemos JA, Khera A. Coronary artery calcium improves risk classification in younger populations. *JACC Cardiovasc Imaging*. 2015;8:1285–1293. doi: 10.1016/j.jcmg.2015.06.015
24. Kramer CK, Zinman B, Gross JL, Canani LH, Rodrigues TC, Azevedo MJ, Retnakaran R. Coronary artery calcium score prediction of all cause mortality and cardiovascular events in people with type 2 diabetes: systematic review and meta-analysis. *BMJ*. 2013;346:f1654. doi: 10.1136/bmj.f1654
25. Leening MJ, Elias-Smale SE, Kavousi M, Felix JF, Deckers JW, Vliegenthart R, Oudkerk M, Hofman A, Steyerberg EW, Stricker BH, Witteman JC. Coronary calcification and the risk of heart failure in the elderly: the Rotterdam Study. *JACC Cardiovasc Imaging*. 2012;5:874–880. doi: 10.1016/j.jcmg.2012.03.016
26. Sharma K, Al Rifai M, Ahmed HM, Dardari Z, Silverman MG, Yeboah J, Nasir K, Sklo M, Yancy C, Russell SD, Blumenthal RS, Blaha MJ. Usefulness of coronary artery calcium to predict heart failure with preserved ejection fraction in men versus women (from the Multi-Ethnic Study of Atherosclerosis). *Am J Cardiol*. 2017;120:1847–1853. doi: 10.1016/j.amjcard.2017.07.089
27. O'Neal WT, Efird JT, Qureshi WT, Yeboah J, Alonso A, Heckbert SR, Nazarian S, Soliman EZ. Coronary artery calcium progression and atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging*. 2015;8:e003786. doi: 10.1161/CIRCIMAGING.115.003786

28. Handy CE, Desai CS, Dardari ZA, Al-Mallah MH, Miedema MD, Ouyang P, Budoff MJ, Blumenthal RS, Nasir K, Blaha MJ. The association of coronary artery calcium with noncardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. *JACC Cardiovasc Imaging*. 2016;9:568–576. doi: 10.1016/j.jcmg.2015.09.020
29. Sarwar A, Shaw LJ, Shapiro MD, Blankstein R, Hoffmann U, Cury RC, Abbara S, Brady TJ, Budoff MJ, Blumenthal RS, Nasir K. Diagnostic and prognostic value of absence of coronary artery calcification [published correction appears in *JACC Cardiovasc Imaging*. 2010;3:1089]. *JACC Cardiovasc Imaging*. 2009;2:675–688. doi: 10.1016/j.jcmg.2008.12.031
30. Budoff MJ, McClelland RL, Nasir K, Greenland P, Kronmal RA, Kondos GT, Shea S, Lima JA, Blumenthal RS. Cardiovascular events with absent or minimal coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am Heart J*. 2009;158:554–561. doi: 10.1016/j.ahj.2009.08.007
31. Malik S, Budoff MJ, Katz R, Blumenthal RS, Bertoni AG, Nasir K, Szklo M, Barr RG, Wong ND. Impact of subclinical atherosclerosis on cardiovascular disease events in individuals with metabolic syndrome and diabetes: the Multi-Ethnic Study of Atherosclerosis. *Diabetes Care*. 2011;34:2285–2290. doi: 10.2337/dc11-0816
32. Bittencourt MS, Blaha MJ, Blankstein R, Budoff M, Vargas JD, Blumenthal RS, Agatston AS, Nasir K. Polypill therapy, subclinical atherosclerosis, and cardiovascular events-implications for the use of preventive pharmacotherapy: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2014;63:434–443. doi: 10.1016/j.jacc.2013.08.1640
33. Chaikriangkrai K, Jhun HY, Palamaner Subash Shantha G, Bin Abdulhak A, Sigurdsson G, Nabi F, Mahmarian JJ, Chang SM. Coronary artery calcium score as a predictor for incident stroke: systematic review and meta-analysis. *Int J Cardiol*. 2017;236:473–477. doi: 10.1016/j.ijcard.2017.01.132
34. Budoff MJ, Young R, Lopez VA, Kronmal RA, Nasir K, Blumenthal RS, Detrano RC, Bild DE, Guerci AD, Liu K, Shea S, Szklo M, Post W, Lima J, Bertoni A, Wong ND. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2013;61:1231–1239. doi: 10.1016/j.jacc.2012.12.035
35. Wong ND, Nelson JC, Granston T, Bertoni AG, Blumenthal RS, Carr JJ, Guerci A, Jacobs DR Jr, Kronmal R, Liu K, Saad M, Selvin E, Tracy R, Detrano R. Metabolic syndrome, diabetes, and incidence and progression of coronary calcium: the Multiethnic Study of Atherosclerosis study. *JACC Cardiovasc Imaging*. 2012;5:358–366. doi: 10.1016/j.jcmg.2011.12.015
36. Ahmed HM, Blaha MJ, Nasir K, Jones SR, Rivera JJ, Agatston A, Blankstein R, Wong ND, Lakoski S, Budoff MJ, Burke GL, Sibley CT, Ouyang P, Blumenthal RS. Low-risk lifestyle, coronary calcium, cardiovascular events, and mortality: results from MESA. *Am J Epidemiol*. 2013;178:12–21. doi: 10.1093/aje/kws453
37. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PWF. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2014;129(suppl 2):S74–S75]. *Circulation*. 2014;129(suppl XXX2):S49–S73. doi: 10.1161/01.cir.0000437741.48606.98
38. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37:2315–2381. doi: 10.1093/eurheartj/ehw106
39. Urbina EM, Srinivasan SR, Tang R, Bond MG, Kieltyka L, Berenson GS; Bogalusa Heart Study. Impact of multiple coronary risk factors on the intima-media thickness of different segments of carotid artery in healthy young adults (the Bogalusa Heart Study). *Am J Cardiol*. 2002;90:953–958.
40. Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM, Berenson GS. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study [published correction appears in *JAMA*. 2003;290:2943]. *JAMA*. 2003;290:2271–2276.
41. Juonala M, Viikari JS, Kähönen M, Taittonen L, Laitinen T, Hutri-Kähönen N, Lehtimäki T, Jula A, Pietikäinen M, Jokinen E, Telama R, Räsänen L, Mikkilä V, Helenius H, Kivimäki M, Raitakari OT. Life-time risk factors and progression of carotid atherosclerosis in young adults: the Cardiovascular Risk in Young Finns study. *Eur Heart J*. 2010;31:1745–1751. doi: 10.1093/eurheartj/ehq141
42. Gijsberts CM, Groenewegen KA, Hoefer IE, Eijkemans MJ, Asselbergs FW, Anderson TJ, Britton AR, Dekker JM, Engström G, Evans GW, de Graaf J, Grobbee DE, Hedblad B, Holewijn S, Ikeda A, Kitagawa K, Kitamura A, de Kleijn DP, Lonn EM, Lorenz MW, Mathiesen EB, Nijpels G, Okazaki S, O'Leary DH, Pasterkamp G, Peters SA, Polak JF, Price JF, Robertson C, Rembold CM, Rosvall M, Rundek T, Salonen JT, Sitzer M, Stehouwer CD, Bots ML, den Ruijter HM. Race/ethnic differences in the associations of the Framingham risk factors with carotid IMT and cardiovascular events. *PLoS One*. 2015;10:e0132321. doi: 10.1371/journal.pone.0132321
43. Manolio TA, Arnold AM, Post W, Bertoni AG, Schreiner PJ, Sacco RL, Saad MF, Detrano RL, Szklo M. Ethnic differences in the relationship of carotid atherosclerosis to coronary calcification: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2008;197:132–138. doi: 10.1016/j.atherosclerosis.2007.02.030
44. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr; for the Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med*. 1999;340:14–22. doi: 10.1056/NEJM199901073400103
45. Polak JF, Pencina MJ, O'Leary DH, D'Agostino RB. Common carotid artery intima-media thickness progression as a predictor of stroke in Multi-Ethnic Study of Atherosclerosis. *Stroke*. 2011;42:3017–3021. doi: 10.1161/STROKEAHA.111.625186
46. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engström G, Evans GW, de Graaf J, Grobbee DE, Hedblad B, Hofman A, Holewijn S, Ikeda A, Kavousi M, Kitagawa K, Kitamura A, Koffijberg H, Lonn EM, Lorenz MW, Mathiesen EB, Nijpels G, Okazaki S, O'Leary DH, Polak JF, Price JF, Robertson C, Rembold CM, Rosvall M, Rundek T, Salonen JT, Sitzer M, Stehouwer CD, Witteman JC, Moons KG, Bots ML. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis [published correction appears in *JAMA*. 2013;310:1739]. *JAMA*. 2012;308:796–803. doi: 10.1001/jama.2012.9630
47. Polak JF, Szklo M, O'Leary DH. Carotid intima-media thickness score, positive coronary artery calcium score, and incident coronary heart disease: the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc*. 2017;6:e004612. doi: 10.1161/JAHA.116.004612
48. Effoe VS, McClendon EE, Rodriguez CJ, Wagenknecht LE, Evans GW, Chang PP, Bertoni AG. Diabetes status modifies the association between carotid intima-media thickness and incident heart failure: the Atherosclerosis Risk in Communities study. *Diabetes Res Clin Pract*. 2017;128:58–66. doi: 10.1016/j.diabres.2017.04.009
49. Chen LY, Leening MJ, Norby FL, Roetker NS, Hofman A, Franco OH, Pan W, Polak JF, Witteman JC, Kronmal RA, Folsom AR, Nazarian S, Stricker BH, Heckbert SR, Alonso A. Carotid intima-media thickness and arterial stiffness and the risk of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) Study, Multi-Ethnic Study of Atherosclerosis (MESA), and the Rotterdam Study. *J Am Heart Assoc*. 2016;5:e002907. doi: 10.1161/JAHA.115.002907
50. Bots ML, Groenewegen KA, Anderson TJ, Britton AR, Dekker JM, Engström G, Evans GW, de Graaf J, Grobbee DE, Hedblad B, Hofman A, Holewijn S, Ikeda A, Kavousi M, Kitagawa K, Kitamura A, Ikram MA, Lonn EM, Lorenz MW, Mathiesen EB, Nijpels G, Okazaki S, O'Leary DH, Polak JF, Price JF, Robertson C, Rembold CM, Rosvall M, Rundek T, Salonen JT, Sitzer M, Stehouwer CD, Franco OH, Peters SA, den Ruijter HM. Common carotid intima-media thickness measurements do not improve cardiovascular risk prediction in individuals with elevated blood pressure: the USE-IMT collaboration. *Hypertension*. 2014;63:1173–1181. doi: 10.1161/HYPERTENSIONAHA.113.02683
51. Baber U, Mehran R, Sartori S, Schoos MM, Sillesen H, Muntendam P, Garcia MJ, Gregson J, Pocock S, Falk E, Fuster V. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. *J Am Coll Cardiol*. 2015;65:1065–1074. doi: 10.1016/j.jacc.2015.01.017
52. Romero JR, Preis SR, Beiser A, DeCarli C, D'Agostino RB, Wolf PA, Vasan RS, Polak JF, Seshadri S. Carotid atherosclerosis and cerebral microbleeds: the Framingham Heart Study. *J Am Heart Assoc*. 2016;5:e002377. doi: 10.1161/JAHA.115.002377
53. Pang Y, Sang Y, Ballew SH, Grams ME, Heiss G, Coresh J, Matsushita K. Carotid intima-media thickness and incident ESRD: the Atherosclerosis Risk in Communities (ARIC) Study. *Clin J Am Soc Nephrol*. 2016;11:1197–1205. doi: 10.2215/CJN.11951115

54. Gepner AD, Young R, Delaney JA, Tattersall MC, Blaha MJ, Post WS, Gottesman RF, Kronmal R, Budoff MJ, Burke GL, Folsom AR, Liu K, Kaufman J, Stein JH. Comparison of coronary artery calcium presence, carotid plaque presence, and carotid intima-media thickness for cardiovascular disease prediction in the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging*. 2015;8:e002262. doi: 10.1161/CIRCIMAGING.114.002262
55. Berry JD, Liu K, Folsom AR, Lewis CE, Carr JJ, Polak JF, Shea S, Sidney S, O'Leary DH, Chan C, Lloyd-Jones DM. Prevalence and progression of subclinical atherosclerosis in younger adults with low short-term but high lifetime estimated risk for cardiovascular disease: the Coronary Artery Risk Development in Young Adults study and Multi-Ethnic Study of Atherosclerosis. *Circulation*. 2009;119:382–389. doi: 10.1161/CIRCULATIONAHA.108.800235
56. Lorenz MW, Price JF, Robertson C, Bots ML, Polak JF, Poppert H, Kavousi M, Dörr M, Stensland E, Ducimetiere P, Ronkainen K, Kiechl S, Sitzer M, Rundek T, Lind L, Liu J, Bergström G, Grigore L, Bokemark L, Friera A, Yanez D, Bickel H, Ikram MA, Völzke H, Johnsen SH, Empana JP, Tuomainen TP, Willeit P, Steinmetz H, Desvarieux M, Xie W, Schmidt C, Norata GD, Suarez C, Sander D, Hofman A, Schminke U, Mathiesen E, Plichart M, Kauhanen J, Willeit J, Sacco RL, McLachlan S, Zhao D, Fagerberg B, Catapano AL, Gabriel R, Franco OH, Bülbül A, Scheckenbach F, Pflug A, Gao L, Thompson SG. Carotid intima-media thickness progression and risk of vascular events in people with diabetes: results from the PROG-IMT collaboration. *Diabetes Care*. 2015;38:1921–1929. doi: 10.2337/dc14-2732
57. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, Naruse H, Ishii J, Hishida H, Wong ND, Virmani R, Kondo T, Ozaki Y, Narula J. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol*. 2009;54:49–57. doi: 10.1016/j.jacc.2009.02.068
58. Cho I, Al'Aref SJ, Berger A, Ó Hartaigh B, Gransar H, Valenti V, Lin FY, Achenbach S, Berman DS, Budoff MJ, Callister TQ, Al-Mallah MH, Cademartiri F, Chinnaiyan K, Chow BJW, DeLago A, Villines TC, Hadamitzky M, Hausleiter J, Leipsic J, Shaw LJ, Kaufmann PA, Feuchtner G, Kim YJ, Maffei E, Raff G, Pontone G, Andreini D, Marques H, Rubinshtein R, Chang HJ, Min JK. Prognostic value of coronary computed tomographic angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective multicentre international CONFIRM study. *Eur Heart J*. 2018;39:934–941. doi: 10.1093/eurheartj/ehx774
59. Cho I, Chang HJ, Ó Hartaigh B, Shin S, Sung JM, Lin FY, Achenbach S, Heo R, Berman DS, Budoff MJ, Callister TQ, Al-Mallah MH, Cademartiri F, Chinnaiyan K, Chow BJ, Dunning AM, DeLago A, Villines TC, Hadamitzky M, Hausleiter J, Leipsic J, Shaw LJ, Kaufmann PA, Cury RC, Feuchtner G, Kim YJ, Maffei E, Raff G, Pontone G, Andreini D, Min JK. Incremental prognostic utility of coronary CT angiography for asymptomatic patients based upon extent and severity of coronary artery calcium: results from the COronary CT Angiography EvaluatioN For Clinical Outcomes InteRnational Multicenter (CONFIRM) study [published correction appears in *Eur Heart J*. 2015;36:3287]. *Eur Heart J*. 2015;36:501–508. doi: 10.1093/eurheartj/ehu358
60. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, Asmar R, Reneman RS, Hoeks AP, Breteler MM, Witteman JC. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation*. 2006;113:657–663. doi: 10.1161/CIRCULATIONAHA.105.555235
61. Willum-Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation*. 2006;113:664–670. doi: 10.1161/CIRCULATIONAHA.105.579342
62. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*. 2010;121:505–511. doi: 10.1161/CIRCULATIONAHA.109.886655
63. Tripathi A, Benjamin EJ, Musani SK, Hamburg NM, Tsao CW, Saraswat A, Vasan RS, Mitchell GF, Fox ER. The association of endothelial function and tone by digital arterial tonometry with MRI left ventricular mass in African Americans: the Jackson Heart Study. *J Am Soc Hypertens*. 2017;11:258–264. doi: 10.1016/j.jash.2017.03.005
64. Xu Y, Arora RC, Hiebert BM, Lerner B, Szwajcer A, McDonald K, Rigatto C, Komenda P, Sood MM, Tangri N. Non-invasive endothelial function testing and the risk of adverse outcomes: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging*. 2014;15:736–746. doi: 10.1093/ehjci/jet256
65. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA*. 2012;308:788–795. doi: 10.1001/jama.2012.9624
66. Blaha MJ, Cainzos-Achirica M, Greenland P, McEvoy JW, Blankstein R, Budoff MJ, Dardari Z, Sibley CT, Burke GL, Kronmal RA, Szklo M, Blumenthal RS, Nasir K. Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2016;133:849–858. doi: 10.1161/CIRCULATIONAHA.115.018524
67. Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, Verwoert GC, Krestin GP, Oudkerk M, de Maat MP, Leebeek FW, Mattace-Raso FU, Lindemans J, Hofman A, Steyerberg EW, van der Lugt A, van den Meiracker AH, Witteman JC. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. *Ann Intern Med*. 2012;156:438–444. doi: 10.7326/0003-4819-156-6-201203200-00006
68. Blaha MJ, Budoff MJ, DeFilippis AP, Blankstein R, Rivera JJ, Agatston A, O'Leary DH, Lima J, Blumenthal RS, Nasir K. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study. *Lancet*. 2011;378:684–692. doi: 10.1016/S0140-6736(11)60784-8
69. Miedema MD, Duprez DA, Misialek JR, Blaha MJ, Nasir K, Silverman MG, Blankstein R, Budoff MJ, Greenland P, Folsom AR. Use of coronary artery calcium testing to guide aspirin utilization for primary prevention: estimates from the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Qual Outcomes*. 2014;7:453–460. doi: 10.1161/CIRCOUTCOMES.113.000690
70. Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ, Miedema MD, Sibley CT, Shaw LJ, Blumenthal RS, Budoff MJ, Krumholz HM. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis) [published correction appears in *J Am Coll Cardiol*. 2015;66:2686]. *J Am Coll Cardiol*. 2015;66:1657–1668. doi: 10.1016/j.jacc.2015.07.066
71. Shah RV, Spahillari A, Mwasongwe S, Carr JJ, Terry JG, Mentz RJ, Addison D, Hoffmann U, Reis J, Freedman JE, Lima JAC, Correa A, Murthy VL. Subclinical atherosclerosis, statin eligibility, and outcomes in African American individuals: the Jackson Heart Study. *JAMA Cardiol*. 2017;2:644–652. doi: 10.1001/jamacardio.2017.0944
72. Natarajan P, Bis JC, Bielak LF, Cox AJ, Dörr M, Feitosa MF, Franceschini N, Guo X, Hwang SJ, Isaacs A, Jhun MA, Kavousi M, Li-Gao R, Lyytikäinen LP, Marioni RE, Schminke U, Stitziel NO, Tada H, van Setten J, Smith AV, Vojinovic D, Yanek LR, Yao J, Yerges-Armstrong LM, Amin N, Baber U, Borecki IB, Carr JJ, Chen YI, Cupples LA, de Jong PA, de Koning H, de Vos BD, Demirkan A, Fuster V, Franco OH, Goodarzi MO, Harris TB, Heckbert SR, Heiss G, Hoffmann U, Hofman A, Išgum I, Jukema JW, Kähönen M, Kardia SL, Kral BG, Launer LJ, Massaro J, Mehran R, Mitchell BD, Mosley TH Jr, de Mutsert R, Newman AB, Nguyen KD, North KE, O'Connell JR, Oudkerk M, Pankow JS, Peloso GM, Post W, Province MA, Raffield LM, Raitakari OT, Reilly DF, Rivadeneira F, Rosendaal F, Sartori S, Taylor KD, Teumer A, Trompet S, Turner ST, Uitterlinden AG, Vaidya D, van der Lugt A, Völker U, Wardlaw JM, Wassel CL, Weiss S, Wojczynski MK, Becker DM, Becker LC, Boerwinkle E, Bowden DW, Deary IJ, Dehghan A, Felix SB, Gudnason V, Lehtimäki T, Mathias R, Mook-Kanamori DO, Psaty BM, Rader DJ, Rotter JI, Wilson JG, van Duijn CM, Völzke H, Kathiresan S, Peyser PA, O'Donnell CJ; CHARGE Consortium. Multiethnic exome-wide association study of subclinical atherosclerosis. *Circ Cardiovasc Genet*. 2016;9:511–520. doi: 10.1161/CIRCGENETICS.116.001572
73. Divers J, Palmer ND, Langefeld CD, Brown WM, Lu L, Hicks PJ, Smith SC, Xu J, Terry JG, Register TC, Wagenknecht LE, Parks JS, Ma L, Chan GC, Buxbaum SG, Correa A, Musani S, Wilson JG, Taylor HA, Bowden DW, Carr JJ, Freedman BI. Genome-wide association study of coronary artery calcified atherosclerotic plaque in African Americans with type 2 diabetes. *BMC Genet*. 2017;18:105. doi: 10.1186/s12863-017-0572-9
74. Wojczynski MK, Li M, Bielak LF, Kerr KF, Reiner AP, Wong ND, Yanek LR, Qu L, White CC, Lange LA, Ferguson JF, He J, Young T, Mosley TH, Smith JA, Kral BG, Guo X, Wong Q, Ganesh SK, Heckbert SR, Griswold ME, O'Leary DH, Budoff M, Carr JJ, Taylor HA Jr, Bluemke DA, Demissie S, Hwang SJ, Paltoo DN, Polak JF, Psaty BM, Becker DM, Province MA, Post WS, O'Donnell CJ, Wilson JG, Harris TB, Kavousi M, Cupples LA, Rotter JI, Fornage M, Becker LC, Peyser PA, Borecki IB, Reilly MP. Genetics of coronary artery calcification among African Americans, a meta-analysis. *BMC Med Genet*. 2013;14:75. doi: 10.1186/1471-2350-14-75
75. Vargas JD, Manichaikul A, Wang XQ, Rich SS, Rotter JI, Post WS, Polak JF, Budoff MJ, Bluemke DA. Common genetic variants and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2016;245:230–236. doi: 10.1016/j.atherosclerosis.2015.11.034

19. CORONARY HEART DISEASE, ACUTE CORONARY SYNDROME, AND ANGINA PECTORIS

See Tables 19-1 through 19-3 and Charts 19-1 through 19-11

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Coronary Heart Disease *ICD-9* 410 to 414, 429.2; *ICD-10* I20 to I25 (includes MI *ICD-10* I21 to I22).

Prevalence (See Tables 19-1 and 19-2 and Charts 19-1 through 19-4)

- On the basis of data from NHANES 2013 to 2016 (unpublished NHLBI tabulation), an estimated 18.2 million Americans ≥20 years of age have CHD (Table 19-1). The prevalence of CHD was higher for males than females for all ages (Chart 19-1).

Abbreviations Used in Chapter 19

ACC	American College of Cardiology
ACS	acute coronary syndrome
ACTION	Acute Coronary Treatment and Intervention Outcomes Network
AHA	American Heart Association
AMI	acute myocardial infarction
AP	angina pectoris
ARIC	Atherosclerosis Risk in Communities Study
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ASCVD	atherosclerotic cardiovascular disease
BEST	Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CABG	coronary artery bypass graft
CAC	coronary artery calcium
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CARDIoGRAM	Coronary Artery Disease Genome-Wide Replication and Meta-Analysis
CARDIoGRAMplusC4D	Coronary Artery Disease Genome-Wide Replication and Meta-Analysis (CARDIoGRAM) plus the Coronary Artery Disease Genetics (C4D)
CARE	Cholesterol and Recurrent Events
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CVD	cardiovascular disease
DM	diabetes mellitus
ED	emergency department
FHS	Framingham Heart Study
FINRISK	Finnish population survey on risk factors for chronic, noncommunicable diseases

(*Continued*)

Abbreviations Used in Chapter 19 Continued

FRS	Framingham Risk Score
GBD	Global Burden of Disease
GWAS	genome-wide association studies
GWTG	Get With The Guidelines
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
HCUP	Healthcare Cost and Utilization Project
HDL-C	high-density lipoprotein cholesterol
HD	heart disease
HF	heart failure
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
IHD	ischemic heart disease
JHS	Jackson Heart Study
JUPITER	Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin
LDL-C	low-density lipoprotein cholesterol
LV	left ventricular
MEPS	Medical Expenditure Panel Survey
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
MI-GENES	Myocardial Infarction Genes Study
NAMCS	National Ambulatory Medical Care Survey
NCDR	National Cardiovascular Data Registry
NCHS	National Center for Health Statistics
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Study
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NSTEMI	non–ST-segment–elevation myocardial infarction
OR	odds ratio
PCI	percutaneous coronary intervention
PRECOMBAT	Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus Stents in Patients With Left Main Coronary Artery Disease
PROVE IT-TIMI 22	Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22
RCT	randomized controlled trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SBP	systolic blood pressure
SE	standard error
SES	socioeconomic status
SHS	Strong Heart Study
SNAP	Supplemental Nutrition Assistance Program
SNP	single-nucleotide polymorphism
STEMI	ST-segment–elevation myocardial infarction
SYNTAX	Synergy Between PCI With Taxus and Cardiac Surgery
TC	total cholesterol
TRACE-CORE	Transitions, Risks, and Actions in Coronary Events–Center for Outcomes Research and Education
UA	unstable angina
WHI	Women's Health Initiative

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- Total CHD prevalence is 6.7% in US adults ≥20 years of age. CHD prevalence is 7.4% for males and 6.2% for females. CHD prevalence by sex and ethnicity is shown in Table 19-1.
- On the basis of data from the 2016 NHIS[1]:
  - Among American Indian/Alaska Natives ≥18 years of age, the CHD prevalence estimate is 12.1%.
- According to data from NHANES 2013 to 2016 (unpublished NHLBI tabulation), the overall prevalence for MI is 3.0% in US adults ≥20 years of age. Males have a higher prevalence of MI than females for all age groups except 20 to 39 years (Chart 19-2). MI prevalence is 4.0% for males and 2.3% for females. MI prevalence by sex and ethnicity is shown in Table 19-1.
- According to data from NHANES 2013 to 2016 (unpublished NHLBI tabulation), the overall prevalence for angina is 3.6% in US adults ≥20 years of age (Table 19-2).
- According to data from NHANES for the period 1988 to 2012, angina prevalence declined in NH whites (from 4.0% to 2.1%) but not in NH blacks (from 4.9% to 4.4%) and in both males and females ≥65 years old (males from 5.1% to 2.9%, females from 5.6% to 2.4%).[2]
- Data from the BRFSS 2016 survey indicated that 4.4% of respondents had been told that they had had an MI. The highest prevalence was in Kentucky (6.4%), and the lowest was in the District of Columbia and California (2.8%; age-adjusted) (Chart 19-3).[3]
- In the same survey, 4.1% of respondents had been told that they had angina or CHD. The highest prevalence was in Puerto Rico (7.0%) and West Virginia (6.5%), and the lowest was in the District of Columbia and Utah (2.6%; age-adjusted) (Chart 19-4).[3]

Incidence
(See Table 19-1 and Charts 19-5 through 19-7)

- Approximately every 40 seconds, an American will have an MI (AHA computation).
- On the basis of data from the 2005 to 2014 ARIC study of the NHLBI[4]:
  - This year, ≈720 000 Americans will have a new coronary event (defined as first hospitalized MI or CHD death), and ≈335 000 will have a recurrent event.
  - The estimated annual incidence of MI is 605 000 new attacks and 200 000 recurrent attacks. Of these 805 000 first and recurrent events, it is estimated that 170 000 are silent.
  - Average age at first MI is 65.6 years for males and 72.0 years for females.
- In the REGARDS study, 37% of adjudicated MIs had a primary hospital discharge diagnosis of MI, whereas 63% had a primary hospital discharge diagnosis other than MI, which suggests that most MIs that result in hospitalization might be occurring during hospitalization for other acute illnesses.[5]
- Self-reported income and education were associated with incident CHD (defined as definite or probable MI or acute CHD death) in the REGARDS study. Those reporting low income and low education had twice the incidence of CHD as those reporting high income and high education (10.1 versus 5.2 per 1000 person-years, respectively).[6]
- Annual numbers for MI or fatal CHD in the NHLBI-sponsored ARIC study and CHS stratified by age and sex are displayed in Chart 19-5. Incidence of heart attacks or fatal CHD stratified by age, race, and sex is displayed in Chart 19-6.
- Incidence of MI by age, sex, and race in the NHLBI-sponsored ARIC study is displayed in Chart 19-7. Black males have a higher incidence of MI in all age groups.
- HRs for incident fatal CHD were higher for black males than for white males aged 45 to 65 years (ARIC: 2.09 [95% CI, 1.42–3.06]; REGARDS: 2.11 [95% CI, 1.32–3.38]). Nonfatal CHD risk was lower (ARIC: 0.82 [95% CI, 0.64–1.05]; REGARDS: 0.94 [95% CI, 0.69–1.28]). However, after adjustment for social determinants of health and cardiovascular risk factors, black males and females have similar risk for fatal CHD but lower risk for nonfatal CHD.[7]
- In 9498 participants in the ARIC study, whites had a higher rate of clinically recognized MI than blacks (5.04 versus 3.24 per 1000 person-years, *P*=0.002).[8]

Trends in Incidence

- The overall body of literature suggests that the incidence of MI has declined significantly over time, including over the past decade.[9] Geographic differences in patient populations, temporal changes in the criteria used to diagnose MI, and differences in study methodology increase the complexity of interpreting these studies, however.
- In Olmsted County, MN, between 1995 and 2012, the population rate of MI declined 3.3% per year; however, these declines varied among types of MI, with the greatest declines occurring for prehospital fatal MI.[10]
- According to data from ARIC and the REGARDS study, between 1987 to 1996 and 2003 to 2009, the incidence of CHD declined from 3.9 to 2.2

per 1000 person-years in people without DM and from 11.1 to 5.4 per 1000 person-years among those with DM.[11]

- Among Medicare beneficiaries between 2002 and 2011, the incidence of MI hospitalization declined from 1485 to 1122 per 100 000 person-years. The incidence of MI as the primary reason for hospitalization decreased over time (from 1063 to 677 per 100 000 person-years between 2002 and 2011), whereas the percentage of MIs as a secondary reason for hospitalization increased (from 190 to 245 per 100 000 person-years). The percentage of MIs that were attributable to a secondary diagnosis increased from 28% to 40%.[12]
- Among Medicare beneficiaries, the incidence of primary hospitalization for MI between 2002 and 2011 declined by 36.6% among NH whites (from 1057 to 670 per 100 000 person-years between 2002 and 2011) and by 26.4% among NH blacks (from 966 to 711 per 100 000 person-years between 2002 and 2011).[13]

Predicted Risk

- The percentage of US adults with a 10-year predicted ASCVD risk (using pooled-cohort risk equations) ≥20% decreased from 13.0% in 1999 to 2000 to 9.4% in 2011 to 2012. The proportion of US adults with 10-year predicted ASCVD risk of 7.5% to <20% was 23.9% in 1999 to 2000 and 26.8% in 2011 to 2012.[14]
- For adults with optimal risk factors (TC of 170 mg/dL, HDL-C of 50 mg/dL, SBP of 110 mm Hg without antihypertensive medication use, no DM, and not a smoker), 10-year CVD risk ≥7.5% will occur at age 65 years for white males, 70 years for black males and females, and 75 years for white females.[15]
- In the REGARDS study, the adjusted HR for CHD death associated with any versus no stroke symptoms was 1.50 (95% CI, 1.10–2.06).[16] Individuals with atherosclerotic stroke should be included among those deemed to be at high risk (20% over 10 years) of further atherosclerotic coronary events. For primary prevention, ischemic stroke should be included among CVD outcomes in absolute risk assessment algorithms. The inclusion of atherosclerotic ischemic stroke as a high-risk condition has important implications, because the number of people considered to be at high risk will increase over time.[17]
- A survey of US family physicians, general internists, and cardiologists published in 2012 found that 41% of respondents reported using global CHD risk assessment at least occasionally.[18] It is unclear whether physicians are using global CHD risk prediction more since the publication of the 2013 ACC/AHA cholesterol management guideline.[19]
- The ASCVD tool might overestimate risk across all strata of risk compared with external contemporary cohorts (Physicians' Health Study, Women's Health Study, and WHI Observational Study), as well as in reanalysis of the original validation cohorts. However, some of the subsequent analyses were not conducted in comparable populations as the original study cohorts.[20]

Mortality
(See Table 19-1)

- On the basis of 2016 mortality data[21]:
  — CHD mortality was 363 452, and CHD any-mention mortality was 533 126 (unpublished NHLBI tabulation) (Table 19-1).
  — MI mortality was 111 777. MI any-mention mortality was 149 615 (unpublished NHLBI tabulation) (Table 19-1).
- From 2006 to 2016, the annual death rate attributable to CHD declined 31.8% and the actual number of deaths declined 14.6% (unpublished NHLBI tabulation).
- CHD age-adjusted death rates per 100 000 were 132.3 for NH white males, 146.5 for NH black males, and 95.6 for Hispanic males; for NH white females, the rate was 67.9; for NH black females, it was 85.4; and for Hispanic females, it was 54.6 (unpublished NHLBI tabulation).
- 77% of CHD deaths occurred out of the hospital. According to NCHS mortality data, 279 171 CHD deaths occur out of the hospital or in hospital EDs annually (NCHS, AHA tabulation).
- The estimated average number of years of life lost because of an MI death is 16.2 (unpublished NHLBI tabulation).
- Approximately 35% of the people who experience a coronary event in a given year will die as a result of it, and ≈14% who experience an MI will die of it (AHA computation).
- Life expectancy after AMI treated in hospitals with high performance on 30-day mortality measures compared with low-performing hospitals was on average between 0.74 and 1.14 years longer.[22]
- Among 194 071 adults who were hospitalized for an AMI in the 2009 to 2010 NIS, in-hospital mortality for those <65 years of age was higher for Hispanic females (3.7%) than for black females (3.1%) and white females (2.5%). Differences were smaller for males <65 years of age. Among older adults (≥65 years), in-hospital mortality was 8.0% for white females and between 6% and 8% for other race-sex groups.[23]

- In a study using data from the Cooperative Cardiovascular Project, survival and life expectancy after AMI were higher in whites than in blacks (7.4% versus 5.7%). White patients living in high SES areas showed the longest life expectancy. Gaps in life expectancy between white and black patients were largest among high SES areas, with smaller differences in medium and low SES areas. These differences were attenuated but did not disappear after adjustment for patient and treatment characteristics.[24]
- Compared with nonparticipants, participants in SNAP have twice the risk of CVD mortality, which likely reflects differences in socioeconomic, environmental, and behavioral characteristics.[25]

Temporal Trends in Mortality

- The decline in CHD mortality rates in part reflects the shift in the pattern of clinical presentations of AMI. There has been a marked decline in STEMI (from 133 to 50 cases per 100 000 person-years from 1999 to 2008).[26]
- In Olmsted County, MN, the age- and sex-adjusted 30-day case fatality rate decreased by 56% from 1987 to 2006.[27] Among Medicare fee-for-service beneficiaries, between 1999 and 2011, the 30-day mortality rate after hospitalized MI declined by 29.4%.[28]
- In a community-based study of Worcester, MA, the percentage of patients dying after cardiogenic shock during their hospitalization for MI declined from 47.1% in 2001 to 2003 to 28.6% in 2009 to 2011.[29]
- Between 2001 and 2011 in the NIS, in-hospital mortality did not change for patients with STEMI with a PCI (3.40% and 3.52% in 2001 and 2011, respectively) or CABG (5.79% and 5.70% in 2001 and 2011, respectively) and increased for patients with no intervention (12.43% and 14.91% in 2001 and 2011, respectively). In-hospital mortality declined for patients with NSTEMI undergoing CABG (from 4.97% to 2.91%) or no procedure (from 8.87% to 6.26%) but did not change for patients with NSTEMI undergoing PCI (1.73% and 1.45%).[30]
- Among US males <55 years of age, CHD mortality declined an annual 5.5% per year between 1979 and 1989; a smaller decline was present in 1990 to 1999 (1.2% per year) and in 2000 to 2011 (1.8% per year). Among US females <55 years of age, CHD mortality declined an annual 4.6% per year in 1979 to 1989, with no decline between 1990 and 1999 and a decline of 1.0% in 2000 to 2011.[31]
- Reflecting trends in change in type and severity of AMI, studies worldwide have documented a reduction in HF and mortality after MI. In a nationwide Swedish registry of 199 851 patients admitted with AMI from 1996 to 2008, the incidence of HF decreased from 46% to 28%, with a greater decline in individuals with STEMI compared with NSTEMI.[32] The in-hospital, 30-day, and 1-year mortality rates for those with HF decreased from 19% to 13%, 23% to 17%, and 36% to 31%, respectively (all *P*<0.001). In Olmsted County, MN, from 1990 to 2010, there was a decline in mortality associated with HF after MI, but this risk was greater for delayed HF than for early-onset HF after MI.[33]
- Taking into account past trends in CHD mortality from 1980, and considering age-period and cohort effects, CHD mortality is likely to continue its decades-long decline, with a reduction in deaths by 2030 of 27%; however, race disparities will persist.[34] Recent reports have suggested a slowing down of all CVD and HD mortality in recent years.[35,36]

Awareness of Warning Signs and Risk for HD

- In 2012, NH black and Hispanic females had lower awareness than white females that HD/heart attack is the leading cause of death for females.[37]
- The percentages of females in 2012 identifying warning signs for a heart attack were as follows: pain in the chest—56%; pain that spreads to the shoulder, neck, or arm—60%; shortness of breath—38%; chest tightness—17%; nausea—18%; and fatigue—10%.[37]
- The 5 most commonly cited HD prevention strategies in 2012 were maintaining a healthy BP (78%), seeing the doctor (78%), and increasing fiber intake, eating food with antioxidants, and maintaining healthy cholesterol levels (each 66%).[37]
- Among online survey participants, 21% responded that their doctor had talked to them about HD risk. Rates were lower among Hispanic females (12%) than whites (22%) or blacks (22%) and increased with age from 6% (25–34 years) to 33% (≥65 years).[37]
- Among 2009 females and 976 males <55 years of age hospitalized for MI, only 48.7% of females and 52.9% of males reported being told they were at risk for HD or a heart problem. Also, 50.3% of females and 59.7% of males reported their healthcare provider discussing HD and things they could do to take care of their heart.[38]

Time of Symptom Onset and Arrival at Hospital

- Data from Worcester, MA, indicate that the median time from symptom onset to hospital

arrival did not improve from 2001 through 2011. In 2009 to 2011, 48.9% of patients reached the hospital within 2 hours of symptom onset compared with 45.8% in 2001 to 2003.[39]
- Among patients hospitalized for ACS between 2001 and 2011 in the NIS, those with STEMI admitted on the weekend versus on a weekday had a 3% higher odds of in-hospital mortality. Those admitted on the weekend versus weekday for non–ST-elevation ACS had a 15% higher odds of in-hospital mortality. The excess mortality associated with weekend versus weekday admission decreased over time.[40]
- A retrospective analysis of the NHAMCS data from 2004 to 2011 that reviewed 15438 visits related to ACS symptoms suggested that blacks have a 30% longer waiting time than whites, the reasons for which are unclear.[41]
- The timing of hospital admission influences management of MI. A study of the NIS database from 2003 to 2011 indicated that admission on a weekend for NSTEMI was associated with a significantly reduced odds for coronary angiography (OR, 0.88 [95% CI, 0.89–0.90]; *P*<0.001) and early invasive strategy (OR, 0.48 [95% CI, 0.47–0.48]; *P*<0.001), with consequences of greater mortality.[42]

Complications

- In a pooled analysis of individuals after PCI in several RCTs, those with STEMI had a greater risk of death within the first 30 days after PCI than those with stable IHD, whereas those with NSTEMI had a greater risk of death during the entire 2 years of follow up.[43]
- From the NCDR registry, in 2014 the unadjusted rate of acute kidney injury was 2.6% (versus 2.3% in 2011), of blood transfusion was 1.4% (versus 1.9% in 2011), of postprocedural stroke was 0.2% (versus 0.2% in 2011), of emergency CABG surgery was 0.2% (versus 0.3% in 2011), and of vascular access site injury was 1.3% (versus 1.2% in 2011).[44]
- STEMI confers greater in-hospital risks than NSTEMI, including death (6.4% for STEMI, 3.4% for NSTEMI), cardiogenic shock (4.4% versus 1.6%, respectively), and bleeding (8.5% versus 5.5%, respectively).[45]
- Among females with AMI, those with spontaneous coronary artery dissection had higher odds of in-hospital mortality (6.8%) than females without spontaneous coronary artery dissection (3.8%; OR, 1.87 [95% CI, 1.65–2.11]; *P*<0.001).[46]
- In the NCDR ACTION Registry–GWTG, patients with STEMI or NSTEMI with nonobstructive coronary arteries (<50% stenosis) had lower in-hospital mortality than patients with obstructive CAD (1.1% versus 2.9%; *P*<0.001). Nonobstructive coronary arteries were more common in females than males (10.5% versus 3.4%; *P*<0.001), but no difference in in-hospital mortality was observed between females and males with nonobstructive coronary arteries (*P*=0.84).[47]
- On the basis of pooled data from the FHS, ARIC, CHS, MESA, CARDIA, and JHS studies of the NHLBI (1995–2012), within 1 year after a first MI (unpublished NHLBI tabulation):
  - At ≥45 years of age, 18% of males and 23% of females will die.
  - At 45 to 64 years of age, 3% of white males, 5% of white females, 9% of black males, and 10% of black females will die.
  - At 65 to 74 years of age, 14% of white males, 18% of white females, 22% of black males, and 21% of black females will die.
  - At ≥75 years of age, 27% of white males, 29% of white females, 19% of black males, and 31% of black females will die.
- In part because females have MIs at older ages than males, they are more likely to die of MI within a few weeks.
- Within 5 years after a first MI:
  - At ≥45 years of age, 36% of males and 47% of females will die.
  - At 45 to 64 years of age, 11% of white males, 17% of white females, 16% of black males, and 28% of black females will die.
  - At 65 to 74 years of age, 25% of white males, 30% of white females, 33% of black males, and 44% of black females will die.
  - At ≥75 years of age, 55% of white males, 60% of white females, 61% of black males, and 64% of black females will die.
- Of those who have a first MI, the percentage with a recurrent MI or fatal CHD within 5 years is as follows:
  - At ≥45 years of age, 17% of males and 21% of females.
  - At 45 to 64 years of age, 11% of white males, 15% of white females, 22% of black males, and 32% of black females.
  - At 65 to 74 years of age, 12% of white males, 17% of white females, 30% of black males, and 30% of black females.
  - At ≥75 years of age, 21% of white males, 20% of white females, 45% of black males, and 20% of black females.
- The percentage of people with a first MI who will have HF in 5 years is as follows:

- At ≥45 years of age, 16% of males and 22% of females.
- At 45 to 64 years of age, 6% of white males, 10% of white females, 13% of black males, and 25% of black females.
- At 65 to 74 years of age, 12% of white males, 16% of white females, 20% of black males, and 32% of black females.
- At ≥75 years of age, 25% of white males, 27% of white females, 23% of black males, and 19% of NH black females.

- The percentage of people with a first MI who will have an incident stroke within 5 years is as follows:
  - At ≥45 years of age, 4% of males and 7% of females.
  - At ≥45 years of age, 5% of white males, 6% of white females, 4% of black males, and 10% of black females.
- The median survival time (in years) after a first MI is as follows:
  - At ≥45 years of age, 8.2 for males and 5.5 for females.
  - At ≥45 years of age, 8.4 for white males, 5.6 for white females, 7.0 for black males, and 5.5 for black females.

Rehospitalizations

- The burden of rehospitalizations for AMI may be substantial: A retrospective cohort study of 78 085 Medicare beneficiaries ≥66 years of age without recent CHD history who were hospitalized for AMI in 2000 to 2010 reported that 20.6% had at least 1 rehospitalization during the 10 years after the index MI. Among patients with a CHD rehospitalization, 35.9% had ≥2 CHD rehospitalizations. Males and patients ≥85 years of age had greater rate ratios for first rehospitalization.[48]
- A study of 3 250 194 Medicare beneficiaries admitted for PCI found that readmission rates declined slightly from 16.1% in 2000 to 15.4% in 2012. The majority of readmissions were because of chronic IHD (26.6%), HF (12%), and chest pain/angina (7.9%). A minority (<8%) of total readmissions were for AMI, UA, or cardiac arrest/cardiogenic shock.[49]
- Rehospitalization can be influenced by clinical, psychosocial, and sociodemographic characteristics not accounted for in traditional Centers for Medicare & Medicaid Services claims-based models, including prior PCI, CKD, low health literacy, lower serum sodium levels, and lack of cigarette smoking.[50]
- In a study of 3 central Massachusetts hospitals, the 90-day rehospitalization rate declined from 31.5% in 2001 to 2003 to 27.3% in 2009 to 2011.[51] Crude 30-day rehospitalization rates decreased from 20.5% in 2001 to 2003 to 15.8% in 2009 to 2011.[52]

Cardiac Rehabilitation

- In the NCDR ACTION Registry–GWTG, cardiac rehabilitation referral after patients were admitted with a primary diagnosis of STEMI or NSTEMI increased from 72.9% to 80.7% between 2007 and 2012.[53]
- In the NCDR between 2009 and 2012, 59% of individuals were referred to cardiac rehabilitation after PCI, with significant site-specific variation.[54]
- In a community-based analysis of residents in Olmsted County, MN, discharged with first MI between 1987 and 2010, 52.5% participated in cardiac rehabilitation. The overall rate of participation did not change during the study period. Cardiac rehabilitation was associated with reductions in all-cause mortality and readmission.[55] A dose-response association between rehabilitation session attendance and lower risk of MI and death was similarly seen in elderly Medicare beneficiaries.[56]
- In the BRFSS from 2005 to 2015, <40% of patients self-reported participation in cardiac rehabilitation after AMI. Between 2011 and 2015, patients who declared participation in cardiac rehabilitation were less likely to be female (OR, 0.76 [95% CI, 0.65–0.90]; *P*=0.002) or black (OR, 0.70 [95% CI, 0.53–0.93]; *P*=0.014), were less well educated (high school versus college graduate: OR, 0.69 [95% CI, 0.59–0.81], *P*<0.001; less than high school versus college graduate: OR, 0.47 [95% CI 0.37–0.61], *P*<0.001), and were more likely to be retired or self-employed (OR, 1.39 [95% CI, 1.24–1.73]; *P*=0.003) than patients who did not participate in cardiac rehabilitation.[57]

Hospital Discharges and Ambulatory Care Visits (See Table 19-1 and Chart 19-8)

- From 2004 to 2014, the number of inpatient discharges from short-stay hospitals with CHD as the first-listed diagnosis decreased from 1 879 000 to 1 021 000 (unpublished NHLBI tabulation) (Table 19-1).
- From 1997 through 2014, the number of hospital discharges for CHD was higher for males than females (Chart 19-8).
- In 2015, there were 11 682 000 physician office visits for CHD (NAMCS, NHLBI tabulation).[58] In 2015, there were 463 000 ED visits with a primary diagnosis of CHD (NHAMCS, NHLBI tabulation).[59]

- Total office visits for angina declined from 3.6 million per year in 1995 to 1998 to 2.3 million per year in 2007 to 2010 based on data from the NAMCS and NHAMCS.[60]
- In the CathPCI registry, a composite of use of evidence-based medical therapies, including aspirin, P2Y12 inhibitors, and statins, was high (89.1% in 2011 and 93.3% in 2014). However, in the ACTION–GWTG registry, metrics that were shown to need improvement were defect-free care (median hospital performance rate of 78.4% in 2014), P2Y12 inhibitor use in eligible medically treated patients with AMI (56.7%), and the use of aldosterone antagonists in patients with LV systolic dysfunction and either DM or HF (12.8%).[44]

Operations and Procedures

- In 2014, an estimated 480 000 percutaneous transluminal coronary angioplasties, 371 000 inpatient bypass procedures, 1 016 000 inpatient diagnostic cardiac catheterizations, 86 000 carotid endarterectomies, and 351 000 pacemaker procedures were performed for inpatients in the United States (unpublished NHLBI tabulation).
- In an analysis of the BEST, PRECOMBAT, and SYNTAX trials comparing individuals with MI and who had left main or multivessel CAD, the outcomes of CABG versus PCI were examined. CABG was associated with a lower risk of recurrent MI and repeat revascularizations.[61] In patients with multivessel CAD, CABG was associated with lower all-cause and cardiovascular mortality; however, no differences in all-cause and cardiovascular mortality between CABG and PCI were observed among patients with multivessel plus left main CAD.[62]
- In a meta-analysis of 6 randomized trials that included 4686 patients with unprotected left main CAD, no significant differences in all-cause and cardiovascular mortality or a composite outcome of death, MI, or stroke were observed between patients treated with PCI versus CABG. However, PCI was associated with a lower risk of the composite outcome within the first 30 days of follow-up (HR, 0.64 [95% CI, 0.47–0.87]).[63]
- In 5-year follow-up of the SYNTAX trial, greater MI-related death in PCI patients was associated with the presence of DM, 3-vessel disease, or high SYNTAX scores.[64]
- At 5 years of follow-up in the SYNTAX and BEST randomized trials, patients with multivessel CAD involving the proximal left anterior descending coronary artery, PCI was associated with increased composite outcome of all-cause death, MI, or stroke (HR, 1.43 [95% CI, 1.05–1.95]; P=0.026), cardiovascular death (HR, 2.17 [95% CI, 1.24–3.81]; P=0.007), and major adverse cardiovascular and cerebrovascular events (HR, 1.68 [95% CI, 1.31–2.15]; P<0.001).[65]
- In the NIS, isolated CABG procedures decreased by 25.4% from 2007 to 2011 (326 to 243 cases per million adults), particularly at higher-volume centers. Low-volume centers were associated with greater risk of all-cause in-hospital mortality in multivariable analysis (OR, 1.39 [95% CI, 1.24–1.56]; P<0.001).[66]
- According to the NIS, the number of PCI procedures declined by 38% between 2006 and 2011. Among patients with stable IHD, a 61% decline in PCI occurred over this time period.[67]
- In Washington State, the overall number of PCIs decreased by 6.8% between 2010 and 2013, with a 43% decline in the number of PCIs performed for elective indications.[68]
- Among Medicare fee-for-service beneficiaries, the total number of revascularization procedures performed peaked in 2010 and declined by >4% per year through 2012. In-hospital and 90-day mortality rates declined after CABG surgery overall, as well as among patients presenting for elective CABG or CABG after NSTEMI.[69]
- Between 2011 and 2014, the use of femoral access declined (from 88.8% to 74.5%) and radial access increased (from 10.9% to 25.2%).[44]
- In a meta-analysis of 13 observational studies and 3 RCTs, a transradial approach for PCI was associated with a reduction in vascular complications (OR, 0.36 [95% CI, 0.30–43]) and stroke (OR, 0.79 [95% CI, 0.64–0.97]) compared with a transfemoral approach. A transradial approach was also associated with a reduced risk of death (OR, 0.56 [95% CI, 0.45–0.69]), although this was driven by the observational studies, because no association with death was observed in the randomized trials.[70]
- In 2014, from the CathPCI registry, median door-to-balloon time for primary PCI for STEMI was 59 minutes for patients receiving PCI in the presenting hospital and 107 minutes for patients transferred from another facility for therapy.[44]
- The importance of adherence to optimal medical therapy was highlighted in an 8-hospital study of NSTEMI patients, in which medication nonadherence was associated with a composite outcome of all-cause mortality, nonfatal MI, and reintervention (HR, 2.79 [95% CI, 2.19–3.54]; P<0.001). In propensity-matched analysis, CABG outcomes were favorable compared with PCI in patients

nonadherent to medical therapy (*P*=0.001), but outcomes were similar in medicine-adherent patients (*P*=0.574).[71]

Cost

- The estimated direct costs of HD in 2014 to 2015 (average annual) were $109.4 billion (MEPS, NHLBI tabulation).
- The estimated direct and indirect cost of HD in 2014 to 2015 (average annual) was $218.7 billion (MEPS, NHLBI tabulation).
- A study of the NIS from 2001 to 2011 showed that costs per hospitalization increased significantly for patients who underwent intervention, but not for those without intervention.[30]
- MI ($12.1 billion) and CHD ($9.0 billion) were 2 of the 10 most expensive conditions treated in US hospitals in 2013.[72]
- Between 2015 and 2030, medical costs of CHD are projected to increase by ≈100%.[73]
- In a multipayer administrative claims database of patients with incident inpatient PCI admissions between 2008 and 2011, post-PCI angina and chest pain were common and costly ($32 437 versus $17 913; *P*<0.001 at 1 year comparing those with and without angina or chest pain).[74]
- Among Medicare beneficiaries linked to the NCDR CathPCI Registry with inpatient or outpatient PCI between July 2009 and December 2012, costs were $3502 (95% CI, $3347–$3648; *P*<0.001) lower for patients with same-day discharge compared with those not discharged the same day. Although a minority of patients receive transradial intervention and same-day discharge (1.2%), a cost savings of $3689 (95% CI, $3486-$3902; *P*<0.001) was observed compared with patients with transfemoral intervention not discharged the same day.[75]

Acute Coronary Syndrome
ICD-9 410, 411; *ICD-10* I20.0, I21, I22.

- In 2014, there were 633 000 ACS principal diagnosis discharges. Of these, an estimated 389 000 were males, and 244 000 were females. This estimate was derived by adding the principal diagnoses for MI (609 000) to those for UA (24 000; HCUP, NHLBI).
- When secondary discharge diagnoses in 2014 were included, the corresponding number of inpatient hospital discharges was 1 339 000 unique hospitalizations for ACS; 785 000 were males, and 554 000 were females. Of the total, 957 000 were for MI alone, and 382 000 were for UA alone (HCUP, NHLBI).
- In a study using the NIS and the State Inpatient Databases for the year 2009, mean charge per ACS discharge was $63 578 (median $41 816). Mean charges, however, were greater for the first compared with the second admission ($71 336 versus $53 290, respectively).[76]
- On the basis of medical, pharmacy, and disability insurance claims data from 2007 to 2010, short-term productivity losses associated with ACS were estimated at $7943 per disability claim, with long-term productivity losses of $52 473 per disability claim. ACS also resulted in substantial wage losses, from $2263 to $20 609 per disability claim, for short- and long-term disability, respectively.[77]
- According to data from the NIS, between 2001 and 2011, the use of PCI for patients with ACS declined by 15%.[67]
- In a report from the TRACE-CORE study, persons with recurrent ACS were more likely to report anxiety, depression, higher perceived stress, and lower mental and physical quality of life; were more likely to have impaired cognition; and had lower levels of health literacy and health numeracy than persons with a first ACS.[78]
- In the NIS from 2012 to 2013, females with non–ST-elevation ACS treated with an early invasive strategy had lower in-hospital mortality than females treated conservatively (2.1% versus 3.8%). However, the survival advantage for invasive management was restricted to females with NSTEMI (OR, 0.52 [95% CI, 0.46–0.58]), and no differences in in-hospital survival for invasive versus conservative treatment were observed among females with UA.[79]
- In a meta-analysis of 8 randomized trials, the risk of long-term all-cause mortality at a mean of 10.3 years of follow-up was similar for non–ST-elevation ACS patients treated with a routine strategy (coronary angiography within 24 to 96 hours of presentation) versus a selective invasive strategy (medical stabilization with or without coronary angiography in those who demonstrated evidence of ischemia on noninvasive stress test or with ongoing symptoms) at 28.5% for both strategies.[80]

Stable AP
ICD-9 413; *ICD-10* I20.1 to I20.9.

Prevalence
(See Table 19-2 and Charts 19-9)

- According to data from NHANES 2013 to 2016, the prevalence of AP among adults

(≥20 years of age) is 3.6% (9.4 million adults) (Table 19-2).
- The prevalence of AP increased with age from <1% among males and females 20 to 39 years of age to >10% among males and females ≥80 years of age (Chart 19-9).
- On the basis of data from NHANES from 1998 to 2004 and the six 2-year surveys from 2001 to 2012, in 2009 to 2012, there were an average of 3.4 million people ≥40 years of age in the United States with angina each year, compared with 4 million in 1988 to 1994. Declines in angina symptoms have occurred for NH whites but not for NH blacks.[2]
- In Americans ≥40 years of age with health insurance, age-adjusted angina prevalence declined from 7.8% in 2001 to 2002 to 5.5% in 2011 to 2012 (*P* for trend <0.001), whereas in those without health insurance, there was an increase from 4.7% to 7.6%, albeit not statistically significant.[81]
- Among patients with a history of CAD (ACS, prior coronary revascularization procedure, or stable angina), 32.7% self-reported at least 1 episode of angina over the past month. Of those reporting angina, 23.3% reported daily or weekly symptoms of angina, and 56.3% of these patients with daily or weekly angina were taking at least 2 antianginal medications.[82]

Incidence
(See Table 19-2)
- The annual rates per 1000 population of new episodes of AP for NH black males are 28.3 for those 65 to 74 years of age, 36.3 for those 75 to 84 years of age, and 33.0 for those ≥85 years of age. For nonblack females in the same age groups, the rates are 14.1, 20.0, and 22.9, respectively. For black males, the rates are 22.4, 33.8, and 39.5, and for black females, the rates are 15.3, 23.6, and 35.9, respectively (CHS, NHLBI).
- The incidence of AP for adults ≥45 years of age is higher in males (370 000) than it is in females (195 000) (Table 19-2).

Social Determinants

- Social determinants of health are complex, integrated, and overlapping social structures and economic systems that are responsible for most health inequities.[83] These social structures and economic systems include the social environment, physical environment, health services, and structural and societal factors. Social determinants of health are shaped by the distribution of money, power, and resources throughout local communities, nations, and the world.[83]
- In an analysis of a population-based register sample of adults aged 40 to 60 years in Finland in 1995 (N=302 885) followed up until the end of 2007, MI incidence and mortality were examined in relation to living arrangements (living with a marital partner was contrasted to 3 alternatives: cohabiting with nonmarital partner, coresidence with people other than a partner, and living alone). Living arrangements were strong determinants for survival after MI independent of other sociodemographic factors. The results demonstrated greater fatality associated with living alone in males (HR, 1.50 [95% CI, 1.29–1.75]) and suggested that cohabitation in midlife might be associated with a greater fatality risk in females (HR, 2.00 [95% CI 1.26–3.17]).[84]
- In an analysis of nationally representative longitudinal register data to examine how childhood socioeconomic factors and later socioeconomic attainment were associated with MI incidence and fatality in Finnish adults who experienced their childhoods during the period from 1940 to the 1950s, when the country was still poor, MI hospitalizations and mortality in 1988 to 2010 were studied in those who were up to 14 years of age at the time of the census and resident in Finland in 1987 (N= 94 501). Crowding increased the risk of MI incidence by 16% (95% CI, 5%–29%) in males and 25% (95% CI, 3%–50%) in females. Most aspects of childhood circumstances did not strongly influence long-term fatality risk. Income and education remained associated with MI incidence when adjusted for unobserved shared family factors in siblings. Low adult socioeconomic resources remained a strong determinant of MI incidence and fatality.[85]
- Among US adults aged 45 to 74 years in 2009 to 2013, factors accounting for the US county variation in CVD mortality included demographic composition (36% of the variation in county CVD); economic/social conditions (32%); and health-care utilization, features of the environment, and health indicators (6%).[86]
- In a follow-up study of consecutive patients ≤65 years old discharged from 8 hospitals after first MI in central Israel, living in poor SES neighborhoods was associated with greater risk for recurrent MI (HR, 1.55 [95% CI, 1.13–2.14) and UA (HR, 1.48 [95% CI, 1.22–1.79).[87]

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Genetics and Family History

Family History as a Risk Factor

- Among adults ≥20 years of age, 12.4% (SE 0.5%) reported having a parent or sibling with a heart attack or angina before the age of 50 years. The racial/ethnic breakdown from NHANES 2013 to 2016 is as follows (unpublished NHLBI tabulation):
  - For NH whites, 12.2% (SE 1.0%) for males, 15.0% (SE 0.9%) for females.
  - For NH blacks, 7.1% (SE 0.9%) for males, 14.0% (SE 1.3%) for females.
  - For Hispanics, 7.7% (SE 0.6%) for males, 10.7% (SE 0.5%) for females.
  - For NH Asians, 6.3% (SE 0.9%) for males, 4.6% (SE 0.8%) for females.
- HD occurs as people age, so the prevalence of family history will vary depending on the age at which it is assessed. The breakdown of reported family history of heart attack by age of survey respondent in the US population as measured by NHANES 2013 to 2016 is as follows (unpublished NHLBI tabulation):
  - Age 20 to 39 years, 8.5% (SE 1.0%) for males, 9.9% (SE 0.6%) for females.
  - Age 40 to 59 years, 11.4% (SE 1.4%) for males, 16.9% (SE 1.2%) for females.
  - Age 60 to 79 years, 13.6% (SE 1.7%) for males, 16.6% (SE 1.6%) for females.
  - Age ≥80 years, 12.5% (SE 2.7%) for males, 13.6% (SE 2.6%) for females.
- Family history of premature angina, MI, angioplasty, or bypass surgery increases lifetime risk by ≈50% for both HD (from 8.9% to 13.7%) and CVD mortality (from 14.1% to 21%).[88]
- In the FHS, addition of a family history of premature CVD provided improved prognostic value over traditional risk factors.[89]
- Among people with a family history, CAC is a robust marker of ASCVD risk.[90]
- In premature ACS (age ≤55 years), a greater percentage of females (28%) than males (20%) have a family history of CAD (*P*=0.008). Compared with patients without a family history, patients with a family history of CAD have a higher prevalence of traditional CVD risk factors.[91]
- Among patients with STEMI in the NIS between 2003 and 2011, those with a family history of CAD were more likely to undergo coronary intervention and had lower in-hospital mortality than patients without a family history (OR, 0.45 [95% CI, 0.43–0.47]; *P*<0.001).[92]
- For the past 20 years, candidate gene studies have been conducted to identify the genetic variants underlying the heritability of CHD, but very few have identified consistent, replicated, and independent genetic variants, and all have had small effect sizes. The total number of CAD-associated regions is 73, with 15 novel CAD associations related to atherosclerosis and traditional risk factors but also highlighting the importance of key biological process in the arterial wall.[93]
- Over the past decade, the application of GWASs to large cohorts of CHD case and control subjects has identified many consistent genetic variants associated with CHD.
- The first GWAS identified the now most consistently replicated genetic marker for CHD and MI in European-derived populations, on chromosome 9p21.3.[94] The frequency of the primary SNP is very common (50% of the white population is estimated to harbor 1 risk allele, and 23% harbors 2 risk alleles).[95]
  - The 10-year HD risk for a 65-year-old male with 2 risk alleles at 9p21.3 and no other traditional risk factors is ≈13.2%, whereas a similar male with 0 alleles would have a 10-year risk of ≈9.2%. The 10-year HD risk for a 40-year-old female with 2 alleles and no other traditional risk factors is ≈2.4%, whereas a similar female with 0 alleles would have a 10-year risk of ≈1.7%.[95]
- The association of SNPs with incident CHD was investigated in a large multiethnic study of multiple cohorts in the United States (including NHANES, WHI, the Multiethnic Cohort Study, CHS, ARIC, CARDIA, HCHS/SOL, and SHS). SNPs, including in 9p21, *APOE*, and *LPL*, were associated with incident CHD in individuals of European ancestry but not African Americans. Effect sizes were greater for those ≤55 years of age and in females.[96]
- More recently, genetic studies of CHD have focused on the coding regions of the genome (exons) and have identified additional genes and SNPs for CHD, including loss-of-function mutations in the angiopoietin-like 4 (*ANGPTL4*) gene, which is an inhibitor of lipoprotein lipase. These mutations are associated with low plasma triglycerides and high HDL-C.[97]
- In a discovery analysis of common SNPs (minor allele frequency of >5%) on an exome array, 6 new loci associated with CAD were identified, including SNPs on the *KCNJ13-GIGYF2*, *C2*, *MRVI1-CTR9*, *LRP1*, *SCARB1*, and *CETP* genes.[98]
- In the DiscovEHR study, loss-of-function variants in the angiopoietin-like 3 gene (*ANGPTL3*) were less common in patients with CAD than in control subjects (0.33% versus 0.45%) and were

associated with 27% lower triglyceride levels, 9% lower LDL-C, and 4% lower HDL-C.[99]

- Protein-truncating variants at the *CETP* gene are associated with increased HDL-C and lower LDL-C and triglycerides. Compared with noncarriers, carriers of protein-truncating variants at *CETP* had a lower risk of CHD (OR, 0.70 [95% CI, 0.54–0.90]; $P=5.1\times10^{-3}$).[100]
- Using a network mendelian randomization analysis, a 1-unit longer genetically determined telomere length was associated with a lower risk of CHD in the CARDIoGRAM Consortium (OR, 0.79 [95% CI, 0.65–0.97; *P*=0.016) and the CARDIoGRAMplusC4D 1000 Genome Consortium (OR, 0.89 [95% CI, 0.79–1.00; *P*=0.052). Fasting insulin can partially mediate the association of telomere length with CHD, accounting for 18.4% of the effect of telomere length on CHD.[101]
- Whole-genome sequencing studies, which offer a deeper and more comprehensive coverage of the genome, have recently identified 13 variants with large effects on blood lipids, with 5 of these also being associated with CHD (*PCSK9*, *APOA1*, *ANGPTL4*, and *LDLR*).[102]

Clinical Utility of Genetic Markers

- Recent advances have demonstrated the utility of genetics in CAD risk prediction. In 48 421 individuals enrolled in the Malmo Diet and Cancer Study and 2 primary prevention trials (JUPITER, ASCOT) and 2 secondary prevention trials of lipid-lowering (CARE, PROVE-IT TIMI22), a genetic risk score consisting of 27 variants of genetic risk for CAD improved risk prediction above models that incorporated traditional risk factors and family history.[103]
- In the Malmo Diet and Cancer Study, application of an additional 23 SNPs known to be associated with CAD resulted in greater discrimination and reclassification (both *P*<0.0001).[104] In the FINRISK and FHS cohorts, with a sample size of 12 676 individuals, a genetic risk score incorporating 49 310 SNPs based on the CARDIoGRAMplusC4D Consortium data showed that the combination of genetic risk score with the FRS improved 10-year cardiac risk prediction, particularly in those ≥60 years of age.[105]
- In the MI-GENES trial of intermediate-risk patients, patient knowledge of their genetic risk score resulted in lower levels of LDL-C than a control group managed by conventional risk factors alone, which suggests the influence of genetic risk score in risk prevention.[106]
- Even in individuals with high genetic risk, prevention strategies have added benefit. For example, in 4 studies across 55 685 participants, genetic and lifestyle factors were independently associated with CHD, but even in participants at high genetic risk, a favorable lifestyle was associated with a nearly 50% lower RR of CHD than was an unfavorable lifestyle.[107]
- Collectively, these results may suggest future roles for incorporation of genetic risk score in clinical practice and emphasize the need for traditional primary prevention measures even in patients with a high genetic risk.

Global Burden (See Table 19-3 and Charts 19-10 and 19-11)

- Globally, it is estimated that 153.5 million people live with IHD, and it is more prevalent in males than in females (86.5 and 67.0 million people, respectively). The number of people with IHD increased by 74.7% from 1990 to 2016, although the rate per 100 000 decreased 8.6% over the same time period (Table 19-3).[108]
- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories.[108]
  - — IHD mortality rates exceed 275 per 100 000 in Eastern Europe, Central Asia, and parts of the North Africa/Middle East region (Chart 19-10).
  - — Eastern Europe and the North Africa/Middle East region have the highest prevalence rates of IHD in the world (Chart 19-11).

Future Research

Although the incidence of CHD has decreased over the past decade, it remains the leading cause of mortality in both the underdeveloped and developed world. However, more cases are expected to occur because of population aging, which makes prevention of CHD a continuing priority. Taking action to develop and fully implement strategies to significantly reduce CHD burden is likely to require new evidence and insights to understand what interventions and programs will be needed to achieve prevention targets, such as the 50×50×50 strategy, and to engage with diverse communities to develop and evaluate programs and across sectors.[109]

- More granularity of morbidity and mortality statistics is needed, ideally at the city level. Cities are becoming important geographic, political, and administrative units to implement CVD prevention initiatives, such as evaluating and modeling the implementations of sugar levies or CVD prevention programs at the city level.[110,111]

- There are substantial gaps in our knowledge of the determinants of social disparities in the occurrence and outcomes of CHD that might have profound implications for prevention and health care. Crucially, a better understanding of how these disparities originate and are maintained over the life course will be essential to design comprehensive strategies to improve CVD health in the coming years.
- It is becoming increasingly important to understand influences on CHD risk across the life course, because it might have important implications for prevention of CHD by intervening in early years.

Table 19-1. Coronary Heart Disease

Population Group	Prevalence, CHD, 2013–2016 Age ≥20 y	Prevalence, MI, 2013–2016 Age ≥20 y	New and Recurrent MI and Fatal CHD, Age ≥35 y	New and Recurrent MI, Age ≥35 y	Mortality,* CHD, 2016 All Ages	Mortality,* MI, 2016 All Ages	Hospital Discharges: CHD, 2014 All Ages
Both sexes	18 200 000 (6.7%)	8 400 000 (3.0%)	1 055 000	805 000	363 452	111 777	1 021 000
Males	9 400 000 (7.4%)	5 100 000 (4.0%)	610 000	470 000	210 156 (57.8%)†	64 713 (57.9%)†	649 000
Females	8 800 000 (6.2%)	3 300 000 (2.3%)	445 000	335 000	153 296 (42.2%)†	47 064 (42.1%)†	372 000
NH white males	7.7%	4.0%	520 000‡	…	167 036	51 594	…
NH white females	6.1%	2.2%	370 000‡	…	119 996	36 664	…
NH black males	7.2%	4.0%	90 000‡	…	21 900	6587	…
NH black females	6.5%	2.2%	75 000‡	…	18 256	5750	…
Hispanic males	6.0%	3.4%	…	…	13 696	4331	…
Hispanic females	6.0%	2.0%	…	…	9878	3086	…
NH Asian males	4.8%	2.4%	…	…	5262	1601§	…
NH Asian females	3.2%	1.0%	…	…	3827	1197§	…
NH American Indian or Alaska Native	…	…	…	…	2069	606	…

CHD includes people who responded "yes" to at least 1 of the questions in "Has a doctor or other health professional ever told you that you had coronary heart disease, angina or angina pectoris, heart attack, or myocardial infarction?" Those who answered "no" but were diagnosed with Rose angina are also included (the Rose questionnaire is only administered to survey participants >40 years of age). CHD indicates coronary heart disease; ellipses (…), data not available; MI, myocardial infarction; and NH, non-Hispanic.

*Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total CHD and MI mortality that is for males vs females.

‡Estimates include Hispanics and non-Hispanics. Estimates for whites include other nonblack races.

§Includes Chinese, Filipino, Hawaiian, Japanese, and Other Asian or Pacific Islander.

Sources: Prevalence: National Health and Nutrition Examination Survey 2013 to 2016 (National Center for Health Statistics [NCHS]) and National Heart, Lung, and Blood Institute (NHLBI). Percentages for racial/ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2016 US population estimates. These data are based on self-reports. Incidence: Atherosclerosis Risk in Communities Study (2005–2014), NHLBI. Mortality: Centers for Disease Control and Prevention/NCHS, 2016 Mortality Multiple Cause-of-Death–United States. Mortality for NH Asians includes Pacific Islanders. Hospital discharges: Healthcare Cost and Utilization Project, Hospital Discharges, 2014 (data include those inpatients discharged alive, dead, or status unknown).

Table 19-2. Angina Pectoris*

Population Group	Prevalence, 2013–2016, Age ≥20 y	Incidence of Stable AP, Age ≥45 y	Hospital Discharges, 2014, All Ages
Both sexes	9 400 000 (3.6%)	565 000	10 000
Males	4 300 000 (3.5%)	370 000	5000
Females	5 100 000 (3.7%)	195 000	5000
NH white males	3.8%	…	…
NH white females	3.8%	…	…
NH black males	3.6%	…	…
NH black females	3.8%	…	…
Hispanic males	2.6%	…	…
Hispanic females	3.6%	…	…
NH Asian or Pacific Islander males	2.0%	…	…
NH Asian or Pacific Islander females	1.6%	…	…

AP includes people who either answered "yes" to the question of ever having angina or AP or who were diagnosed with Rose angina (the Rose questionnaire is only administered to survey participants >40 years of age). AP indicates angina pectoris; ellipses (…), data not available; and NH, non-Hispanic.

*AP is chest pain or discomfort that results from insufficient blood flow to the heart muscle. Stable AP is predictable chest pain on exertion or under mental or emotional stress. The incidence estimate is for AP without myocardial infarction.

Sources: Prevalence: NHANES (National Health and Nutrition Examination Survey) 2013 to 2016 (National Center for Health Statistics [NCHS]) and National Heart, Lung, and Blood Institute (NHLBI). Percentages for racial/ethnic groups are age adjusted for US adults ≥20 years of age. Estimates from NHANES 2013 to 2016 (NCHS) were applied to 2016 population estimates (≥20 years of age). Incidence: AP uncomplicated by a myocardial infarction or with no myocardial infarction (Framingham Heart Study [the original cohort and the Offspring Cohort 1986–2009], NHLBI). Hospital discharges: Healthcare Cost and Utilization Project, Hospital Discharges, 2014; data include those inpatients discharged alive, dead, or status unknown.

Table 19-3. Global Burden of Ischemic Heart Disease and Trends[108]

	Both Sexes Combined		Males		Females	
	Death (95% CI)	Prevalence (95% CI)	Death (95% CI)	Prevalence (95% CI)	Death (95% CI)	Prevalence (95% CI)
Total number (millions)	9.5 (9.2 to 9.8)	153.5 (146.0 to 160.8)	5.1 (5.0 to 5.3)	86.5 (82.1 to 90.8)	4.4 (4.2 to 4.6)	67.0 (63.8 to 70.2)
Percent change total number 1990 to 2016	55.0 (50.7 to 59.4)	74.7 (72.2 to 77.5)	63.9 (58.6 to 69.2)	75.2 (72.3 to 78.4)	45.7 (39.1 to 53.1)	74.0 (71.7 to 76.7)
Percent change total number 2006 to 2016	19.0 (16.2 to 22.1)	24.5 (22.2 to 26.7)	21.8 (18.6 to 25.3)	23.8 (21.3 to 26.2)	16.0 (11.5 to 21.2)	25.3 (23.3 to 27.5)
Rate per 100 000	149.7 (145.8 to 154.1)	2,270.2 (2158.4 to 2380.2)	182.8 (177.4 to 188.3)	2,730.8 (2594.2 to 2864.8)	121.7 (116.3 to 127.2)	1,861.9 (1771.8 to 1950.5)
Percent change rate 2006 to 2016	−11.6 (−13.6 to −9.3)	−3.8 (−5.6 to −2.0)	−9.8 (−12.0 to −7.4)	−5.4 (−7.3 to −3.5)	−13.9 (−17.2 to −10.1)	−2.3 (−3.9 to −0.5)
Percent change rate 1990 to 2016	−26.2 (−28.2 to −24.2)	−8.6 (−9.9 to −7.0)	−23.6 (−25.8 to −21.4)	−11.3 (−12.8 to −9.6)	−29.8 (−32.9 to −26.3)	−6.7 (−7.9 to −5.2)

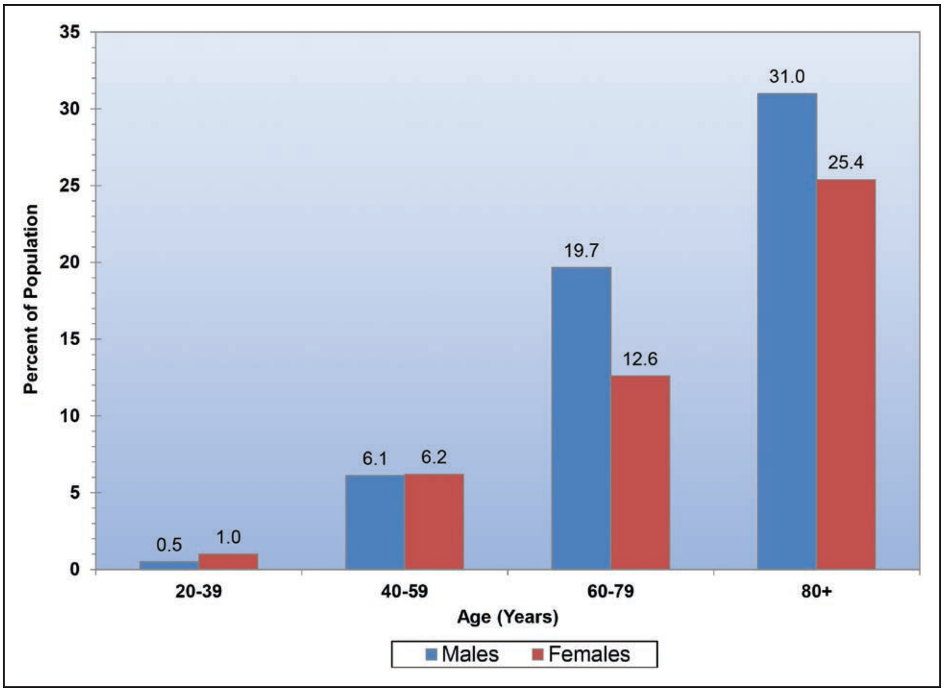

Chart 19-1. Prevalence of coronary heart disease by age and sex (NHANES, 2013–2016).
NHANES indicates National Health and Nutrition Examination Survey.
Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

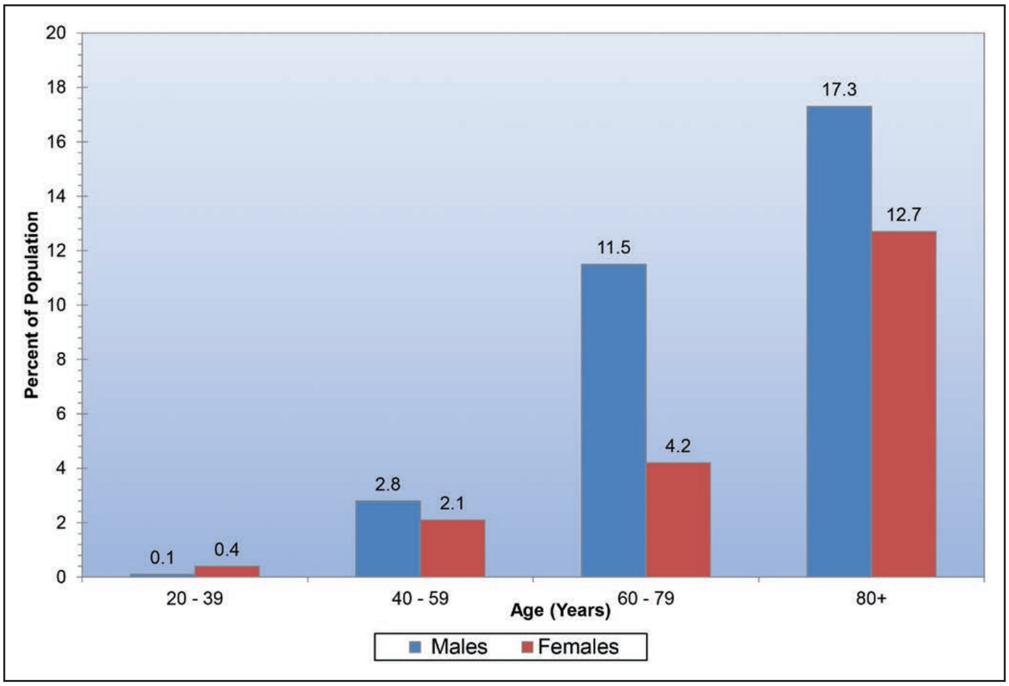

Chart 19-2. Prevalence of myocardial infarction by age and sex (NHANES, 2013–2016).
Myocardial infarction includes people who answered "yes" to the question of ever having had a heart attack or myocardial infarction.
NHANES indicates National Health and Nutrition Examination Survey.
Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

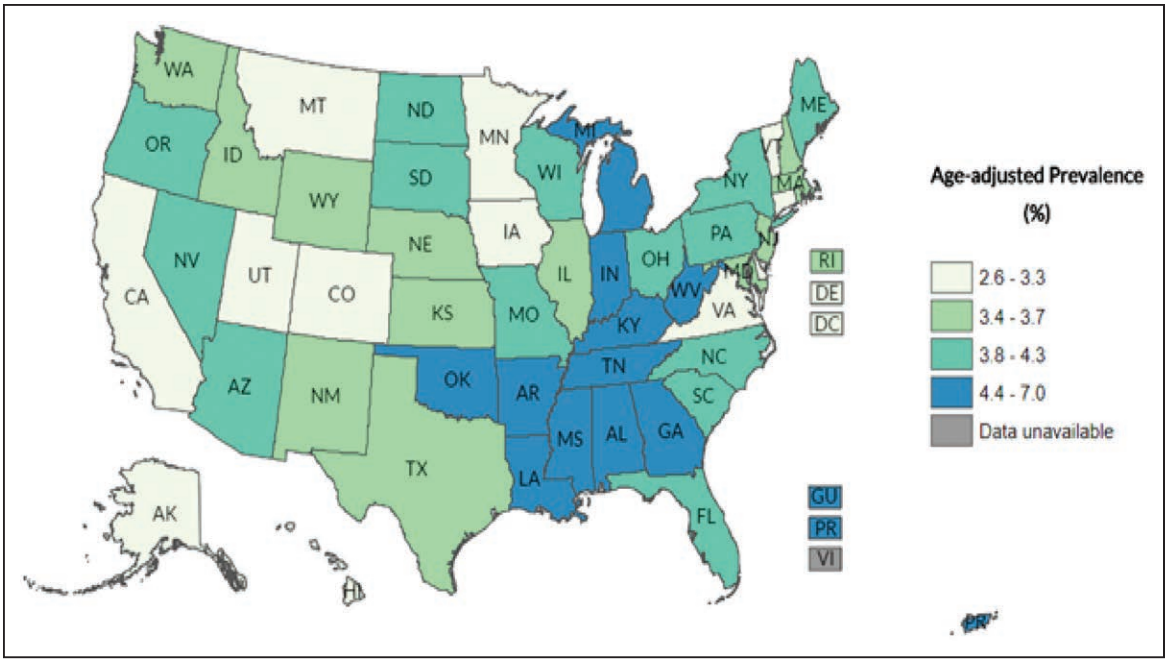

Chart 19-3. "**Ever told you had a heart attack (myocardial infarction)?" Age-adjusted prevalence by state, BRFSS Prevalence & Trends Data, 2016.**
BRFSS indicates Behavioral Risk Factor Surveillance System; GU, Guam; PR, Puerto Rico; and VI, Virgin Islands.
Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health.

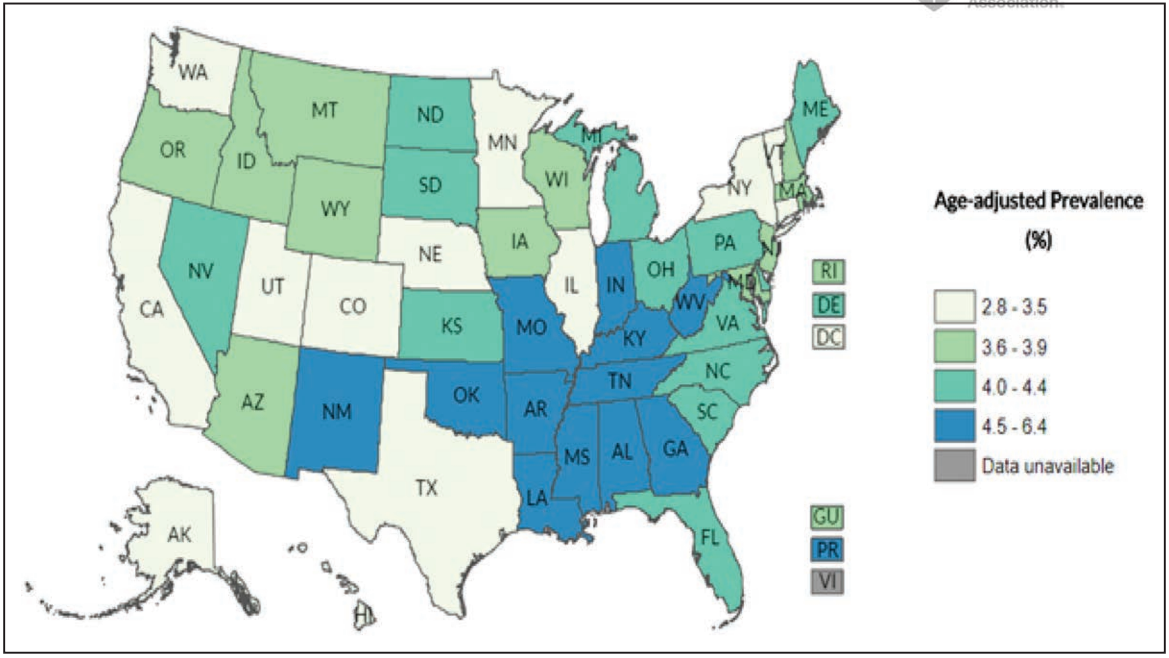

Chart 19-4. "Ever told you had angina or coronary heart disease?" Age-adjusted prevalence by state, BRFSS Prevalence & Trends Data, 2016.
BRFSS indicates Behavioral Risk Factor Surveillance System; GU, Guam; PR, Puerto Rico; and VI, Virgin Islands.
Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health.

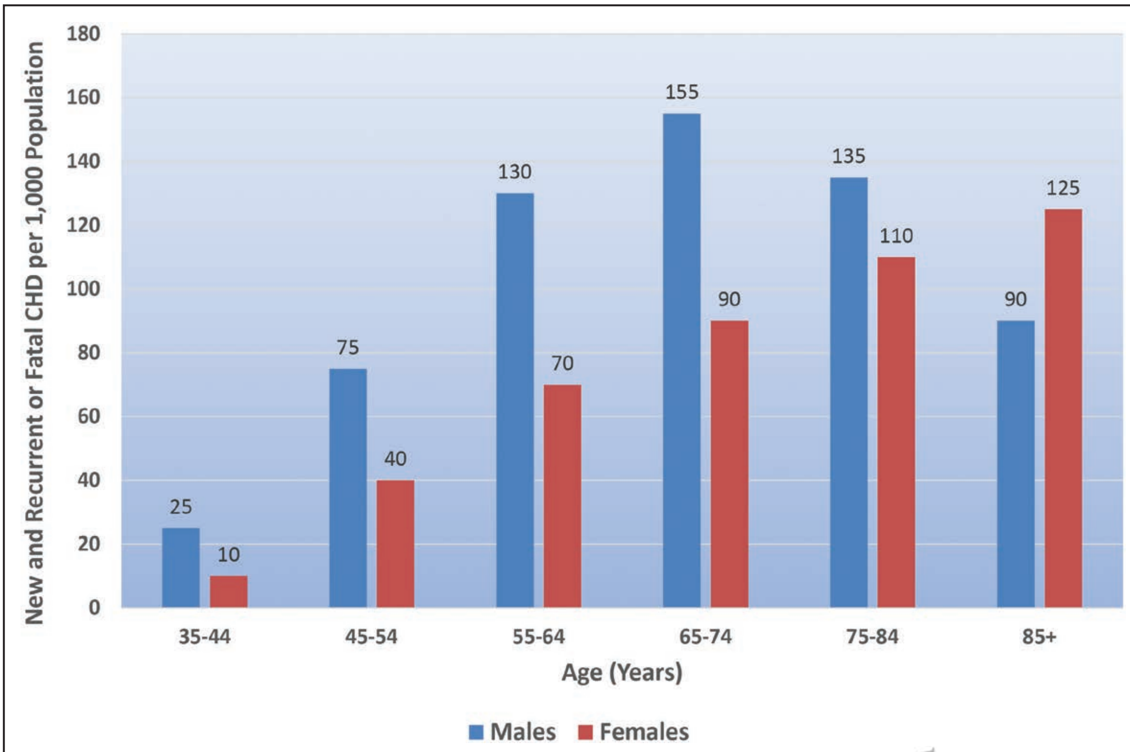

Chart 19-5. Annual number of adults per 1000 having diagnosed heart attack or fatal CHD by age and sex (ARIC surveillance, 2005–2014 and CHS).
These data include myocardial infarction and fatal CHD but not silent myocardial infarction.
ARIC indicates Atherosclerosis Risk in Communities; CHD, coronary heart disease; and CHS, Cardiovascular Health Study.
Source: National Heart, Lung, and Blood Institute.

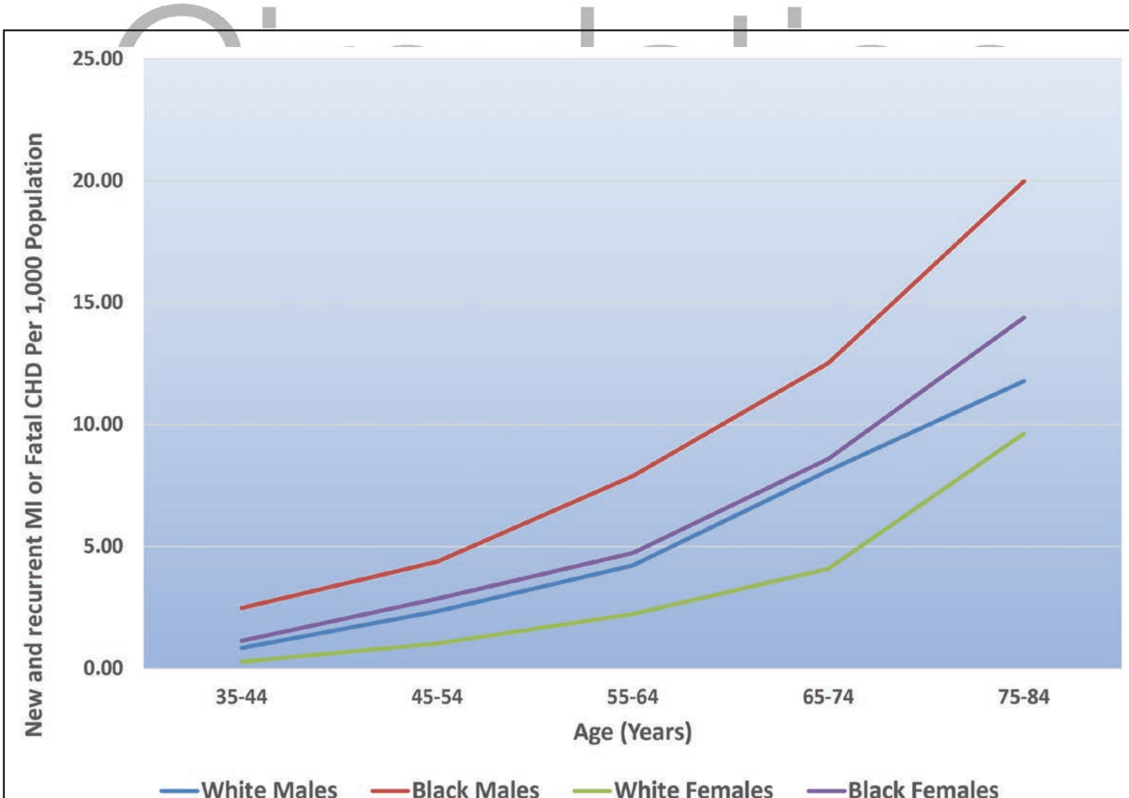

Chart 19-6. Incidence of heart attack or fatal CHD by age, sex, and race (ARIC Surveillance, 2005–2014).
ARIC indicates Atherosclerosis Risk in Communities; CHD, coronary heart disease; and MI, myocardial infarction.
Source: National Heart, Lung, and Blood Institute.

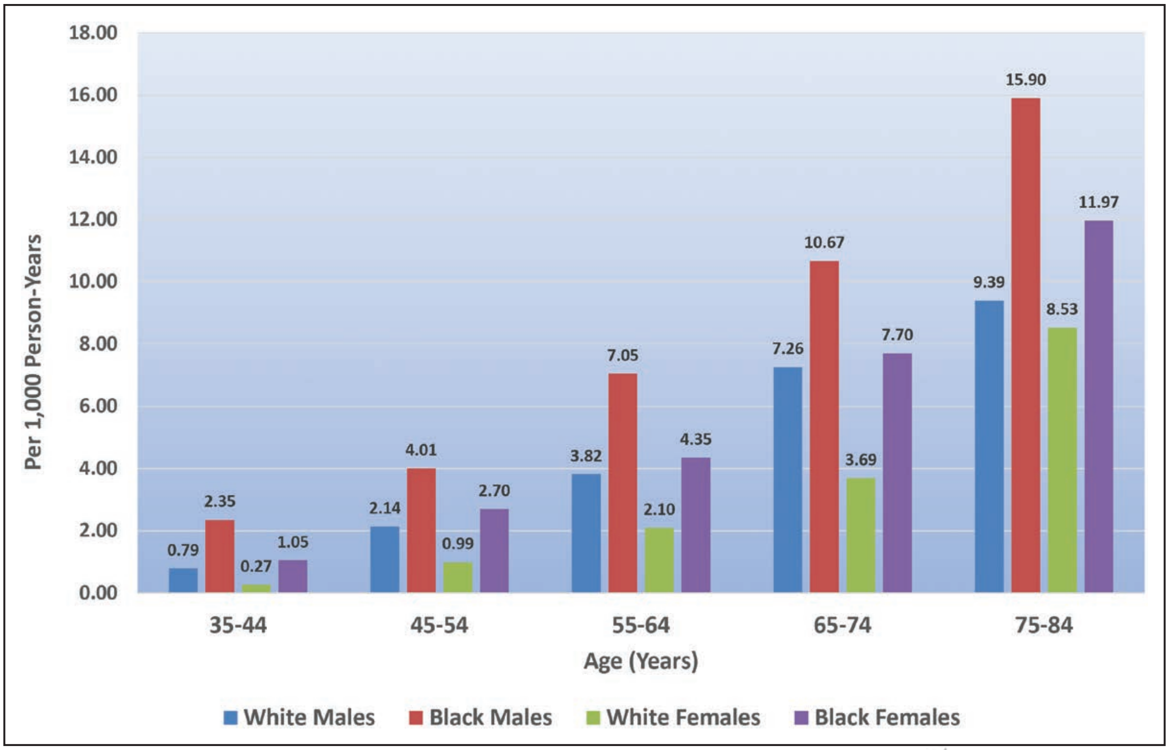

Chart 19-7. Incidence of myocardial infarction by age, sex, and race (ARIC Surveillance, 2005–2014).
ARIC indicates Atherosclerosis Risk in Communities.
Source: Unpublished data from ARIC, National Heart, Lung, and Blood Institute.

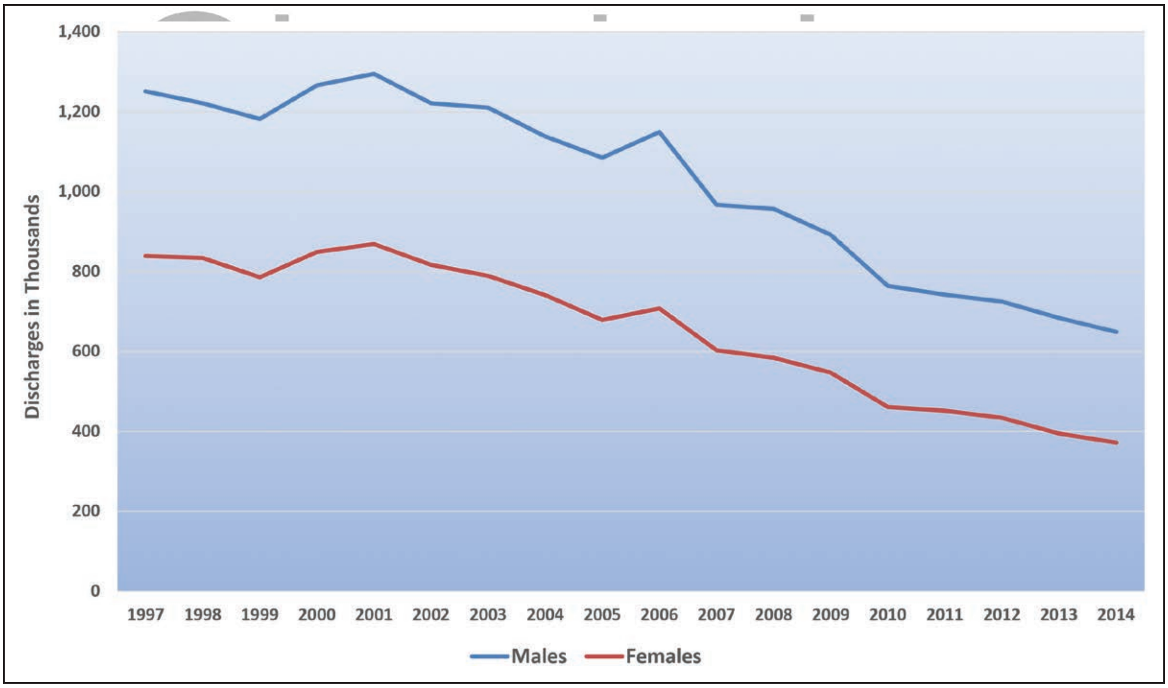

Chart 19-8. Hospital discharges for coronary heart disease by sex (United States, 1997–2014).
Hospital discharges include people discharged alive, dead, and "status unknown.
"Source: Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality and National Heart, Lung, and Blood Institute.

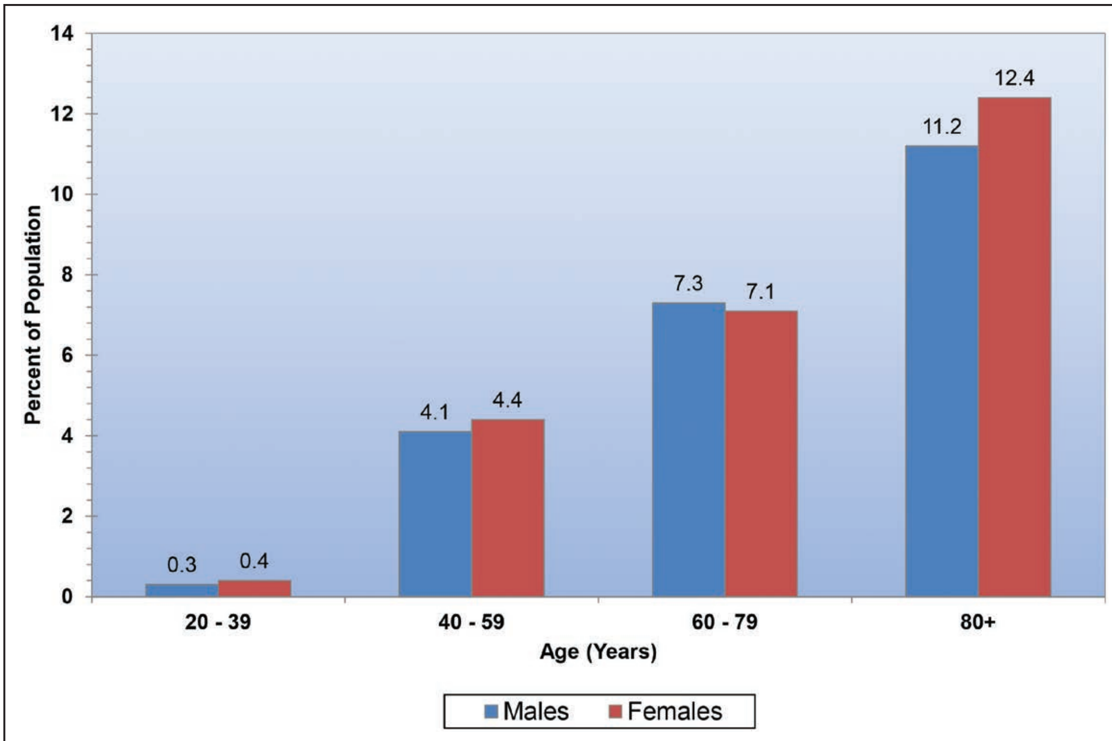

Chart 19-9. Prevalence of angina pectoris by age and sex (NHANES, 2013–2016).
Angina pectoris includes people who either answered "yes" to the question of ever having angina or angina pectoris or who were diagnosed with Rose angina. NHANES indicates National Health and Nutrition Examination Survey.
Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

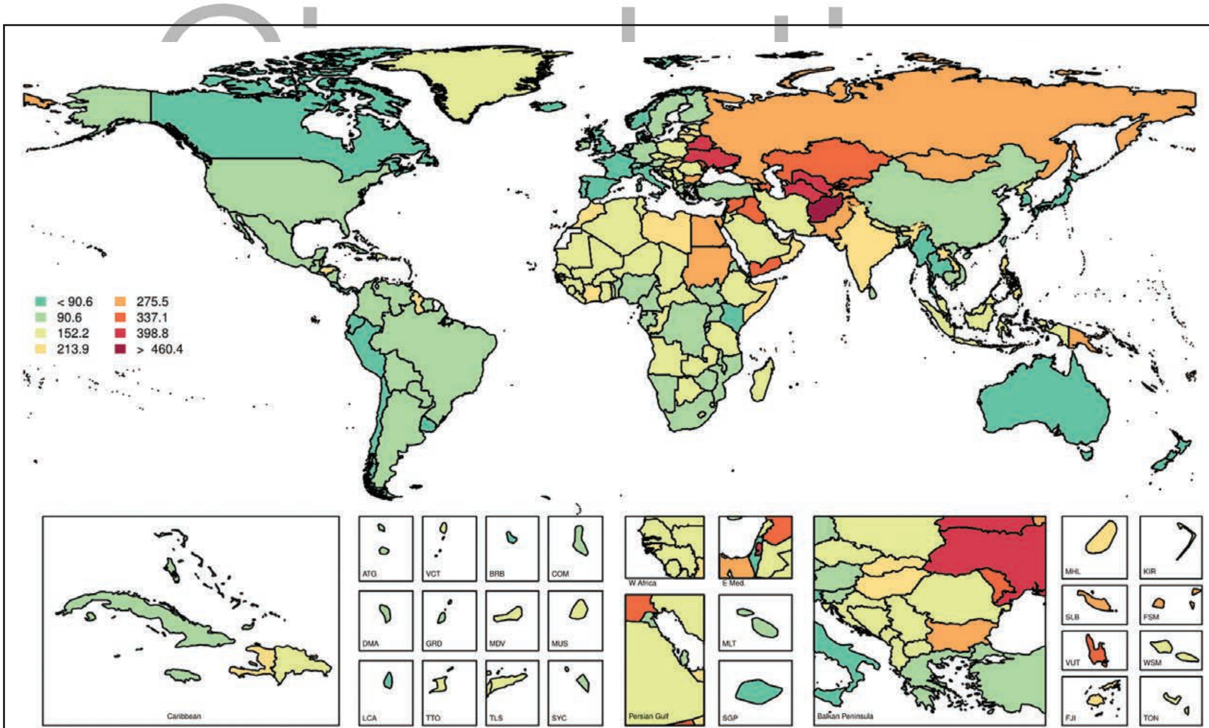

Chart 19-10. Age-standardized global mortality rates of ischemic heart disease per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[108] Printed with permission. Copyright © 2017, University of Washington.

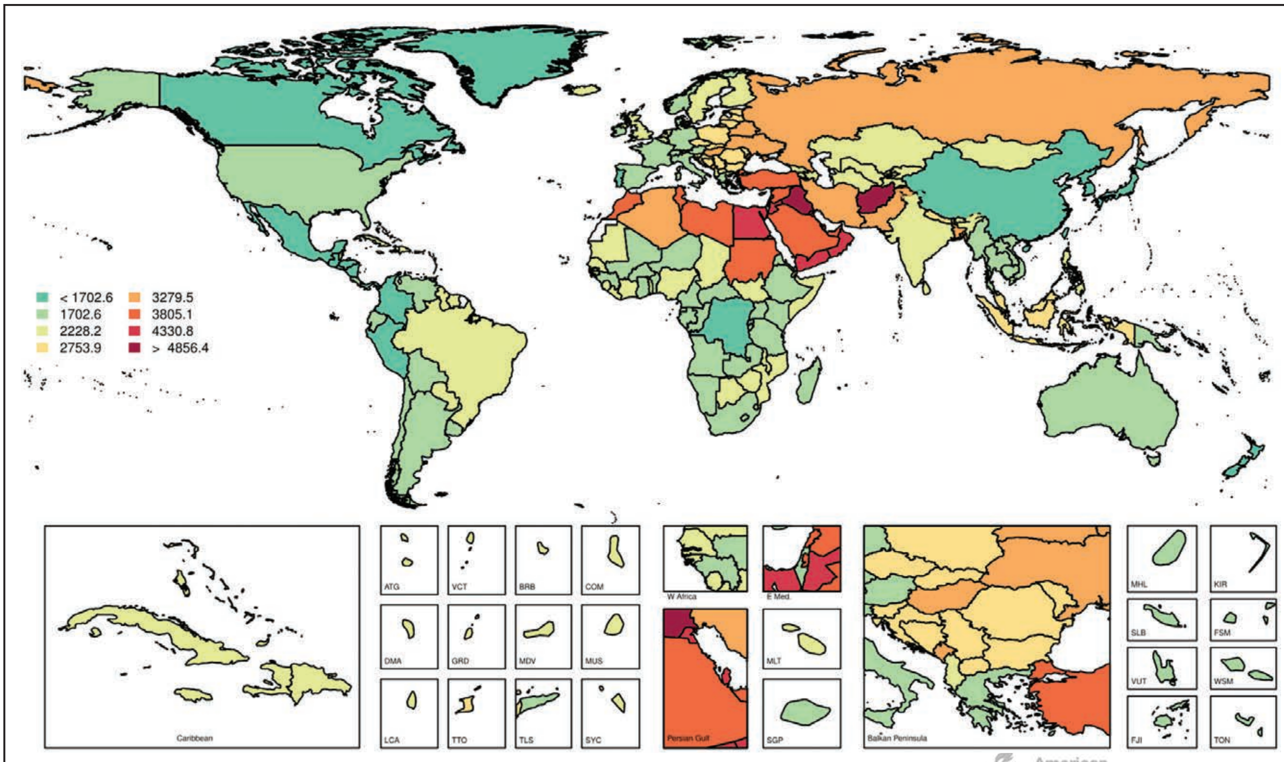

Chart 19-11. Age-standardized global prevalence rates of ischemic heart disease per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[108] Printed with permission. Copyright © 2017, University of Washington.

REFERENCES

1. Centers for Disease Control and Prevention website. National Center for Health Statistics. National Health Interview Survey, 2016: Summary Health Statistics, Table A-1. https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2016_SHS_Table_A-1.pdf. Accessed September 11, 2018.
2. Will JC, Yuan K, Ford E. National trends in the prevalence and medical history of angina: 1988 to 2012. *Circ Cardiovasc Qual Outcomes*. 2014;7:407–413. doi: 10.1161/CIRCOUTCOMES.113.000779
3. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health website. BRFSS Prevalence & Trends Data [online] (2016). https://www.cdc.gov/brfss/brfssprevalence/. Accessed June 15, 2018.
4. Atherosclerosis Risk in Communities Study, 2005–2014. http://www.cscc.unc.edu/aric/displaydata.php?pg_id=37. Accessed September 1, 2017.
5. Levitan EB, Olubowale OT, Gamboa CM, Rhodes JD, Brown TM, Muntner P, Deng L, Safford MM. Characteristics and prognosis of acute myocardial infarction by discharge diagnosis: the Reasons for Geographic and Racial Differences in Stroke study. *Ann Epidemiol*. 2015;25:499–504.e1. doi: 10.1016/j.annepidem.2015.02.004
6. Lewis MW, Khodneva Y, Redmond N, Durant RW, Judd SE, Wilkinson LL, Howard VJ, Safford MM. The impact of the combination of income and education on the incidence of coronary heart disease in the prospective Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort study. *BMC Public Health*. 2015;15:1312. doi: 10.1186/s12889-015-2630-4
7. Colantonio LD, Gamboa CM, Richman JS, Levitan EB, Soliman EZ, Howard G, Safford MM. Black-white differences in incident fatal, nonfatal, and total coronary heart disease. *Circulation*. 2017;136:152–166. doi: 10.1161/CIRCULATIONAHA.116.025848
8. Zhang ZM, Rautaharju PM, Prineas RJ, Rodriguez CJ, Loehr L, Rosamond WD, Kitzman D, Couper D, Soliman EZ. Race and sex differences in the incidence and prognostic significance of silent myocardial infarction in the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2016;133:2141–2148. doi: 10.1161/CIRCULATIONAHA.115.021177
9. Ford ES, Roger VL, Dunlay SM, Go AS, Rosamond WD. Challenges of ascertaining national trends in the incidence of coronary heart disease in the United States. *J Am Heart Assoc*. 2014;3:e001097. doi: 10.1161/JAHA.114.001097
10. Gerber Y, Weston SA, Jiang R, Roger VL. The changing epidemiology of myocardial infarction in Olmsted County, Minnesota, 1995-2012. *Am J Med*. 2015;128:144–151. doi: 10.1016/j.amjmed.2014.09.012
11. Carson AP, Tanner RM, Yun H, Glasser SP, Woolley JM, Thacker EL, Levitan EB, Farkouh ME, Rosenson RS, Brown TM, Howard G, Safford MM, Muntner P. Declines in coronary heart disease incidence and mortality among middle-aged adults with and without diabetes. *Ann Epidemiol*. 2014;24:581–587. doi: 10.1016/j.annepidem.2014.05.007
12. Sacks NC, Ash AS, Ghosh K, Rosen AK, Wong JB, Rosen AB. Trends in acute myocardial infarction hospitalizations: are we seeing the whole picture? *Am Heart J*. 2015;170:1211–1219. doi: 10.1016/j.ahj.2015.09.009
13. Sacks NC, Ash AS, Ghosh K, Rosen AK, Wong JB, Cutler DM, Rosen AB. Recent national trends in acute myocardial infarction hospitalizations in Medicare: shrinking declines and growing disparities. *Epidemiology*. 2015;26:e46–e47. doi: 10.1097/EDE.0000000000000298
14. Ford ES, Will JC, Mercado CI, Loustalot F. Trends in predicted risk for atherosclerotic cardiovascular disease using the pooled cohort risk equations among US adults from 1999 to 2012. *JAMA Intern Med*. 2015;175:299–302. doi: 10.1001/jamainternmed.2014.6403
15. Karmali KN, Goff DC Jr, Ning H, Lloyd-Jones DM. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. *J Am Coll Cardiol*. 2014;64:959–968. doi: 10.1016/j.jacc.2014.06.1186
16. Colantonio LD, Gamboa CM, Kleindorfer DO, Carson AP, Howard VJ, Muntner P, Cushman M, Howard G, Safford MM. Stroke symptoms and risk for incident coronary heart disease in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Int J Cardiol*. 2016;220:122–128. doi: 10.1016/j.ijcard.2016.06.030

17. Lackland DT, Elkind MS, D'Agostino R Sr, Dhamoon MS, Goff DC Jr, Higashida RT, McClure LA, Mitchell PH, Sacco RL, Sila CA, Smith SC Jr, Tanne D, Tirschwell DL, Touzé E, Wechsler LR; on behalf of the American Heart Association Stroke Council; Council on Epidemiology and Prevention; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research. Inclusion of stroke in cardiovascular risk prediction instruments: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43:1998–2027. doi: 10.1161/STR.0b013e31825bcdac
18. Shillinglaw B, Viera AJ, Edwards T, Simpson R, Sheridan SL. Use of global coronary heart disease risk assessment in practice: a cross-sectional survey of a sample of U.S. physicians. *BMC Health Serv Res*. 2012;12:20. doi: 10.1186/1472-6963-12-20
19. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PWF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published corrections appear in *Circulation*. 2014;129(suppl 2):S46–S48 and *Circulation*. 2015;132:e396]. *Circulation*. 2014;129(suppl 2):S1–S45. doi: 10.1161/01.cir.0000437738.63853.7a
20. Cook NR, Ridker PM. Calibration of the pooled cohort equations for atherosclerotic cardiovascular disease: an update. *Ann Intern Med*. 2016;165:786–794. doi: 10.7326/M16-1739
21. National Center for Health Statistics. Centers for Disease Control and Prevention website. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2016. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed May 21, 2018.
22. Bucholz EM, Butala NM, Ma S, Normand ST, Krumholz HM. Life expectancy after myocardial infarction, according to hospital performance. *N Engl J Med*. 2016;375:1332–1342. doi: 10.1056/NEJMoa1513223
23. Rodriguez F, Foody JM, Wang Y, López L. Young Hispanic women experience higher in-hospital mortality following an acute myocardial infarction. *J Am Heart Assoc*. 2015;4:e002089. doi: 10.1161/JAHA.115.002089
24. Bucholz EM, Ma S, Normand SL, Krumholz HM. Race, socioeconomic status, and life expectancy after acute myocardial infarction. *Circulation*. 2015;132:1338–1346. doi: 10.1161/CIRCULATIONAHA.115.017009
25. Conrad Z, Rehm CD, Wilde P, Mozaffarian D. Cardiometabolic mortality by Supplemental Nutrition Assistance Program participation and eligibility in the United States. *Am J Public Health*. 2017;107:466–474. doi: 10.2105/AJPH.2016.303608
26. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155–2165. doi: 10.1056/NEJMoa0908610
27. Roger VL, Weston SA, Gerber Y, Killian JM, Dunlay SM, Jaffe AS, Bell MR, Kors J, Yawn BP, Jacobsen SJ. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. *Circulation*. 2010;121:863–869. doi: 10.1161/CIRCULATIONAHA.109.897249
28. Krumholz HM, Normand SL, Wang Y. Trends in hospitalizations and outcomes for acute cardiovascular disease and stroke, 1999-2011. *Circulation*. 2014;130:966–975. doi: 10.1161/CIRCULATIONAHA.113.007787
29. Goldberg RJ, Makam RC, Yarzebski J, McManus DD, Lessard D, Gore JM. Decade-long trends (2001-2011) in the incidence and hospital death rates associated with the in-hospital development of cardiogenic shock after acute myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2016;9:117–125. doi: 10.1161/CIRCOUTCOMES.115.002359
30. Sugiyama T, Hasegawa K, Kobayashi Y, Takahashi O, Fukui T, Tsugawa Y. Differential time trends of outcomes and costs of care for acute myocardial infarction hospitalizations by ST elevation and type of intervention in the United States, 2001-2011. *J Am Heart Assoc*. 2015;4:e001445. doi: 10.1161/JAHA.114.001445
31. Wilmot KA, O'Flaherty M, Capewell S, Ford ES, Vaccarino V. Coronary heart disease mortality declines in the United States from 1979 through 2011: evidence for stagnation in young adults, especially women. *Circulation*. 2015;132:997–1002. doi: 10.1161/CIRCULATIONAHA.115.015293
32. Desta L, Jernberg T, Löfman I, Hofman-Bang C, Hagerman I, Spaak J, Persson H. Incidence, temporal trends, and prognostic impact of heart failure complicating acute myocardial infarction: the SWEDEHEART Registry (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies): a study of 199,851 patients admitted with index acute myocardial infarctions, 1996 to 2008. *JACC Heart Fail*. 2015;3:234–242. doi: 10.1016/j.jchf.2014.10.007
33. Gerber Y, Weston SA, Enriquez-Sarano M, Berardi C, Chamberlain AM, Manemann SM, Jiang R, Dunlay SM, Roger VL. Mortality associated with heart failure after myocardial infarction: a contemporary community perspective. *Circ Heart Fail*. 2016;9:e002460. doi: 10.1161/CIRCHEARTFAILURE.115.002460
34. Pearson-Stuttard J, Guzman-Castillo M, Penalvo JL, Rehm CD, Afshin A, Danaei G, Kypridemos C, Gaziano T, Mozaffarian D, Capewell S, O'Flaherty M. Modeling future cardiovascular disease mortality in the United States: national trends and racial and ethnic disparities. *Circulation*. 2016;133:967–978. doi: 10.1161/CIRCULATIONAHA.115.019904
35. Lloyd-Jones DM. Slowing progress in cardiovascular mortality rates: you reap what you sow. *JAMA Cardiol*. 2016;1:599–600. doi: 10.1001/jamacardio.2016.1348
36. Case A, Deaton A. Mortality and Morbidity in the 21st Century. https://www.brookings.edu/wp-content/uploads/2017/03/case-deaton-postconference-april-10-2017-with-appendix-figs.pdf. Accessed April 20, 2017.
37. Mosca L, Hammond G, Mochari-Greenberger H, Towfighi A, Albert MA; on behalf of the American Heart Association Cardiovascular Disease and Stroke in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Cardiovascular Nursing, Council on High Blood Pressure Research, and Council on Nutrition, Physical Activity and Metabolism. Fifteen-year trends in awareness of heart disease in women: results of a 2012 American Heart Association national survey. *Circulation*. 2013;127:1254–1263, e1–e29. doi: 10.1161/CIR.0b013e318287cf2f
38. Leifheit-Limson EC, D'Onofrio G, Daneshvar M, Geda M, Bueno H, Spertus JA, Krumholz HM, Lichtman JH. Sex differences in cardiac risk factors, perceived risk, and health care provider discussion of risk and risk modification among young patients with acute myocardial infarction: the VIRGO study. *J Am Coll Cardiol*. 2015;66:1949–1957. doi: 10.1016/j.jacc.2015.08.859
39. Makam RP, Erskine N, Yarzebski J, Lessard D, Lau J, Allison J, Gore JM, Gurwitz J, McManus DD, Goldberg RJ. Decade long trends (2001–2011) in duration of pre-hospital delay among elderly patients hospitalized for an acute myocardial infarction. *J Am Heart Assoc*. 2016;5:e002664. doi: 10.1161/JAHA.115.002664
40. Khoshchehreh M, Groves EM, Tehrani D, Amin A, Patel PM, Malik S. Changes in mortality on weekend versus weekday admissions for acute coronary syndrome in the United States over the past decade. *Int J Cardiol*. 2016;210:164–172. doi: 10.1016/j.ijcard.2016.02.087
41. Alrwisan A, Eworuke E. Are discrepancies in waiting time for chest pain at emergency departments between African Americans and whites improving over time? *J Emerg Med*. 2016;50:349–355. doi: 10.1016/j.jemermed.2015.07.033
42. Agrawal S, Garg L, Sharma A, Mohananey D, Bhatia N, Singh A, Shirani J, Dixon S. Comparison of inhospital mortality and frequency of coronary angiography on weekend versus weekday admissions in patients with non-ST-segment elevation acute myocardial infarction. *Am J Cardiol*. 2016;118:632–634. doi: 10.1016/j.amjcard.2016.06.022
43. Pilgrim T, Vranckx P, Valgimigli M, Stefanini GG, Piccolo R, Rat J, Rothenbühler M, Stortecky S, Räber L, Blöchlinger S, Hunziker L, Silber S, Jüni P, Serruys PW, Windecker S. Risk and timing of recurrent ischemic events among patients with stable ischemic heart disease, non-ST-segment elevation acute coronary syndrome, and ST-segment elevation myocardial infarction. *Am Heart J*. 2016;175:56–65. doi: 10.1016/j.ahj.2016.01.021
44. Masoudi FA, Ponirakis A, de Lemos JA, Jollis JG, Kremers M, Messenger JC, Moore JW, Moussa I, Oetgen WJ, Varosy PD, Vincent RN, Wei J, Curtis JP, Roe MT, Spertus JA. Trends in U.S. cardiovascular care: 2016 report from 4 ACC National Cardiovascular Data Registries. *J Am Coll Cardiol*. 2017;69:1427–1450. doi: 10.1016/j.jacc.2016.12.005
45. Masoudi FA, Ponirakis A, de Lemos JA, Jollis JG, Kremers M, Messenger JC, Moore JW, Moussa I, Oetgen WJ, Varosy PD, Vincent RN, Wei J, Curtis JP, Roe MT, Spertus JA. Executive summary: trends in U.S. cardiovascular care: 2016 report from 4 ACC national cardiovascular data registries. *J Am Coll Cardiol*. 2017;69:1424–1426. doi: 10.1016/j.jacc.2016.12.004
46. Mahmoud AN, Taduru SS, Mentias A, Mahtta D, Barakat AF, Saad M, Elgendy AY, Mojadidi MK, Omer M, Abuzaid A, Agarwal N, Elgendy IY, Anderson RD, Saw J. Trends of incidence, clinical presentation, and in-hospital mortality among women with acute myocardial infarction with or without spontaneous coronary artery dissection: a population-based analysis. *JACC Cardiovasc Interv*. 2018;11:80–90. doi: 10.1016/j.jcin.2017.08.016
47. Smilowitz NR, Mahajan AM, Roe MT, Hellkamp AS, Chiswell K, Gulati M, Reynolds HR. Mortality of myocardial infarction by sex, age, and obstructive coronary artery disease status in the ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines). *Circ Cardiovasc Qual Outcomes*. 2017;10:e003443. doi: 10.1161/CIRCOUTCOMES.116.003443

48. Levitan EB, Muntner P, Chen L, Deng L, Kilgore ML, Becker D, Glasser SP, Safford MM, Howard G, Kilpatrick R, Rosenson RS. Burden of coronary heart disease rehospitalizations following acute myocardial infarction in older adults. *Cardiovasc Drugs Ther*. 2016;30:323–331. doi: 10.1007/s10557-016-6653-6
49. McNeely C, Markwell S, Vassileva CM. Readmission after inpatient percutaneous coronary intervention in the Medicare population from 2000 to 2012. *Am Heart J*. 2016;179:195–203. doi: 10.1016/j.ahj.2016.07.002
50. McManus DD, Saczynski JS, Lessard D, Waring ME, Allison J, Parish DC, Goldberg RJ, Ash A, Kiefe CI; TRACE-CORE Investigators. Reliability of predicting early hospital readmission after discharge for an acute coronary syndrome using claims-based data. *Am J Cardiol*. 2016;117:501–507. doi: 10.1016/j.amjcard.2015.11.034
51. Chen HY, Tisminetzky M, Lapane KL, Yarzebski J, Person SD, Kiefe CI, Gore JM, Goldberg RJ. Decade-long trends in 30-day rehospitalization rates after acute myocardial infarction. *J Am Heart Assoc*. 2015;4:e002291. doi: 10.1161/JAHA.115.002291
52. Chen HY, Tisminetzky M, Yarzebski J, Gore JM, Goldberg RJ. Decade-long trends in the frequency of 90-day rehospitalizations after hospital discharge for acute myocardial infarction. *Am J Cardiol*. 2016;117:743–748. doi: 10.1016/j.amjcard.2015.12.006
53. Beatty AL, Li S, Thomas L, Amsterdam EA, Alexander KP, Whooley MA. Trends in referral to cardiac rehabilitation after myocardial infarction: data from the National Cardiovascular Data Registry 2007 to 2012. *J Am Coll Cardiol*. 2014;63:2582–2583. doi: 10.1016/j.jacc.2014.03.030
54. Aragam KG, Dai D, Neely ML, Bhatt DL, Roe MT, Rumsfeld JS, Gurm HS. Gaps in referral to cardiac rehabilitation of patients undergoing percutaneous coronary intervention in the United States. *J Am Coll Cardiol*. 2015;65:2079–2088. doi: 10.1016/j.jacc.2015.02.063
55. Dunlay SM, Pack QR, Thomas RJ, Killian JM, Roger VL. Participation in cardiac rehabilitation, readmissions, and death after acute myocardial infarction. *Am J Med*. 2014;127:538–546. doi: 10.1016/j.amjmed.2014.02.008
56. Hammill BG, Curtis LH, Schulman KA, Whellan DJ. Relationship between cardiac rehabilitation and long-term risks of death and myocardial infarction among elderly Medicare beneficiaries. *Circulation*. 2010;121:63–70. doi: 10.1161/CIRCULATIONAHA.109.876383
57. Peters AE, Keeley EC. Trends and predictors of participation in cardiac rehabilitation following acute myocardial infarction: data from the Behavioral Risk Factor Surveillance System. *J Am Heart Assoc*. 2017;7:e007664. doi: 10.1161/JAHA.117.007664
58. Centers for Disease Control and Prevention website. National Ambulatory Medical Care Survey: 2015 State and National Summary Tables. https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2015_namcs_web_tables.pdf. Accessed June 14, 2018.
59. Centers for Disease Control and Prevention website. National Hospital Ambulatory Medical Care Survey: 2015 Emergency Department Summary Tables. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2015_ed_web_tables.pdf. Accessed June 14, 2018.
60. Will JC, Loustalot F, Hong Y. National trends in visits to physician offices and outpatient clinics for angina 1995 to 2010. *Circ Cardiovasc Qual Outcomes*. 2014;7:110–117. doi: 10.1161/CIRCOUTCOMES.113.000450
61. Chang M, Lee CW, Ahn JM, Cavalcante R, Sotomi Y, Onuma Y, Zeng Y, Park DW, Kang SJ, Lee SW, Kim YH, Park SW, Serruys PW, Park SJ. Coronary artery bypass grafting versus drug-eluting stents implantation for previous myocardial infarction. *Am J Cardiol*. 2016;118:17–22. doi: 10.1016/j.amjcard.2016.04.009
62. Chang M, Lee CW, Ahn JM, Cavalcante R, Sotomi Y, Onuma Y, Park DW, Kang SJ, Lee SW, Kim YH, Park SW, Serruys PW, Park SJ. Impact of multivessel coronary artery disease with versus without left main coronary artery disease on long-term mortality after coronary bypass grafting versus drug-eluting stent implantation. *Am J Cardiol*. 2017;119:225–230. doi: 10.1016/j.amjcard.2016.09.048
63. Palmerini T, Serruys P, Kappetein AP, Genereux P, Riva DD, Reggiani LB, Christiansen EH, Holm NR, Thuesen L, Makikallio T, Morice MC, Ahn JM, Park SJ, Thiele H, Boudriot E, Sabatino M, Romanello M, Biondi-Zoccai G, Cavalcante R, Sabik JF, Stone GW. Clinical outcomes with percutaneous coronary revascularization vs coronary artery bypass grafting surgery in patients with unprotected left main coronary artery disease: a meta-analysis of 6 randomized trials and 4,686 patients. *Am Heart J*. 2017;190:54–63. doi: 10.1016/j.ahj.2017.05.005
64. Milojevic M, Head SJ, Parasca CA, Serruys PW, Mohr FW, Morice MC, Mack MJ, Ståhle E, Feldman TE, Dawkins KD, Colombo A, Kappetein AP, Holmes DR Jr. Causes of death following PCI versus CABG in complex CAD: 5-year follow-up of SYNTAX. *J Am Coll Cardiol*. 2016;67:42–55. doi: 10.1016/j.jacc.2015.10.043
65. Cavalcante R, Sotomi Y, Zeng Y, Lee CW, Ahn JM, Collet C, Tenekecioglu E, Suwannasom P, Onuma Y, Park SJ, Serruys PW. Coronary bypass surgery versus stenting in multivessel disease involving the proximal left anterior descending coronary artery. *Heart*. 2017;103:428–433. doi: 10.1136/heartjnl-2016-309720
66. Kim LK, Looser P, Swaminathan RV, Minutello RM, Wong SC, Girardi L, Feldman DN. Outcomes in patients undergoing coronary artery bypass graft surgery in the United States based on hospital volume, 2007 to 2011. *J Thorac Cardiovasc Surg*. 2016;151:1686–1692. doi: 10.1016/j.jtcvs.2016.01.050
67. Bangalore S, Gupta N, Généreux P, Guo Y, Pancholy S, Feit F. Trend in percutaneous coronary intervention volume following the COURAGE and BARI-2D trials: insight from over 8.1 million percutaneous coronary interventions. *Int J Cardiol*. 2015;183:6–10. doi: 10.1016/j.ijcard.2015.01.053
68. Bradley SM, Bohn CM, Malenka DJ, Graham MM, Bryson CL, McCabe JM, Curtis JP, Lambert-Kerzner A, Maynard C. Temporal trends in percutaneous coronary intervention appropriateness: insights from the Clinical Outcomes Assessment Program. *Circulation*. 2015;132:20–26. doi: 10.1161/CIRCULATIONAHA.114.015156
69. Culler SD, Kugelmass AD, Brown PP, Reynolds MR, Simon AW. Trends in coronary revascularization procedures among Medicare beneficiaries between 2008 and 2012. *Circulation*. 2015;131:362–370. doi: 10.1161/CIRCULATIONAHA.114.012485
70. Alnasser SM, Bagai A, Jolly SS, Cantor WJ, Dehghani P, Rao SV, Cheema AN. Transradial approach for coronary angiography and intervention in the elderly: a meta-analysis of 777,841 patients. *Int J Cardiol*. 2017;228:45–51. doi: 10.1016/j.ijcard.2016.11.207
71. Kurlansky P, Herbert M, Prince S, Mack M. Coronary artery bypass graft versus percutaneous coronary intervention: meds matter: impact of adherence to medical therapy on comparative outcomes. *Circulation*. 2016;134:1238–1246. doi: 10.1161/CIRCULATIONAHA.115.021183
72. Torio CM, Moore BJ. National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2013. HCUP Statistical Brief #204. Rockville, MD: Agency for Healthcare Research and Quality; May 2016. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb204-Most-Expensive-Hospital-Conditions.pdf. Accessed April 1, 2017.
73. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, Lloyd-Jones DM, Nelson SA, Nichol G, Orenstein D, Wilson PW, Woo YJ; on behalf of the American Heart Association Advocacy Coordinating Committee; Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Cardiopulmonary; Critical Care; Perioperative and Resuscitation; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease; Council on Cardiovascular Surgery and Anesthesia, and Interdisciplinary Council on Quality of Care and Outcomes Research. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123:933–944. doi: 10.1161/CIR.0b013e31820a55f5
74. Ben-Yehuda O, Kazi DS, Bonafede M, Wade SW, Machacz SF, Stephens LA, Hlatky MA, Hernandez JB. Angina and associated healthcare costs following percutaneous coronary intervention: a real-world analysis from a multi-payer database. *Catheter Cardiovasc Interv*. 2016;88:1017–1024. doi: 10.1002/ccd.26365
75. Amin AP, Patterson M, House JA, Giersiefen H, Spertus JA, Baklanov DV, Chhatriwalla AK, Safley DM, Cohen DJ, Rao SV, Marso SP. Costs associated with access site and same-day discharge among Medicare beneficiaries undergoing percutaneous coronary intervention: an evaluation of the current percutaneous coronary intervention care pathways in the United States. *JACC Cardiovasc Interv*. 2017;10:342–351. doi: 10.1016/j.jcin.2016.11.049
76. LaMori JC, Shoheiber O, Dudash K, Crivera C, Mody SH. The economic impact of acute coronary syndrome on length of stay: an analysis using the Healthcare Cost and Utilization Project (HCUP) databases. *J Med Econ*. 2014;17:191–197. doi: 10.3111/13696998.2014.885907
77. Page RL 2nd, Ghushchyan V, Gifford B, Read RA, Raut M, Crivera C, Naim AB, Damaraju CV, Nair KV. The economic burden of acute coronary syndromes for employees and their dependents: medical and productivity costs. *J Occup Environ Med*. 2013;55:761–767. doi: 10.1097/JOM.0b013e318297323a
78. Goldberg RJ, Saczynski JS, McManus DD, Waring ME, McManus R, Allison J, Parish DC, Lessard D, Person S, Gore JM, Kiefe CI; TRACE-CORE Investigators. Characteristics of contemporary patients discharged from the hospital after an acute coronary syndrome. *Am J Med*. 2015;128:1087–1093. doi: 10.1016/j.amjmed.2015.05.002

79. Elgendy IY, Mahmoud AN, Mansoor H, Bavry AA. Early invasive versus initial conservative strategies for women with non-ST-elevation acute coronary syndromes: a nationwide analysis. *Am J Med*. 2017;130:1059–1067. doi: 10.1016/j.amjmed.2017.01.049
80. Elgendy IY, Mahmoud AN, Wen X, Bavry AA. Meta-analysis of randomized trials of long-term all-cause mortality in patients with non-ST-elevation acute coronary syndrome managed with routine invasive versus selective invasive strategies. *Am J Cardiol*. 2017;119:560–564. doi: 10.1016/j.amjcard.2016.11.005
81. Yoon SS, Dillon CF, Illoh K, Carroll M. Trends in the prevalence of coronary heart disease in the U.S.: National Health and Nutrition Examination Survey, 2001–2012. *Am J Prev Med*. 2016;51:437–445. doi: 10.1016/j.amepre.2016.02.023
82. Kureshi F, Shafiq A, Arnold SV, Gosch K, Breeding T, Kumar AS, Jones PG, Spertus JA. The prevalence and management of angina among patients with chronic coronary artery disease across US outpatient cardiology practices: insights from the Angina Prevalence and Provider Evaluation of Angina Relief (APPEAR) study. *Clin Cardiol*. 2017;40:6–10. doi: 10.1002/clc.22628
83. Sheiham A. Closing the gap in a generation: health equity through action on the social determinants of health: a report of the WHO Commission on Social Determinants of Health (CSDH) 2008. *Community Dent Health*. 2009;26:2–3.
84. Kilpi F, Konttinen H, Silventoinen K, Martikainen P. Living arrangements as determinants of myocardial infarction incidence and survival: a prospective register study of over 300,000 Finnish men and women. *Soc Sci Med*. 2015;133:93–100. doi: 10.1016/j.socscimed.2015.03.054
85. Kilpi F, Silventoinen K, Konttinen H, Martikainen P. Early-life and adult socioeconomic determinants of myocardial infarction incidence and fatality. *Soc Sci Med*. 2017;177:100–109. doi: 10.1016/j.socscimed.2017.01.055
86. Patel SA, Ali MK, Narayan KM, Mehta NK. County-level variation in cardiovascular disease mortality in the United States in 2009-2013: comparative assessment of contributing factors. *Am J Epidemiol*. 2016;184:933–942. doi: 10.1093/aje/kww081
87. Koren A, Steinberg DM, Drory Y, Gerber Y; Israel Study Group on First Acute Myocardial Infarction. Socioeconomic environment and recurrent coronary events after initial myocardial infarction. *Ann Epidemiol*. 2012;22:541–546. doi: 10.1016/j.annepidem.2012.04.023
88. Bachmann JM, Willis BL, Ayers CR, Khera A, Berry JD. Association between family history and coronary heart disease death across long-term follow-up in men: the Cooper Center Longitudinal Study. *Circulation*. 2012;125:3092–3098. doi: 10.1161/CIRCULATIONAHA.111.065490
89. Lloyd-Jones DM, Nam BH, D'Agostino RB Sr, Levy D, Murabito JM, Wang TJ, Wilson PW, O'Donnell CJ. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *JAMA*. 2004;291:2204–2211. doi: 10.1001/jama.291.18.2204
90. Patel J, Al Rifai M, Blaha MJ, Budoff MJ, Post WS, Polak JF, Bluemke DA, Scheuner MT, Kronmal RA, Blumenthal RS, Nasir K, McEvoy JW. Coronary artery calcium improves risk assessment in adults with a family history of premature coronary heart disease: results from Multiethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging*. 2015;8:e003186. doi: 10.1161/CIRCIMAGING.115.003186
91. Choi J, Daskalopoulou SS, Thanassoulis G, Karp I, Pelletier R, Behlouli H, Pilote L; GENESIS-PRAXY Investigators. Sex- and gender-related risk factor burden in patients with premature acute coronary syndrome. *Can J Cardiol*. 2014;30:109–117. doi: 10.1016/j.cjca.2013.07.674
92. Agarwal MA, Garg L, Lavie CJ, Reed GL, Khouzam RN. Impact of family history of coronary artery disease on in-hospital clinical outcomes in ST-segment myocardial infarction. *Ann Transl Med*. 2018;6:3. doi: 10.21037/atm.2017.09.27
93. Howson JMM, Zhao W, Barnes DR, Ho WK, Young R, Paul DS, Waite LL, Freitag DF, Fauman EB, Salfati EL, Sun BB, Eicher JD, Johnson AD, Sheu WHH, Nielsen SF, Lin WY, Surendran P, Malarstig A, Wilk JB, Tybjærg-Hansen A, Rasmussen KL, Kamstrup PR, Deloukas P, Erdmann J, Kathiresan S, Samani NJ, Schunkert H, Watkins H, Do R, Rader DJ, Johnson JA, Hazen SL, Quyyumi AA, Spertus JA, Pepine CJ, Franceschini N, Justice A, Reiner AP, Buyske S, Hindorff LA, Carty CL, North KE, Kooperberg C, Boerwinkle E, Young K, Graff M, Peters U, Absher D, Hsiung CA, Lee WJ, Taylor KD, Chen YH, Lee IT, Guo X, Chung RH, Hung YJ, Rotter JI, Juang JJ, Quertermous T, Wang TD, Rasheed A, Frossard P, Alam DS, Majumder AAS, Di Angelantonio E, Chowdhury R, Chen YI, Nordestgaard BG, Assimes TL, Danesh J, Butterworth AS, Saleheen D; CARDIoGRAMplusC4D; EPIC-CVD. Fifteen new risk loci for coronary artery disease highlight arterial-wall-specific mechanisms. *Nat Genet*. 2017;49:1113–1119. doi: 10.1038/ng.3874
94. Helgadottir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, Jonasdottir A, Sigurdsson A, Baker A, Palsson A, Masson G, Gudbjartsson DF, Magnusson KP, Andersen K, Levey AI, Backman VM, Matthiasdottir S, Jonsdottir T, Palsson S, Einarsdottir H, Gunnarsdottir S, Gylfason A, Vaccarino V, Hooper WC, Reilly MP, Granger CB, Austin H, Rader DJ, Shah SH, Quyyumi AA, Gulcher JR, Thorgeirsson G, Thorsteinsdottir U, Kong A, Stefansson K. A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science*. 2007;316:1491–1493. doi: 10.1126/science.1142842
95. Palomaki GE, Melillo S, Bradley LA. Association between 9p21 genomic markers and heart disease: a meta-analysis. *JAMA*. 2010;303:648–656. doi: 10.1001/jama.2010.118
96. Franceschini N, Carty C, Bůzková P, Reiner AP, Garrett T, Lin Y, Vöckler JS, Hindorff LA, Cole SA, Boerwinkle E, Lin DY, Bookman E, Best LG, Bella JN, Eaton C, Greenland P, Jenny N, North KE, Taverna D, Young AM, Deelman E, Kooperberg C, Psaty B, Heiss G. Association of genetic variants and incident coronary heart disease in multiethnic cohorts: the PAGE study. *Circ Cardiovasc Genet*. 2011;4:661–672. doi: 10.1161/CIRCGENETICS.111.960096
97. Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators. Coding variation in ANGPTL4, LPL, and SVEP1 and the risk of coronary disease [published correction appears in *N Engl J Med*. 2016;374:1898]. *N Engl J Med*. 2016;374:1134–1144. doi: 10.1056/NEJMoa1507652
98. Webb TR, Erdmann J, Stirrups KE, Stitziel NO, Masca NG, Jansen H, Kanoni S, Nelson CP, Ferrario PG, König IR, Eicher JD, Johnson AD, Hamby SE, Betsholtz C, Ruusalepp A, Franzén O, Schadt EE, Björkegren JL, Weeke PE, Auer PL, Schick UM, Lu Y, Zhang H, Dube MP, Goel A, Farrall M, Peloso GM, Won HH, Do R, van Iperen E, Kruppa J, Mahajan A, Scott RA, Willenborg C, Braund PS, van Capelleveen JC, Doney AS, Donnelly LA, Asselta R, Merlini PA, Duga S, Marziliano N, Denny JC, Shaffer C, El-Mokhtari NE, Franke A, Heilmann S, Hengstenberg C, Hoffmann P, Holmen OL, Hveem K, Jansson JH, Jöckel KH, Kessler T, Kriebel J, Laugwitz KL, Marouli E, Martinelli N, McCarthy MI, Van Zuydam NR, Meisinger C, Esko T, Mihailov E, Escher SA, Alver M, Moebus S, Morris AD, Virtamo J, Nikpay M, Olivieri O, Provost S, AlQarawi A, Robertson NR, Akinsansya KO, Reilly DF, Vogt TF, Yin W, Asselbergs FW, Kooperberg C, Jackson RD, Stahl E, Müller-Nurasyid M, Strauch K, Varga TV, Waldenberger M; Wellcome Trust Case Control Consortium, Zeng L, Chowdhury R, Salomaa V, Ford I, Jukema JW, Amouyel P, Kontto J; MORGAM Investigators, Nordestgaard BG, Ferrières J, Saleheen D, Sattar N, Surendran P, Wagner A, Young R, Howson JM, Butterworth AS, Danesh J, Ardissino D, Bottinger EP, Erbel R, Franks PW, Girelli D, Hall AS, Hovingh GK, Kastrati A, Lieb W, Meitinger T, Kraus WE, Shah SH, McPherson R, Orho-Melander M, Melander O, Metspalu A, Palmer CN, Peters A, Rader DJ, Reilly MP, Loos RJ, Reiner AP, Roden DM, Tardif JC, Thompson JR, Wareham NJ, Watkins H, Willer CJ, Samani NJ, Schunkert H, Deloukas P, Kathiresan S; Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators. Systematic evaluation of pleiotropy identifies 6 further loci associated with coronary artery disease. *J Am Coll Cardiol*. 2017;69:823–836. doi: 10.1016/j.jacc.2016.11.056
99. Dewey FE, Gusarova V, Dunbar RL, O'Dushlaine C, Schurmann C, Gottesman O, McCarthy S, Van Hout CV, Bruse S, Dansky HM, Leader JB, Murray MF, Ritchie MD, Kirchner HL, Habegger L, Lopez A, Penn J, Zhao A, Shao W, Stahl N, Murphy AJ, Hamon S, Bouzelmat A, Zhang R, Shumel B, Pordy R, Gipe D, Herman GA, Sheu WHH, Lee IT, Liang KW, Guo X, Rotter JI, Chen YI, Kraus WE, Shah SH, Damrauer S, Small A, Rader DJ, Wulff AB, Nordestgaard BG, Tybjærg-Hansen A, van den Hoek AM, Princen HMG, Ledbetter DH, Carey DJ, Overton JD, Reid JG, Sasiela WJ, Banerjee P, Shuldiner AR, Borecki IB, Teslovich TM, Yancopoulos GD, Mellis SJ, Gromada J, Baras A. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *N Engl J Med*. 2017;377:211–221. doi: 10.1056/NEJMoa1612790
100. Nomura A, Won HH, Khera AV, Takeuchi F, Ito K, McCarthy S, Emdin CA, Klarin D, Natarajan P, Zekavat SM, Gupta N, Peloso GM, Borecki IB, Teslovich TM, Asselta R, Duga S, Merlini PA, Correa A, Kessler T, Wilson JG, Bown MJ, Hall AS, Braund PS, Carey DJ, Murray MF, Kirchner HL, Leader JB, Lavage DR, Manus JN, Hartze DN, Samani NJ, Schunkert H, Marrugat J, Elosua R, McPherson R, Farrall M, Watkins H, Juang JJ, Hsiung CA, Lin SY, Wang JS, Tada H, Kawashiri MA, Inazu A, Yamagishi M, Katsuya T, Nakashima E, Nakatochi M, Yamamoto K, Yokota M, Momozawa Y, Rotter JI, Lander ES, Rader DJ, Danesh J, Ardissino D, Gabriel S, Willer CJ, Abecasis GR, Saleheen D, Kubo M, Kato N, Ida Chen

YD, Dewey FE, Kathiresan S. Protein-truncating variants at the cholesteryl ester transfer protein gene and risk for coronary heart disease. *Circ Res*. 2017;121:81–88. doi: 10.1161/CIRCRESAHA.117.311145
101. Zhan Y, Karlsson IK, Karlsson R, Tillander A, Reynolds CA, Pedersen NL, Hägg S. Exploring the causal pathway from telomere length to coronary heart disease: a network mendelian randomization study. *Circ Res*. 2017;121:214–219. doi: 10.1161/CIRCRESAHA.116.310517
102. Helgadottir A, Gretarsdottir S, Thorleifsson G, Hjartarson E, Sigurdsson A, Magnusdottir A, Jonasdottir A, Kristjansson H, Sulem P, Oddsson A, Sveinbjornsson G, Steinthorsdottir V, Rafnar T, Masson G, Jonsdottir I, Olafsson I, Eyjolfsson GI, Sigurdardottir O, Daneshpour MS, Khalili D, Azizi F, Swinkels DW, Kiemeney L, Quyyumi AA, Levey AI, Patel RS, Hayek SS, Gudmundsdottir IJ, Thorgeirsson G, Thorsteinsdottir U, Gudbjartsson DF, Holm H, Stefansson K. Variants with large effects on blood lipids and the role of cholesterol and triglycerides in coronary disease. *Nat Genet*. 2016;48:634–639. doi: 10.1038/ng.3561
103. Mega JL, Stitziel NO, Smith JG, Chasman DI, Caulfield M, Devlin JJ, Nordio F, Hyde C, Cannon CP, Sacks F, Poulter N, Sever P, Ridker PM, Braunwald E, Melander O, Kathiresan S, Sabatine MS. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. *Lancet*. 2015;385:2264–2271. doi: 10.1016/S0140-6736(14)61730-X
104. Tada H, Melander O, Louie JZ, Catanese JJ, Rowland CM, Devlin JJ, Kathiresan S, Shiffman D. Risk prediction by genetic risk scores for coronary heart disease is independent of self-reported family history. *Eur Heart J*. 2016;37:561–567. doi: 10.1093/eurheartj/ehv462
105. Abraham G, Havulinna AS, Bhalala OG, Byars SG, De Livera AM, Yetukuri L, Tikkanen E, Perola M, Schunkert H, Sijbrands EJ, Palotie A, Samani NJ, Salomaa V, Ripatti S, Inouye M. Genomic prediction of coronary heart disease. *Eur Heart J*. 2016;37:3267–3278. doi: 10.1093/eurheartj/ehw450
106. Kullo IJ, Jouni H, Austin EE, Brown SA, Kruisselbrink TM, Isseh IN, Haddad RA, Marroush TS, Shameer K, Olson JE, Broeckel U, Green RC, Schaid DJ, Montori VM, Bailey KR. Incorporating a genetic risk score into coronary heart disease risk estimates: effect on low-density lipoprotein cholesterol levels (the MI-GENES clinical trial). *Circulation*. 2016;133:1181–1188. doi: 10.1161/CIRCULATIONAHA.115.020109
107. Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, Chasman DI, Baber U, Mehran R, Rader DJ, Fuster V, Boerwinkle E, Melander O, Orho-Melander M, Ridker PM, Kathiresan S. Genetic risk, adherence to a healthy lifestyle, and coronary disease. *N Engl J Med*. 2016;375:2349–2358. doi: 10.1056/NEJMoa1605086
108. Global Burden of Disease Study 2016. Global Burden of Disease Study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed May 1, 2018.
109. Labarthe DR, Lloyd-Jones DM. 50×50×50: cardiovascular health and the cardiovascular disease endgame. *Circulation*. 2018;138:968–970. doi: 10.1161/CIRCULATIONAHA.118.035985
110. Kypridemos C, Collins B, McHale P, Bromley H, Parvulescu P, Capewell S, O'Flaherty M. Future cost-effectiveness and equity of the NHS Health Check cardiovascular disease prevention programme: microsimulation modelling using data from Liverpool, UK. *PLoS Med*. 2018;15:e1002573. doi: 10.1371/journal.pmed.1002573
111. Huang Y, Pomeranz J, Wilde P, Capewell S, Gaziano T, O'Flaherty M, Kersh R, Whitsel L, Mozaffarian D, Micha R. Adoption and design of emerging dietary policies to improve cardiometabolic health in the US. *Curr Atheroscler Rep*. 2018;20:25. doi: 10.1007/s11883-018-0726-x

20. CARDIOMYOPATHY AND HEART FAILURE

See Tables 20-1 and 20-2 and Charts 20-1 through 20-7

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Cardiomyopathy

ICD-9 425; *ICD-10* I42.

2016: Mortality—22 114. Any-mention mortality—43 707.

Using HCUP data for cardiomyopathy in 2014, there were 16 000 inpatient hospitalizations for which cardiomyopathy was the principal diagnosis and 966 000 where it was included among all-listed diagnoses (NHLBI unpublished tabulation).

Abbreviations Used in Chapter 20

ACEI	angiotensin-converting enzyme inhibitor
ACR	albumin-to-creatinine ratio
AF	atrial fibrillation
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities Study
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults Study
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CRP	C-reactive protein
CVD	cardiovascular disease
DCM	dilated cardiomyopathy
DM	diabetes mellitus
ED	emergency department
EF	ejection fraction
FHS	Framingham Heart Study
GBD	Global Burden of Disease
GWAS	genome-wide association study
GWTG	Get With The Guidelines
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HCM	hypertrophic cardiomyopathy
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
Health ABC	Health, Aging, and Body Composition
HF	heart failure
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
IHD	ischemic heart disease
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
LV	left ventricular
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction

(*Continued*)

Abbreviations Used in Chapter 20 Continued

MRI	magnetic resonance imaging
NAMCS	National Ambulatory Medical Care Survey
NCHS	National Center for Health Statistics
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
OR	odds ratio
PA	physical activity
PAR	population attributable risk
PPCM	peripartum cardiomyopathy
PVC	premature ventricular contraction
QALY	quality-adjusted life-year
RR	relative risk
SBP	systolic blood pressure
SCD	sudden cardiac death
SES	socioeconomic status

Hypertrophic Cardiomyopathy

- Approximately 1 in 500 individuals have unexplained LVH, of whom 20% to 30% are likely to have a sarcomere mutation that suggests clinically expressed HCM; however, not all people with sarcomere mutations manifest clinical HCM because of incomplete penetrance, even among members of the same family (see Family History and Genetics for more details).[1]
- The Sarcomeric Human Cardiomyopathy Registry studied 4591 HCM patients, contributing >24 000 person-years of follow-up, and found that the mortality risk of patients with HCM is ≈3-fold higher than that of similarly aged individuals in the US general population. Risk for adverse events (ie, any ventricular arrhythmia, HF, AF, stroke, or death) was highest in patients diagnosed before age 40 years versus after age 60 years (77% [95% CI, 72%–80%] versus 32% [95% CI, 29%–36%] cumulative incidence). Adverse events were also 2-fold higher in patients with versus without sarcomere mutations. AF and HF accounted for a substantial proportion of the adverse events, despite not typically manifesting until years after initial diagnosis.[2]

Dilated Cardiomyopathy

- Commonly recognized causes of chronic DCM are mutations in a diverse group of genes that are inherited in an autosomal dominant fashion with age-dependent penetrance and variable clinical expression (see Family History and Genetics for more details). Other causes of DCM of variable chronicity and reversibility include cardiomyopathies that can develop after an identifiable exposure such as tachyarrhythmia, stress, neurohormonal disorder, alcoholism, chemotherapy, infection, or pregnancy (see Peripartum Cardiomyopathy).[3]

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- The annual incidence of chronic idiopathic DCM has been reported as between 5 and 8 cases per 100 000, although these estimates could be low because of underrecognition, especially in light of prevalent asymptomatic LV dysfunction observed in community studies (see LV Function).[4]

Peripartum Cardiomyopathy

- Data from the NIS databases indicate that the incidence of PPCM increased between 2004 and 2011 from 8.5 to 11.8 per 10 000 live births (P_{trend}<0.001), likely related to rising average maternal age and prevalence of PPCM risk factors such as obesity, hypertension, pregnancy-related hypertension, and DM.[5]
- The NIS data also show that maternal age has increased in all racial/ethnic groups, except Hispanics and Asians/Pacific Islanders, and across all census regions in the United States. When stratifying by race/ethnicity, incidence of PPCM was lowest in Hispanics and highest in African Americans. When stratifying by region, incidence was lowest in the West (6.5 [95% CI, 6.3–6.7]) and highest in the South (13.1 [95% CI, 12.9–13.1]).[5]
- In females diagnosed with PPCM, data from a prospective cohort indicate that 13% of females had major events (death, cardiac transplantation, or implantation of an LVAD) or persistent severe cardiomyopathy at 12 months. Black females had worse LV dysfunction at presentation and at 6 and 12 months postpartum than nonblack females.[6]

Youth

- Since 1996, the NHLBI-sponsored Pediatric Cardiomyopathy Registry has collected data on children with newly diagnosed cardiomyopathy in New England and the central Southwest (Texas, Oklahoma, and Arkansas).[7]
  - — The overall incidence of cardiomyopathy is 1.13 cases per 100 000 among children <18 years of age.
  - — Among children <1 year of age, the incidence is 8.34, and among children 1 to 18 years of age, it is 0.70 per 100 000.
  - — The annual incidence is higher in black children than in white children, in boys than in girls, and in New England (1.44 per 100 000) than in the central Southwest (0.98 per 100 000).
- The estimated annual incidence of HCM in children was 4.7 per 1 million children, with higher incidence in New England than in the central Southwest region and in boys than in girls.[8] Long-term outcomes of children with HCM suggest that 9% progress to HF and 12% to SCD.[9] See Chapter 16 (Disorders of Heart Rhythm) for statistics regarding sudden death in HCM.
- The estimated annual incidence of DCM in children <18 years of age is 0.57 per 100 000 overall, with higher incidence in boys than girls (0.66 versus 0.47 cases per 100 000, respectively) and blacks than whites (0.98 versus 0.46 cases per 100 000, respectively). The most commonly recognized causes of DCM were myocarditis (46%) and neuromuscular disease (26%).[10] The 5-year incidence rate of SCD among children with DCM is 3%.[11]
- Data from the Childhood Cancer Survivor Study cohort of 14 358 survivors of childhood or adolescent cancers show that these individuals are at 6-fold increased risk for future HF,[12] usually preceded by asymptomatic cardiomyopathy. This risk is especially pronounced for individuals who were treated with chest radiation or anthracycline chemotherapy and persists up to 30 years after the original cancer diagnosis.

Global Burden of Cardiomyopathy (See Table 20-1 and Charts 20-1 through 20-3)

- Chart 20-1 shows the incidence of PPCM globally.[13]
- Between 1990 and 2016, the global number of deaths attributable to cardiomyopathy and myocarditis decreased 27.3%, and the age-adjusted death rate is 5.2 per 100 000[14] (Table 20-1).
- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories.[14]
  - — The highest mortality rates attributed to cardiomyopathy and myocarditis were in Central and Eastern Europe (Chart 20-2).
  - — The prevalence of cardiomyopathy and myocarditis was highest in Central and Eastern Europe (Chart 20-3).

Heart Failure
ICD-9 428; *ICD-10* I50.

2016: Mortality—78 356. Any-mention mortality—336 732. 2014: Hospital discharges—900 000.

Prevalence (See Table 20-2 and Chart 20-4)

- On the basis of data from NHANES 2013 to 2016, an estimated 6.2 million Americans ≥20 years of age had HF (Chart 20-4). This represents an increase from an estimated 5.7 million US adults with HF based on NHANES 2009 to 2012 (NHLBI unpublished tabulation).

- Projections show that the prevalence of HF will increase 46% from 2012 to 2030, resulting in >8 million people ≥18 years of age with HF. Additionally, the total percentage of the population with HF is predicted to increase from 2.42% in 2012 to 2.97% in 2030.[15]

Incidence
(See Table 20-2 and Chart 20-5)

- Data from the NHLBI-sponsored Chicago Heart Association Detection Project in Industry, ARIC, and CHS cohorts indicate that HF incidence approaches 21 per 1000 population after 65 years of age.[16]
- Data from Kaiser Permanente indicated an increase in the incidence of HF among the elderly and improved HF survival, resulting in increased HF prevalence, with both trends being more pronounced in males.[17]
- Data from Olmsted County, MN, indicate that the age- and sex-adjusted incidence of HF declined substantially, from 315.8 per 100 000 in 2000 to 219.3 per 100 000 in 2010, with a greater rate reduction for HF with reduced EF (–45.1% [95% CI, –33.0% to –55.0%]) than for HF with preserved EF (–27.9% [95% CI, –12.9% to –40.3%]).[18]
- In the CARDIA study, HF before 50 years of age was more common among blacks than whites. Hypertension, obesity, and systolic dysfunction were important risk factors that may be targets for prevention.[19]
- Data from the 2005 to 2014 community surveillance component of the ARIC study indicate that rates of hospitalizations for HF are increasing over time, apparently driven by rises in HF with preserved EF. Overall events included 50% HF with reduced EF and 39% HF with preserved EF, where the former was more common in black males and white males and the latter was most common in white females. Age-adjusted rates of HF hospitalization were highest in blacks (38 per 1000 black males, 31 per 1000 black females).[20]
- In MESA, African Americans had the highest risk of developing HF, followed by Hispanic, white, and Chinese Americans (4.6, 3.5, 2.4, and 1.0 per 1000 person-years, respectively). This higher risk reflected differences in the prevalence of hypertension, DM, and low SES.[21] African Americans had the highest proportion of incident HF not preceded by clinical MI (75%).[21]

Lifetime Risk

- Because most forms of HF tend to present in older age, and the population is aging, lifetime risk for HF in the community is high. Data from the NHLBI-sponsored Chicago Heart Association Detection Project in Industry, ARIC, and CHS cohorts indicated the following[16]:
  - — Overall, at age 45 years through age 95 years, lifetime risks for HF were high (20%–45%).
  - — Lifetime risks for HF were 30% to 42% in white males, 20% to 29% in black males, 32% to 39% in white females, and 24% to 46% in black females. The lower lifetime risk in black males appears likely to be attributable to competing risks.
  - — Lifetime risk for HF was higher with higher BP and BMI at all ages.
  - — The lifetime risk of HF occurring for people with BMI ≥30 kg/m² was approximately double that of those with BMI <25 kg/m².
  - — The lifetime risk of HF occurring for people with BP >160/90 mm Hg was 1.6 times that of those with BP <120/90 mm Hg.

Risk Factors

- Traditional risk factors for HF are common in the US adult population. Data from NHANES indicate that at least 1 HF risk factor is present in up to one-third of the US adult population.[22]
- Traditional factors account for a considerable proportion of HF risk. Data from Olmstead County, MN, indicate that CHD, hypertension, DM, obesity, and smoking are responsible for 52% of incident HF cases in the population, with ORs or RRs and their PARs as follows[23]: CHD OR, 3.1 and overall PAR, 20% (highest in males, 23% versus 16% in females); cigarette smoking RR, 1.4 and PAR, 14%; hypertension RR, 1.4 and PAR, 20% (highest in females, 28% versus 13% in males); obesity RR, 2.0 and PAR, 12%; DM OR, 2.7 and PAR, 12%.
- Racial disparities in risks for HF persist, as shown in the Health ABC Study, a US cohort of 2934 adults aged 70 to 79 years followed up for 7 years.[24] Among blacks, a greater proportion of HF risk (68% versus 49% among whites) was attributable to modifiable risk factors, including elevated SBP, elevated fasting glucose level, CHD, LVH, and smoking. LVH was 3-fold more prevalent in blacks than in whites. CHD (PAR, 23.9% for white participants, 29.5% for black participants) and uncontrolled BP (PAR, 21.3% for white participants, 30.1% for black participants) had the highest PARs in both races.[24] Hispanics carry a predominance of HF risk factors and healthcare disparities, which suggests a relatively elevated HF risk in this population as well.[25]
- Risk factors appear to differ by HF subtype. As a group, patients with HF with preserved

EF are older, are more likely to be female, and have greater prevalence of hypertension, obesity, and anemia than those with HF with reduced EF.[26]

- Dietary and lifestyle factors also impact HF risk.
- Among 20 900 male physicians in the Physicians' Health Study, the lifetime risk of HF was higher in males with hypertension, whereas healthy lifestyle factors (normal weight, not smoking, regular PA, moderate alcohol intake, consumption of breakfast cereals, and consumption of fruits and vegetables) were related to lower risk of HF.[26a]
- In the ARIC study, greater adherence to the AHA's Life's Simple 7 guidelines (better profiles in smoking, BMI, PA, diet, cholesterol, BP, and glucose) was associated with a lower lifetime risk of HF, as well as more optimal echocardiographic parameters of cardiac structure and function.[27]
- Multiple nontraditional risk factors for HF have been identified.
  - In the NHLBI-sponsored FHS, circulating BNP, urinary ACR, elevated serum γ-glutamyl transferase, and higher levels of hematocrit were identified as risk factors for incident HF.[28–30] Circulating concentrations of resistin were also associated with incident HF independent of prevalent coronary disease, obesity, insulin resistance, and inflammation.[31] Circulating adiponectin concentrations were also related to incident HF, with a J-shaped relationship.[32] Inflammatory markers (interleukin-6 and tumor necrosis factor-α), serum albumin levels, and cigarette smoking exposure additionally were associated with increased HF risk.[33–35]
  - In the CHS, baseline cardiac high-sensitivity troponin and changes in high-sensitivity troponin levels were significantly associated with incident HF.[36] Conversely, circulating individual and total omega-3 fatty acid concentrations were associated with lower incidence of HF.[37]
  - In the ARIC study, white blood cell count, CRP, albuminuria, HbA_{1c} among individuals without DM, cardiac troponin, PVCs, and socioeconomic position over the life course were all identified as risk factors for HF.[38–43]
  - In MESA, plasma N-terminal pro-BNP provided incremental prognostic information beyond the traditional risk factors and the MRI-determined LV mass index for incident symptomatic HF.[44]

LV Function

- Measures of impaired systolic or diastolic LV function are common precursors to clinical HF.
  - In the FHS, the prevalence of asymptomatic LV systolic dysfunction was 5% and diastolic dysfunction was 36%. LV systolic and diastolic dysfunction were associated with increased risk of incident HF. Measures of major organ system dysfunction (higher serum creatinine, lower ratios of forced expiratory volume in 1 second to forced vital capacity, and lower hemoglobin concentrations) were also associated with an adjusted increased risk of new-onset HF.[45]
  - In Olmsted County, MN, diastolic dysfunction (HR, 1.81 [95% CI, 1.01–3.48]) was observed to progress with advancing age and was associated with an increased risk of incident clinical HF during 6 years of subsequent follow-up after adjustment for age, hypertension, DM, and CAD.[46]
  - With respect to variation by race/ethnicity, presence of asymptomatic LV systolic dysfunction in MESA was higher in African Americans than in whites, Chinese, and Hispanics (1.7% overall and 2.7% in blacks). After 9 years of follow-up, asymptomaic LV dysfunction was associated with increased risk of overt HF (HR, 8.69 [95% CI, 4.89–15.45]), as well as CVD and all-cause mortality.[47]
  - In the Echocardiographic Study of Hispanic/Latinos, more than half (49.7%) of middle-aged or older Hispanics had some form of cardiac dysfunction (systolic, diastolic, or both), although fewer than 1 in 20 Hispanic/Latinos had symptomatic or clinically recognized HF.[48]
- LV function is variably abnormal in the setting of clinically overt HF.
  - GWTG–HF data from 2005 to 2010 indicate that of 110 621 patients hospitalized with HF, half had a reduced EF (<40%), 14% had an EF that was ≥40% and <50%, and 36% had an EF of ≥50%.[26]
  - Data collected between 1985 and 2014 from 12 857 person-observations in the FHS showed that the frequency of HF with reduced EF (EF <40%) decreased over time, whereas HF with mid-range EF (40% to <50%) remained stable, and HF with preserved EF (EF ≥50%) increased over time. These findings appeared attributable to trends in risk factors, especially a

decrease in prevalent CHD among people with HF.[49]

Hospital Discharges/Ambulatory Care Visits (See Table 20-2 and Chart 20-6)

- Hospital discharges for HF (including discharged alive, dead, and status unknown) are shown for the United States (1997–2014) by sex in Chart 20-6. Discharges for HF decreased from 2004 to 2014, with principal diagnosis discharges of 1 042 000 and 900 000, respectively (NCHS, NHLBI unpublished tabulation).[50]
- In 2015, there were 2 671 000 physician office visits with a primary diagnosis of HF (NAMCS, NHLBI unpublished tabulation).[51] In 2015, there were 481 000 ED visits for HF (NHAMCS, NHLBI unpublished tabulation).[52]
- Among 1077 patients with HF in Olmsted County, MN, hospitalizations were common after HF diagnosis, with 83% patients hospitalized at least once and 43% hospitalized at least 4 times. More than one-half of all hospitalizations were related to noncardiovascular causes.[53]
- Among Medicare beneficiaries, the overall HF hospitalization rate declined substantially from 1998 to 2008 but at a lower rate for black males,[54] and the temporal trend findings were uneven across states.
- In the GWTG–HF Registry, only one-tenth of eligible HF patients received cardiac rehabilitation referral at discharge after hospitalization for HF.[55]
- Among Medicare part D coverage beneficiaries, HF medication adherence (ACEI/angiotensin receptor blocker, β-blockers, and diuretic agents) after HF hospitalization discharge decreased over 2 to 4 months after discharge, followed by a plateau over the subsequent year for all 3 medication classes.[56]
- Rates of HF rehospitalization or cardiovascular death were greatest for those previously hospitalized for HF.[57]
- Although Hispanic patients hospitalized with HF were significantly younger than NH whites, the prevalence of DM, hypertension, and overweight/obesity was higher among them. In multivariate analysis, a 45% lower in-hospital mortality risk was observed among Hispanics with HF with preserved EF compared with NH whites but not among those with HF with reduced EF.[58]
- On the basis of data from the community surveillance component of the ARIC study of the NHLBI[59]:
  - — The average incidence of hospitalized HF for those aged ≥55 years was 11.6 per 1000 people per year; incidence of recurrent hospitalized HF was 6.6 per 1000 people per year.
  - — Age-adjusted annual hospitalized HF incidence was highest for black males (15.7 per 1000), followed by black females (13.3 per 1000), white males (12.3 per 1000), and white females (9.9 per 1000).
  - — Of incident hospitalized HF events, 53% had HF with reduced EF and 47% had preserved EF. Black males had the highest proportion of hospitalized HF with reduced EF (70%); white females had the highest proportion of hospitalized HF with preserved EF (59%).
  - — Age-adjusted 28-day and 1-year case fatality after hospitalized HF was 10.4% and 29.5%, respectively, and did not differ by race or sex.
- Data from the Health and Retirement Study from 1998 to 2014 show racial/ethnic differences in hospitalization trajectories over 24 months after HF diagnosis.[60] Compared with NH males, Hispanic males have declines in hospitalization after initial diagnosis but then increases in hospitalizations in later stages of disease. Among females, compared with whites, blacks had significantly more hospitalizations throughout the follow-up period.
- Data from Olmsted County, MN, indicate that among those with HF, hospitalizations were particularly common among males and did not differ by HF with reduced EF versus preserved EF, with 63% of hospitalizations for noncardiovascular causes. Among those with HF, hospitalization rates for cardiovascular causes did not change over time, whereas those for noncardiovascular causes increased from 2000 to 2010.[18]

Mortality (See Table 20-2)

- Survival after the onset of HF in older adults has improved, as indicated by data from Kaiser Permanente[17]; however, improvements in HF survival have not been even across all demographics. Among Medicare beneficiaries, the overall 1-year HF mortality rate declined slightly from 1998 to 2008 but remained high at 29.6%, and rates of decline were uneven across states.[61,61a] In the NHLBI's ARIC study, the 30-day, 1-year, and 5-year case fatality rates after hospitalization for HF were 10.4%, 22%, and 42.3%, respectively, and blacks had a greater 5-year case fatality rate than whites ($P<0.05$).[62]

- Observed mortality declines have been primarily attributed to evidence-based approaches to treat HF risk factors and the implementation of ACEIs, β-blockers, coronary revascularization, implantable cardioverter-defibrillators, and cardiac resynchronization therapies.[63] Contemporary evidence from the GWTG–HF registry suggests that ≈47% of individuals admitted to the hospital with HF should have had initiation of ≥1 new medication on discharge; ≈24% need to start ≥1 new medication and ≈14% need to start ≥3 new medications to be in compliance with current guidelines.[64]
- In a large Swedish registry of patients with HF with preserved EF, statins improved 1-year cardiovascular hospitalization, mortality, and cardiovascular mortality.[65] Accordingly, 5-year survival of HF diagnosis after an MI in Olmstead County, MN, improved in 2001 to 2010 versus 1990 to 2000, from 54% to 61%.[66]
- Some data suggest that improvements in survival could be leveling off over time. Data from the Rochester Epidemiology Project in Olmsted County, MN, showed improved survival after HF diagnosis between 1979 and 2000[67]; however, 5-year mortality did not decline from 2000 to 2010 and remained high at ≈50% (52.6% overall; 24.4% for 60-year-olds and 54.4% for 80-year-olds). Importantly, mortality was more frequently ascribed to noncardiovascular causes (54.3%), and the risk of noncardiovascular death was greater in HF with preserved EF than in HF with reduced EF.[18]
- Given improvements in HF survival overall, the number of individuals carrying a diagnosis of HF at death has increased. Mortality associated with HF is substantial, such that 1 in 8 deaths has HF mentioned on the death certificate (NCHS, NHLBI unpublished tabulation).[68]
- In 2016, HF was the underlying cause in 78 356 deaths (35 424 males and 42 932 females).[68] Table 20-2 shows the numbers of these deaths that were coded for HF as the underlying cause.
- The number of underlying cause of deaths attributable to HF was 27.7% higher in 2015 (75 251) than it was in 2005 (58 933) (NCHS, NHLBI unpublished tabulation).
- In 2015, the overall any-mention age-adjusted death rate for HF was 87.9 per 100 000, with variation across racial/ethnic groups: in males, the rates were 107.4 for NH whites, 112.6 for NH blacks, 47.0 for NH Asians or Pacific Islanders, 100.9 for NH American Indians or Alaska Natives, and 67.5 for Hispanics; in females, the respective rates were 79.6 for NH whites, 83.9 for NH blacks, 33.3 for NH Asians or Pacific Islanders, 75.0 for NH American Indians or Alaska Natives, and 48.8 for Hispanics.[68]

Cost

The overall cost of HF continues to rise. See Chapter 26 (Economic Cost of Cardiovascular Disease) for further statistics.

- In 2012, total cost for HF was estimated to be $30.7 billion (2010$), of which over two-thirds was attributable to direct medical costs.[15] Projections suggest that by 2030, the total cost of HF will increase by 127%, to $69.8 billion, amounting to ≈$244 for every US adult.[15]
- Implantable cardioverter-defibrillators could be cost-effective in the guideline-recommended groups of individuals with HF with reduced EF; however, the benefit might not be as great in those with high overall mortality risk (eg, age ≥75 years, New York Heart Association functional class III, LVEF ≤20%, BNP ≥700 pg/mL, SBP ≤120 mm Hg, AF, DM, chronic lung disease, and CKD).[69,70]
- The costs associated with treating HF comorbidities and HF exacerbations in youths are significant, totaling nearly $1 billion in inpatient costs, and may be rising. The associated cost burden of HF is anticipated to constitute a large portion of total pediatric healthcare costs.[71]

Open Heart Transplantation and Assist Device Placement in the United States (See Chart 20-7)

From September 1987 to December 2012, 40 253 people were waiting for heart transplants, with a median survival of 2.3 years; 26 943 received transplants, with median survival of 9.5 years. Life-years saved were 465 296; life-years saved per patient were 5.0.

- The 7th INTERMACS report of >15 000 LVAD implantations from June 2006 to December 2014 revealed 80% survival at 1 year and 70% at 2 years.[72]
- The number of patients receiving LVADs increased from 98 in 2006 to 2423 in 2014.
- The proportion of LVADs as destination therapy increased from 14.7% in 2006 to 2007 to 19.6% in 2008 to 2010, 41.6% in 2011 to 2013, and 45.7% in 2014[72] (Chart 20-7).
- The NIS reported 2038 LVAD implantations from 2005 to 2011, with 127 in 2005 and increasing to 506 procedures in 2011.[73]
- In-hospital mortality with LVAD implantation decreased significantly from 47.2% in 2005 to 12.7% in 2011. An inflection point was seen with a sharp rise in LVAD implantation

and decrease in the in-hospital mortality rate in 2008. Average hospital length of stay decreased from the pulsatile LVAD (pre-2008) to the continuous-flow LVAD (2008–2011) eras.[74] The mean cost of LVAD-related hospitalization increased from $194 380 in 2005 to $234 808 in 2011.[75]

- In a meta-analysis of 8 studies (7957 patients total) comparing mortality rates in patients treated with heart transplantation versus bridge-to-transplantation LVAD or LVAD as destination therapy, there was no difference in late (>6 months) all-cause mortality between heart transplantation and LVAD (pooled OR, 0.91 [95% CI, 0.62–1.32] for transplantation versus bridge-to-transplantation LVAD; pooled OR, 1.49 [95% CI, 0.48–4.66] for transplantation versus destination therapy LVAD).[76]
- In a Markov model analysis, compared with nonbridged heart transplant recipients (who did not receive an LVAD bridge), receiving a bridge-to-transplantation LVAD increased survival, with greater associated cost (range, $84 964 per life-year to $119 574 per life-year for high-risk and low-risk patients, respectively). Open heart transplantation increased life expectancy and was cost-effective (8.5 years with <$100 000 per QALY relative to medical therapy), but LVAD either for bridge to transplantation (12.3 years at $226 000 per QALY) or as destination therapy (4.4 years at $202 000 per QALY) was not cost-effective.[77]
- Elevated LVAD index admission costs could be related to procurement costs and length of stay. Hospital readmissions also contribute significantly to overall cost of LVAD therapy: with continuous-flow LVAD, 44% of patients were readmitted within 30 days of discharge, with a median cost of $7546. The most common causes of readmission were gastrointestinal bleeding, infection, and stroke, with device malfunction and arrhythmias the most costly causes of readmission. There was no difference in survival between patients who were and were not readmitted, although median follow-up was only 11 months.[78]

LVAD and Open Heart Transplantation Disparities

- The 7th INTERMACS report did not specifically address the influence of race or ethnicity on mortality after LVAD procedures but did report that a higher mortality was seen in females (HR, 1.16; *P*=0.005).[72]
- In the United Network for Organ Sharing Database of 18 085 patients who had open heart transplantation performed at 102 centers, blacks had a higher adjusted 1-year mortality, particularly at poor-performing centers (observed-to-expected mortality ratio >1.2; OR, 1.37 [95% CI, 1.12–1.69]; *P*=0.002).[79] Compared with whites and Hispanics, a higher proportion of blacks were treated at centers with higher than expected mortality, which persisted after adjustment for insurance type and education level.

Family History and Genetics

- HCM and familial DCM are the most common mendelian cardiomyopathies, with autosomal dominant or recessive transmission, in addition to X-linked and mitochondrial inheritance.
- Familial DCM accounts for up to 50% of cases of DCM, with a prevalence of 1 in 2500, but is likely underestimated.[80] Familial DCM often displays an age-dependent penetrance.[81] Up to 40% of cases have an identifiable genetic cause.[80]
- Given the heterogeneous nature of the underlying genetics, manifestation of the disease is highly variable, even in cases for which the causal mutation has been identified.[82] Variants in the β-myosin heavy chain gene (*MYH7*) were some of the earliest to be associated with familial HCM,[83,84] with >30 other genes implicated since, each accounting for <5% of cases, as reviewed elsewhere.[81,85,86] The considerable variability in the penetrance and pathogenicity of specific mutations makes clinical interpretation of sequence data particularly challenging.
- Missense and truncating variants in the Titin gene have been linked to autosomal dominant cardiomyopathy,[87] as well as to DCM, with incomplete penetrance in the general population.[87] Analysis of sequence data in 7855 cardiomyopathy case subjects and >60 000 control subjects revealed the variance in penetrance of putative disease variants, which further highlights the challenges in clinical interpretation of variation in mendelian disease genes.[88]
- Several GWASs have been conducted to identify common variations associated with cardiomyopathy and HF in the general population, albeit with modest results,[81,84] highlighting a small number of putative loci, including *HSPB7*[89–91] and *CACNB4*.[92] Given the heterogeneous multifactorial nature of common HF, identification of causal genetic loci remains a challenge.
- Genetic variation within subjects with HF may determine outcomes, with a locus on chromosome 5q22 associated with mortality in HF patients.[93] A large meta-analysis of >73 000 subjects identified

52 loci associated with myocardial mass.[94] The clinical utility of genetic testing for variants associated with common HF and related phenotypes remains unclear.

- HCM is a monogenic disorder with primarily autosomal dominant inheritance and is caused by one of hundreds of mutations in up to 18 genes that primarily encode components of the sarcomere, with mutations in *MYH7* and cardiac myosin-binding protein C (*MYBPC3*) being the most common, with each having 40 HCM cases attributed to it.[95] A mutation is identifiable in 50% to 75% of familial HCM cases.
- Clinical genetic testing is recommended for patients with DCM with significant conduction system disease or a family history of SCD, as well as in patients with a strong clinical index of suspicion for HCM. It can be considered in other forms of DCM and restrictive cardiomyopathy and in LV noncompaction.[96]
- Genetic testing is also recommended in family members of patients with DCM, HCM, restrictive cardiomyopathy, and LV noncompaction.[96]

Global Burden of HF

- HF is common throughout sub-Saharan Africa. Forty-four percent of patients with newly diagnosed CVD have HF, whereas only 10% have CAD.[97] Common causes include nonischemic cardiomyopathies, rheumatic HD, congenital HD, hypertensive HD, and endomyocardial fibrosis; IHD remains relatively uncommon. HF strikes individuals in sub-Saharan Africa at a much younger age than in the United States and Europe.[98]
- The prevalence estimates for HF across Asia range from 1.26% to 6.7%. Rheumatic HD is a major contributor to HF in certain parts of South Asia, such as India, but recently, trends toward an ischemic cause for HF have been observed in Asia, such as in China and Japan.[99]
- Ischemic HF prevalence in 2010 was highest (>5 per 1000) in high-income North America, Oceania, and Eastern Europe. In particular, HF prevalence in 2010 was highest in Oceania (4.53 [95% CI, 3.19–6.29] per 1000 in females; 5.22 [95% CI, 3.84–7.08] per 1000 in males), followed by high-income North America and North Africa/Middle East. HF prevalence was lowest in west sub-Saharan Africa (0.74 [95% CI, 0.58–0.98] per 1000 in males and 0.57 [96% CI, 0.44–0.76] per 1000 in females).[100] HF made the largest contribution to age-standardized years lived with disability among males in high-income North America, Oceania, Eastern and Western Europe, southern Latin America, and Central Asia.[100]
- HF risk factors vary substantially across world regions, with hypertension being highly associated with HF in all regions but most commonly in Latin America, the Caribbean, Eastern Europe, and sub-Saharan Africa, and with a minimal association of IHD with HF in sub-Saharan Africa.[101] IHD prevalence among HF patients is highest in Europe and North America but rare in sub-Saharan Africa, whereas hypertension prevalence among HF patients was highest in Eastern Europe and sub-Saharan Africa; valvular and rheumatic HD prevalence among HF patients was highest in East Asia and Asia-Pacific countries.[101] Follow-up from a multiethnic cohort composed of individuals from low- to middle-income countries in Africa, Asia, the Middle East, and South America will provide additional data regarding the global burden of HF.[102]

Table 20-1. Global Prevalence and Mortality of Cardiomyopathy and Myocarditis[52]

	Both Sexes Combined		Males		Females	
	Death (95% CI)	Prevalence (95% CI)	Death (95% CI)	Prevalence (95% CI)	Death (95% CI)	Prevalence (95% CI)
Total number (millions)	0.3 (0.3 to 0.4)	6.1 (5.6 to 6.7)	0.2 (0.2 to 0.2)	2.8 (2.5 to 3.0)	0.1 (0.1 to 0.2)	3.4 (3.1 to 3.7)
Percent change total number 2006 to 2016	13.1 (5.1 to 23.9)	19.8 (18.0 to 21.6)	12.0 (1.3 to 25.3)	21.4 (19.1 to 23.7)	14.7 (5.2 to 27.1)	18.6 (16.5 to 20.7)
Percent change total number 1990 to 2016	46.1 (32.1 to 69.7)	36.5 (33.5 to 39.4)	52.5 (35.1 to 78.2)	37.6 (33.7 to 41.2)	38.6 (22.1 to 70.7)	35.5 (32.2 to 38.7)
Rate per 100 000	5.2 (4.3 to 5.7)	88.9 (81.2 to 98.1)	6.3 (5.1 to 7.0)	84.9 (77.2 to 94.3)	4.1 (3.2 to 4.6)	92.2 (84.6 to 101.2)
Percent change rate 1990 to 2016	−27.3 (−34.8 to −10.9)	−24.1 (−25.8 to −22.3)	−24.1 (−32.9 to −5.8)	−24.4 (−26.5 to −22.3)	−31.4 (−40.2 to −12.0)	−23.1 (−24.9 to −21.1)
Percent change rate 2006 to 2016	−13.0 (−19.0 to −4.7)	−4.7 (−5.9 to −3.4)	−12.5 (−20.0 to −3.0)	−3.8 (−5.6 to −2.1)	−13.5 (−20.6 to −4.0)	−4.8 (−6.2 to −3.2)

Table 20-2. Heart Failure

Population Group	Prevalence, 2013–2016, Age ≥20 y	Incidence, 2014, Age ≥55 y	Mortality, 2016, All Ages*	Hospital Discharge, 2014, All Ages	Cost, 2012†
Both sexes	6 200 000 (2.2%)	1 000 000	78 356	900 000	$30.7 billion
Males	3 000 000 (2.4%)	495 000	35 424 (45.2%)‡	462 000	…
Females	3 200 000 (2.1%)	505 000	42 932 (54.8%)‡	438 000	…
NH white males	2.2%	430 000§	29 155	…	…
NH white females	1.9%	425 000§	35 526	…	…
NH black males	3.5%	65 000§	3777	…	…
NH black females	3.9%	80 000§	4584	…	…
Hispanic males	2.5%	…	1721	…	…
Hispanic females	2.1%	…	1905	…	…
NH Asian males	1.7%	…	561‖	…	…
NH Asian females	0.7%	…	715‖	…	…
NH American Indian or Alaska Native	…	…	262	…	…

Heart failure includes people who answered "yes" to the question of ever having congestive heart failure. Ellipses (…) indicate data not available; and NH, non-Hispanic.

*Mortality data for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†Cost data are from Heidenreich et al.[15]

‡These percentages represent the portion of total mortality attributable to heart failure that is for males vs females.

§Estimates for whites include other nonblack races.

‖Includes Chinese, Filipino, Hawaiian, Japanese, and Other Asian or Pacific Islander.

Sources: Prevalence: National Health and Nutrition Examination Survey 2013 to 2016 (National Center for Health Statistics [NCHS]) and National Heart, Lung, and Blood Institute (NHLBI). Percentages are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2016 US population estimates. These data are based on self-reports. Incidence: Atherosclerosis Risk in Communities Study Community Surveillance, 2005 to 2014 from the NHLBI. Mortality: Centers for Disease Control and Prevention/NCHS, 2016 Mortality Multiple Cause-of-Death–United States. Mortality for NH Asians includes Pacific Islanders. Hospital discharges: Healthcare Cost and Utilization Project, Hospital Discharges, 2014 (data include those inpatients discharged alive, dead, or status unknown).

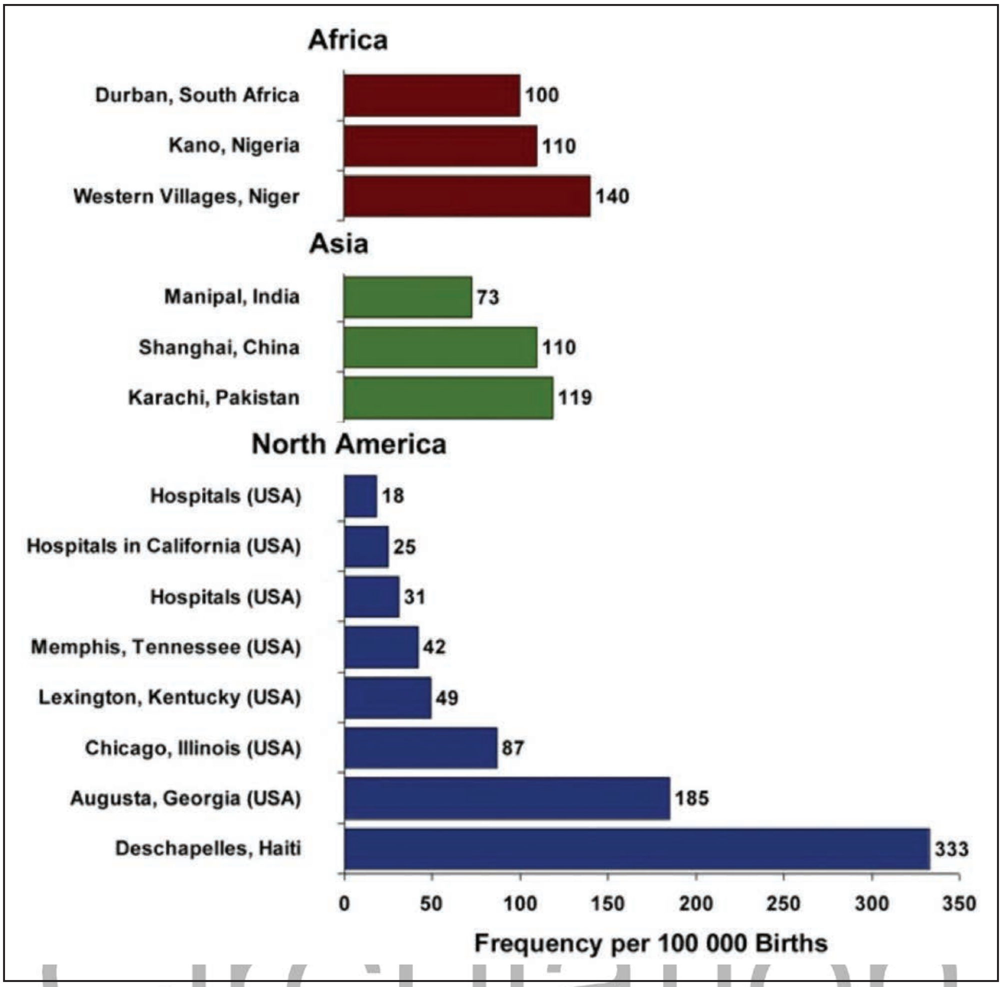

Chart 20-1. Incidence of peripartum cardiomyopathy.
Adapted from Blauwet et al[103] with permission from BMJ Publishing Group Ltd. Copyright © 2011, BMJ Publishing Group Ltd and the British Cardiovascular Society.

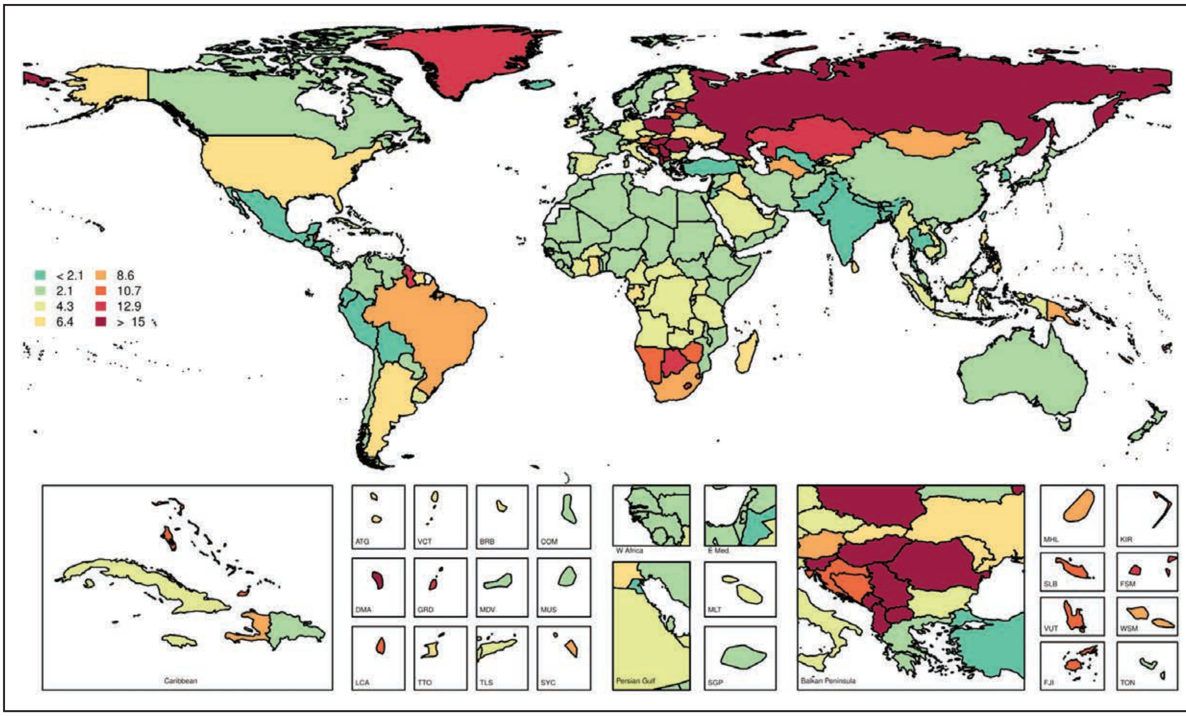

Chart 20-2. Age-standardized global mortality rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[14] Printed with permission. Copyright © 2017, University of Washington.

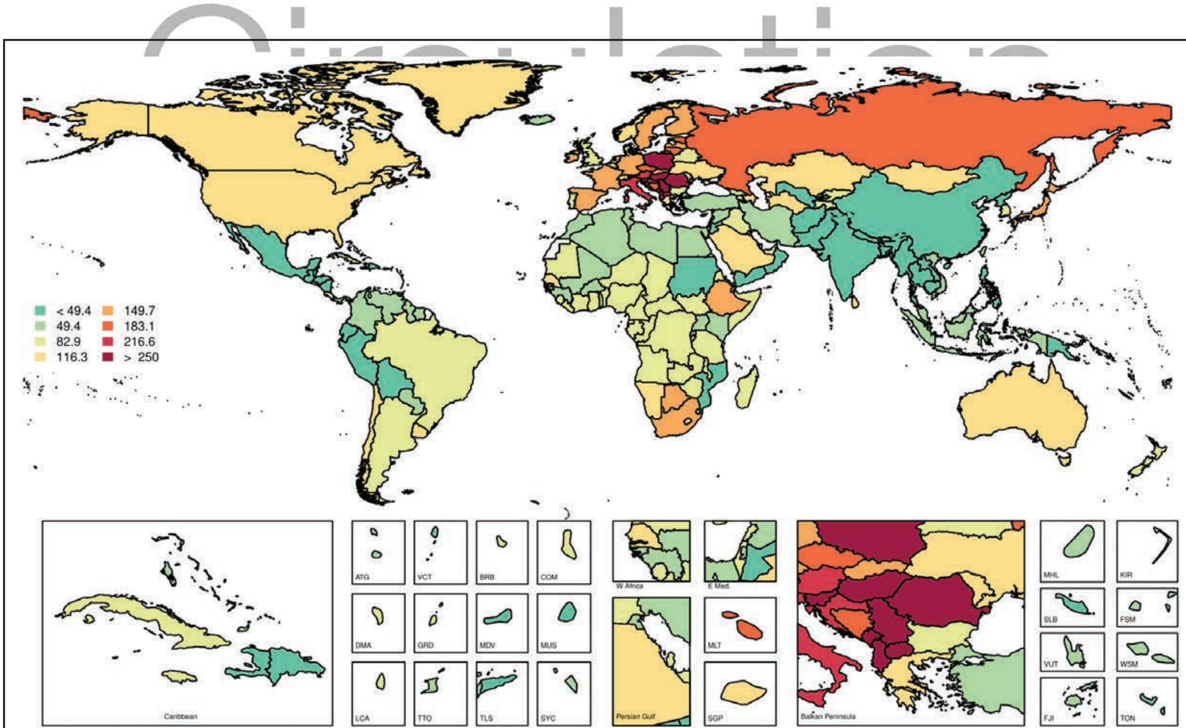

Chart 20-3. Age-standardized global prevalence rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[14] Printed with permission. Copyright © 2017, University of Washington.

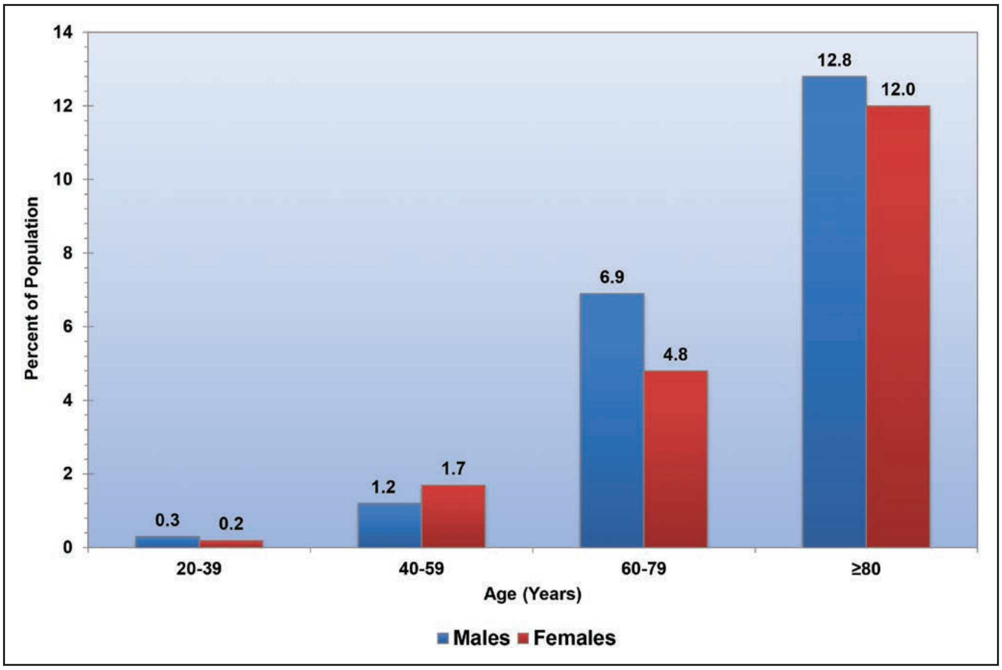

Chart 20-4. Prevalence of heart failure for adults ≥20 years by sex and age (NHANES, 2013–2016).
NHANES indicates National Health and Nutrition Examination Survey.
Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

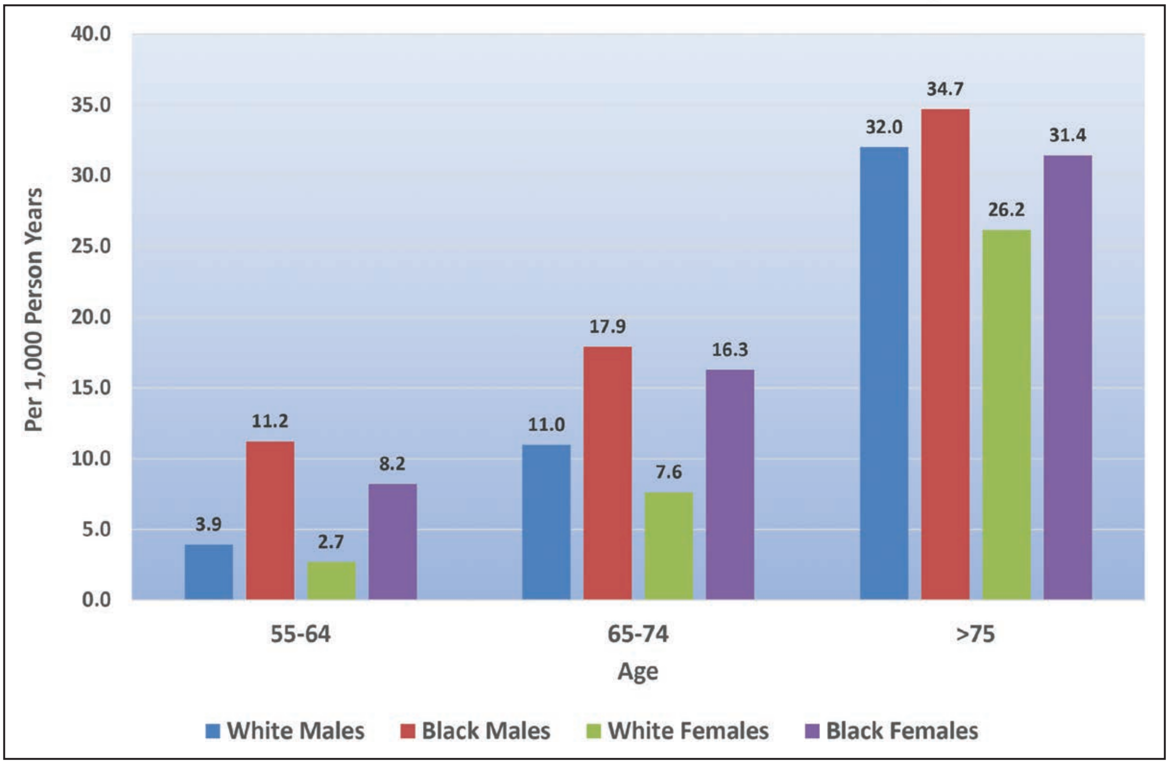

Chart 20-5. First acute decompensated heart failure annual event rates per 1000 from ARIC Community Surveillance (2005–2014).
ARIC indicates Atherosclerosis Risk in Communities Study.
Source: ARIC and National Heart, Lung, and Blood Institute.

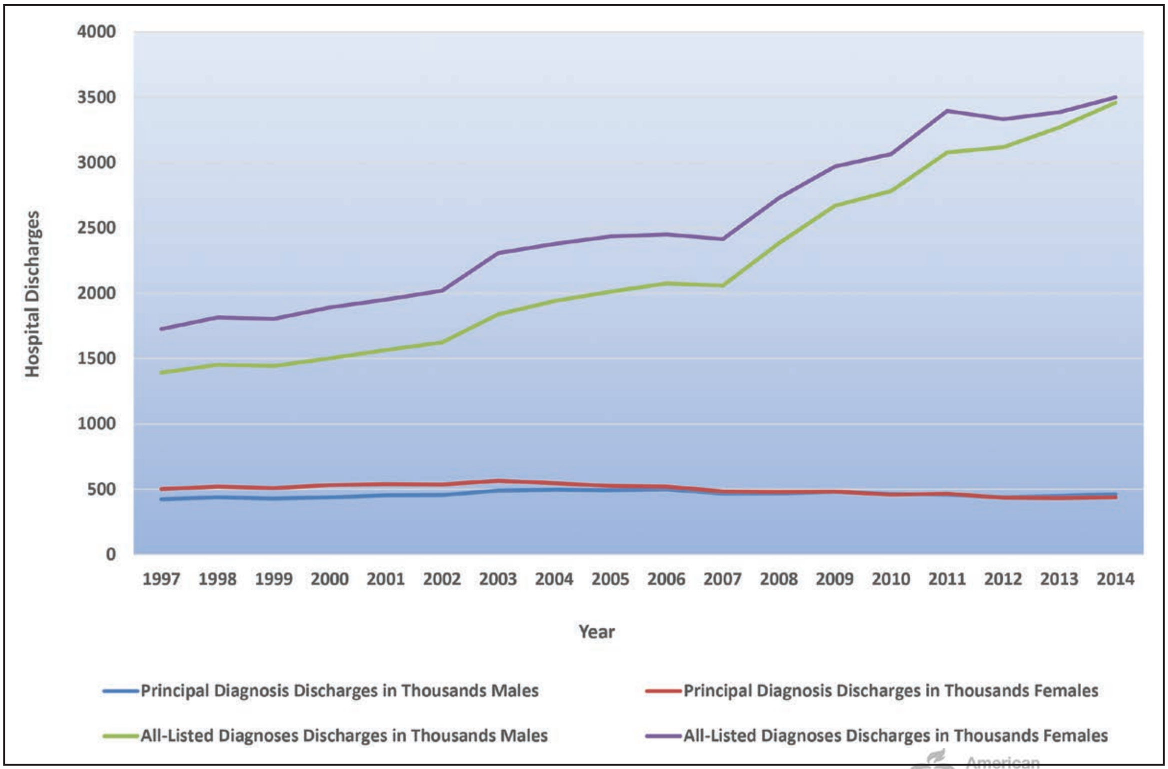

Chart 20-6. Hospital discharges for heart failure by sex (United States, 1997–2014).
Hospital discharges include people discharged alive, dead, and status unknown.
Source: National Hospital Discharge Survey/National Center for Health Statistics and National Heart, Lung, and Blood Institute.

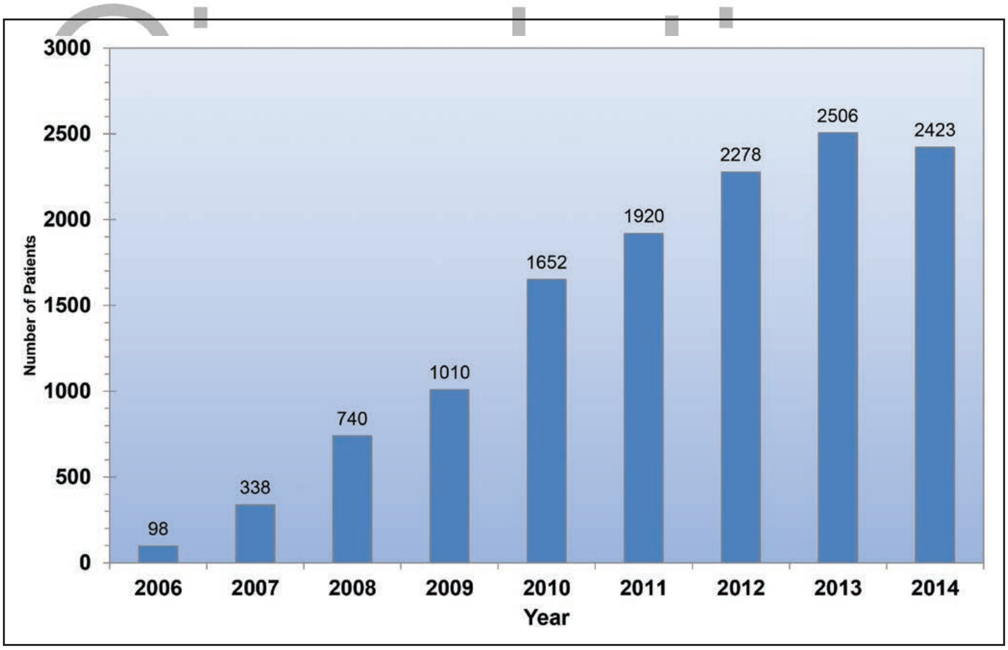

Chart 20-7. Number of patients receiving left ventricular assist devices in the United States, 2006 to 2014.
Adapted from Kirklin et al.[72] with permission from the International Society for Heart and Lung Transplantation. Copyright © 2015, International Society for Heart and Lung Transplantation.

REFERENCES

1. Bick AG, Flannick J, Ito K, Cheng S, Vasan RS, Parfenov MG, Herman DS, DePalma SR, Gupta N, Gabriel SB, Funke BH, Rehm HL, Benjamin EJ, Aragam J, Taylor HA Jr, Fox ER, Newton-Cheh C, Kathiresan S, O'Donnell CJ, Wilson JG, Altshuler DM, Hirschhorn JN, Seidman JG, Seidman C. Burden of rare sarcomere gene variants in the Framingham and Jackson Heart Study cohorts. *Am J Hum Genet*. 2012;91:513–519. doi: 10.1016/j.ajhg.2012.07.017
2. Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, Cirino AL, Fox JC, Lakdawala NK, Ware JS, Caleshu CA, Helms AS, Colan SD, Girolami F, Cecchi F, Seidman CE, Sajeev G, Signorovitch J, Green EM, Olivotto I. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). *Circulation*. 2018;138:1387–1398. doi: 10.1161/CIRCULATIONAHA.117.003200
3. Givertz MM, Mann DL. Epidemiology and natural history of recovery of left ventricular function in recent onset dilated cardiomyopathies. *Curr Heart Fail Rep*. 2013;10:321–330. doi: 10.1007/s11897-013-0157-5
4. Dec GW, Fuster V. Idiopathic dilated cardiomyopathy. *N Engl J Med*. 1994;331:1564–1575. doi: 10.1056/NEJM199412083312307
5. Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, Ahn C, Jain D, Gass A, Ahmed A, Panza JA, Fonarow GC. Temporal trends in incidence and outcomes of peripartum cardiomyopathy in the United States: a nationwide population-based study. *J Am Heart Assoc*. 2014;3:e001056. doi: 10.1161/JAHA.114.001056
6. McNamara DM, Elkayam U, Alharethi R, Damp J, Hsich E, Ewald G, Modi K, Alexis JD, Ramani GV, Semigran MJ, Haythe J, Markham DW, Marek J, Gorcsan J 3rd, Wu WC, Lin Y, Halder I, Pisarcik J, Cooper LT, Fett JD; IPAC Investigators. Clinical outcomes for peripartum cardiomyopathy in North America: results of the IPAC study (Investigations of Pregnancy-Associated Cardiomyopathy). *J Am Coll Cardiol*. 2015;66:905–914. doi: 10.1016/j.jacc.2015.06.1309
7. Wilkinson JD, Landy DC, Colan SD, Towbin JA, Sleeper LA, Orav EJ, Cox GF, Canter CE, Hsu DT, Webber SA, Lipshultz SE. The pediatric cardiomyopathy registry and heart failure: key results from the first 15 years. *Heart Fail Clin*. 2010;6:401–13, vii. doi: 10.1016/j.hfc.2010.05.002
8. Colan SD, Lipshultz SE, Lowe AM, Sleeper LA, Messere J, Cox GF, Lurie PR, Orav EJ, Towbin JA. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. *Circulation*. 2007;115:773–781. doi: 10.1161/CIRCULATIONAHA.106.621185
9. Ziółkowska L, Turska-Kmieć A, Petryka J, Kawalec W. Predictors of long-term outcome in children with hypertrophic cardiomyopathy. *Pediatr Cardiol*. 2016;37:448–458. doi: 10.1007/s00246-015-1298-y
10. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, Messere J, Cox GF, Lurie PR, Hsu D, Canter C, Wilkinson JD, Lipshultz SE. Incidence, causes, and outcomes of dilated cardiomyopathy in children. *JAMA*. 2006;296:1867–1876. doi: 10.1001/jama.296.15.1867
11. Pahl E, Sleeper LA, Canter CE, Hsu DT, Lu M, Webber SA, Colan SD, Kantor PF, Everitt MD, Towbin JA, Jefferies JL, Kaufman BD, Wilkinson JD, Lipshultz SE; Pediatric Cardiomyopathy Registry Investigators. Incidence of and risk factors for sudden cardiac death in children with dilated cardiomyopathy: a report from the Pediatric Cardiomyopathy Registry. *J Am Coll Cardiol*. 2012;59:607–615. doi: 10.1016/j.jacc.2011.10.878
12. Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, Donaldson SS, Green DM, Sklar CA, Robison LL, Leisenring WM. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ*. 2009;339:b4606. doi: 10.1136/bmj.b4606
13. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basáñez MG, Baxter A, Bell ML, Benjamin EJ, Bennett D, Bernabé E, Bhalla K, Bhandari B, Bikbov B, Bin Abdulhak A, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bolliger I, Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F, Chen H, Cheng AT, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahiya M, Dahodwala N, Damsere-Derry J, Danaei G, Davis A, De Leo D, Degenhardt L, Dellavalle R, Delossantos A, Denenberg J, Derrett S, Des Jarlais DC, Dharmaratne SD, Dherani M, Diaz-Torne C, Dolk H, Dorsey ER, Driscoll T, Duber H, Ebel B, Edmond K, Elbaz A, Ali SE, Erskine H, Erwin PJ, Espindola P, Ewoigbokhan SE, Farzadfar F, Feigin V, Felson DT, Ferrari A, Ferri CP, Fèvre EM, Finucane MM, Flaxman S, Flood L, Foreman K, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabbe BJ, Gabriel SE, Gakidou E, Ganatra HA, Garcia B, Gaspari F, Gillum RF, Gmel G, Gosselin R, Grainger R, Groeger J, Guillemin F, Gunnell D, Gupta R, Haagsma J, Hagan H, Halasa YA, Hall W, Haring D, Haro JM, Harrison JE, Havmoeller R, Hay RJ, Higashi H, Hill C, Hoen B, Hoffman H, Hotez PJ, Hoy D, Huang JJ, Ibeanusi SE, Jacobsen KH, James SL, Jarvis D, Jasrasaria R, Jayaraman S, Johns N, Jonas JB, Karthikeyan G, Kassebaum N, Kawakami N, Keren A, Khoo JP, King CH, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lalloo R, Laslett LL, Lathlean T, Leasher JL, Lee YY, Leigh J, Lim SS, Limb E, Lin JK, Lipnick M, Lipshultz SE, Liu W, Loane M, Ohno SL, Lyons R, Ma J, Mabweijano J, MacIntyre MF, Malekzadeh R, Mallinger L, Manivannan S, Marcenes W, March L, Margolis DJ, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGill N, McGrath J, Medina-Mora ME, Meltzer M, Mensah GA, Merriman TR, Meyer AC, Miglioli V, Miller M, Miller TR, Mitchell PB, Mocumbi AO, Moffitt TE, Mokdad AA, Monasta L, Montico M, Moradi-Lakeh M, Moran A, Morawska L, Mori R, Murdoch ME, Mwaniki MK, Naidoo K, Nair MN, Naldi L, Narayan KM, Nelson PK, Nelson RG, Nevitt MC, Newton CR, Nolte S, Norman P, Norman R, O'Donnell M, O'Hanlon S, Olives C, Omer SB, Ortblad K, Osborne R, Ozgediz D, Page A, Pahari B, Pandian JD, Rivero AP, Patten SB, Pearce N, Padilla RP, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Phillips MR, Pierce K, Pion S, Polanczyk GV, Polinder S, Pope CA 3rd, Popova S, Porrini E, Pourmalek F, Prince M, Pullan RL, Ramaiah KD, Ranganathan D, Razavi H, Regan M, Rehm JT, Rein DB, Remuzzi G, Richardson K, Rivara FP, Roberts T, Robinson C, De Leòn FR, Ronfani L, Room R, Rosenfeld LC, Rushton L, Sacco RL, Saha S, Sampson U, Sanchez-Riera L, Sanman E, Schwebel DC, Scott JG, Segui-Gomez M, Shahraz S, Shepard DS, Shin H, Shivakoti R, Singh D, Singh GM, Singh JA, Singleton J, Sleet DA, Sliwa K, Smith E, Smith JL, Stapelberg NJ, Steer A, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Syed S, Tamburlini G, Tavakkoli M, Taylor HR, Taylor JA, Taylor WJ, Thomas B, Thomson WM, Thurston GD, Tleyjeh IM, Tonelli M, Towbin JA, Truelsen T, Tsilimbaris MK, Ubeda C, Undurraga EA, van der Werf MJ, van Os J, Vavilala MS, Venketasubramanian N, Wang M, Wang W, Watt K, Weatherall DJ, Weinstock MA, Weintraub R, Weisskopf MG, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams SR, Witt E, Wolfe F, Woolf AD, Wulf S, Yeh PH, Zaidi AK, Zheng ZJ, Zonies D, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010 [published correction appears in *Lancet*. 2013;381:628]. *Lancet*. 2012;380:2163–2196. doi: 10.1016/S0140-6736(12)61729-2
14. Global Burden of Disease Study 2016. Global Burden of Disease Study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed May 1, 2018.
15. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Piña IL, Trogdon JG; on behalf of the American Heart Association Advocacy Coordinating Committee; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Stroke Council. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail*. 2013;6:606–619. doi: 10.1161/HHF.0b013e318291329a
16. Huffman MD, Berry JD, Ning H, Dyer AR, Garside DB, Cai X, Daviglus ML, Lloyd-Jones DM. Lifetime risk for heart failure among white and black Americans: cardiovascular lifetime risk pooling project. *J Am Coll Cardiol*. 2013;61:1510–1517. doi: 10.1016/j.jacc.2013.01.022
17. Barker WH, Mullooly JP, Getchell W. Changing incidence and survival for heart failure in a well-defined older population, 1970-1974 and 1990-1994. *Circulation*. 2006;113:799–805. doi: 10.1161/CIRCULATIONAHA.104.492033
18. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, Killian JM, Roger VL. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med*. 2015;175:996–1004. doi: 10.1001/jamainternmed.2015.0924
19. Bibbins-Domingo K, Pletcher MJ, Lin F, Vittinghoff E, Gardin JM, Arynchyn A, Lewis CE, Williams OD, Hulley SB. Racial differences in incident heart

failure among young adults. *N Engl J Med*. 2009;360:1179–1190. doi: 10.1056/NEJMoa0807265
20. Chang PP, Wruck LM, Shahar E, Rossi JS, Loehr LR, Russell SD, Agarwal SK, Konety SH, Rodriguez CJ, Rosamond WD. Trends in hospitalizations and survival of acute decompensated heart failure in four US communities (2005–2014): the Atherosclerosis Risk in Communities (ARIC) study community surveillance. *Circulation*. 2018;138:12–24. doi: 10.1161/CIRCULATIONAHA.117.027551
21. Bahrami H, Kronmal R, Bluemke DA, Olson J, Shea S, Liu K, Burke GL, Lima JA. Differences in the incidence of congestive heart failure by ethnicity: the Multi-Ethnic Study of Atherosclerosis. *Arch Intern Med*. 2008;168:2138–2145. doi: 10.1001/archinte.168.19.2138
22. Kovell LC, Juraschek SP, Russell SD. Stage A heart failure is not adequately recognized in US adults: analysis of the National Health and Nutrition Examination Surveys, 2007-2010. *PLoS One*. 2015;10:e0132228. doi: 10.1371/journal.pone.0132228
23. Dunlay SM, Weston SA, Jacobsen SJ, Roger VL. Risk factors for heart failure: a population-based case-control study. *Am J Med*. 2009;122:1023–1028. doi: 10.1016/j.amjmed.2009.04.022
24. Kalogeropoulos A, Georgiopoulou V, Kritchevsky SB, Psaty BM, Smith NL, Newman AB, Rodondi N, Satterfield S, Bauer DC, Bibbins-Domingo K, Smith AL, Wilson PW, Vasan RS, Harris TB, Butler J. Epidemiology of incident heart failure in a contemporary elderly cohort: the Health, Aging, and Body Composition Study. *Arch Intern Med*. 2009;169:708–715. doi: 10.1001/archinternmed.2009.40
25. Vivo RP, Krim SR, Cevik C, Witteles RM. Heart failure in Hispanics. *J Am Coll Cardiol*. 2009;53:1167–1175. doi: 10.1016/j.jacc.2008.12.037
26. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, Hernandez AF, Fonarow GC; for the Get With the Guidelines Scientific Advisory Committee and Investigators. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation*. 2012;126:65–75. doi: 10.1161/CIRCULATIONAHA.111.080770
26a. Djousse L, Driver JA, Gaziano JM. Relation between modifiable lifestyle factors and lifetime risk of heart failure: The Physicians' Health Study I. *JAMA*. 2009;302:394–400. doi: 10.1001/jama.2009.1062
27. Folsom AR, Shah AM, Lutsey PL, Roetker NS, Alonso A, Avery CL, Miedema MD, Konety S, Chang PP, Solomon SD. American Heart Association's Life's Simple 7: avoiding heart failure and preserving cardiac structure and function. *Am J Med*. 2015;128:970–6.e2. doi: 10.1016/j.amjmed.2015.03.027
28. Dhingra R, Gona P, Wang TJ, Fox CS, D'Agostino RB Sr, Vasan RS. Serum gamma-glutamyl transferase and risk of heart failure in the community. *Arterioscler Thromb Vasc Biol*. 2010;30:1855–1860. doi: 10.1161/ATVBAHA.110.207340
29. Coglianese EE, Qureshi MM, Vasan RS, Wang TJ, Moore LL. Usefulness of the blood hematocrit level to predict development of heart failure in a community. *Am J Cardiol*. 2012;109:241–245. doi: 10.1016/j.amjcard.2011.08.037
30. Velagaleti RS, Gona P, Larson MG, Wang TJ, Levy D, Benjamin EJ, Selhub J, Jacques PF, Meigs JB, Tofler GH, Vasan RS. Multimarker approach for the prediction of heart failure incidence in the community. *Circulation*. 2010;122:1700–1706. doi: 10.1161/CIRCULATIONAHA.109.929661
31. Frankel DS, Vasan RS, D'Agostino RB Sr, Benjamin EJ, Levy D, Wang TJ, Meigs JB. Resistin, adiponectin, and risk of heart failure the Framingham offspring study. *J Am Coll Cardiol*. 2009;53:754–762. doi: 10.1016/j.jacc.2008.07.073
32. Djoussé L, Wilk JB, Hanson NQ, Glynn RJ, Tsai MY, Gaziano JM. Association between adiponectin and heart failure risk in the Physicians' Health Study. *Obesity (Silver Spring)*. 2013;21:831–834. doi: 10.1002/oby.20260
33. Gopal DM, Kalogeropoulos AP, Georgiopoulou VV, Tang WW, Methvin A, Smith AL, Bauer DC, Newman AB, Kim L, Harris TB, Kritchevsky SB, Butler J; Health ABC Study. Serum albumin concentration and heart failure risk: the Health, Aging, and Body Composition Study. *Am Heart J*. 2010;160:279–285. doi: 10.1016/j.ahj.2010.05.022
34. Gopal DM, Kalogeropoulos AP, Georgiopoulou VV, Smith AL, Bauer DC, Newman AB, Kim L, Bibbins-Domingo K, Tindle H, Harris TB, Tang WW, Kritchevsky SB, Butler J. Cigarette smoking exposure and heart failure risk in older adults: the Health, Aging, and Body Composition Study. *Am Heart J*. 2012;164:236–242. doi: 10.1016/j.ahj.2012.05.013
35. Kalogeropoulos A, Georgiopoulou V, Psaty BM, Rodondi N, Smith AL, Harrison DG, Liu Y, Hoffmann U, Bauer DC, Newman AB, Kritchevsky SB, Harris TB, Butler J; Health ABC Study Investigators. Inflammatory markers and incident heart failure risk in older adults: the Health ABC (Health, Aging, and Body Composition) study. *J Am Coll Cardiol*. 2010;55:2129–2137. doi: 10.1016/j.jacc.2009.12.045
36. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, Seliger SL. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA*. 2010;304:2494–2502. doi: 10.1001/jama.2010.1708
37. Mozaffarian D, Lemaitre RN, King IB, Song X, Spiegelman D, Sacks FM, Rimm EB, Siscovick DS. Circulating long-chain ω-3 fatty acids and incidence of congestive heart failure in older adults: the cardiovascular health study: a cohort study. *Ann Intern Med*. 2011;155:160–170. doi: 10.7326/0003-4819-155-3-201108020-00006
38. Agarwal SK, Simpson RJ Jr, Rautaharju P, Alonso A, Shahar E, Massing M, Saba S, Heiss G. Relation of ventricular premature complexes to heart failure (from the Atherosclerosis Risk In Communities [ARIC] Study). *Am J Cardiol*. 2012;109:105–109. doi: 10.1016/j.amjcard.2011.08.009
39. Bekwelem W, Lutsey PL, Loehr LR, Agarwal SK, Astor BC, Guild C, Ballantyne CM, Folsom AR. White blood cell count, C-reactive protein, and incident heart failure in the Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol*. 2011;21:739–748. doi: 10.1016/j.annepidem.2011.06.005
40. Blecker S, Matsushita K, Köttgen A, Loehr LR, Bertoni AG, Boulware LE, Coresh J. High-normal albuminuria and risk of heart failure in the community. *Am J Kidney Dis*. 2011;58:47–55. doi: 10.1053/j.ajkd.2011.02.391
41. Matsushita K, Blecker S, Pazin-Filho A, Bertoni A, Chang PP, Coresh J, Selvin E. The association of hemoglobin A1C with incident heart failure among people without diabetes: the Atherosclerosis Risk in Communities study. *Diabetes*. 2010;59:2020–2026. doi: 10.2337/db10-0165
42. Roberts CB, Couper DJ, Chang PP, James SA, Rosamond WD, Heiss G. Influence of life-course socioeconomic position on incident heart failure in blacks and whites: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 2010;172:717–727. doi: 10.1093/aje/kwq193
43. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, Hoogeveen RC, Liu X, Astor BC, Mosley TH, Folsom AR, Heiss G, Coresh J, Ballantyne CM. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation*. 2011;123:1367–1376. doi: 10.1161/CIRCULATIONAHA.110.005264
44. Choi EY, Bahrami H, Wu CO, Greenland P, Cushman M, Daniels LB, Almeida AL, Yoneyama K, Opdahl A, Jain A, Criqui MH, Siscovick D, Darwin C, Maisel A, Bluemke DA, Lima JA. N-terminal pro-B-type natriuretic peptide, left ventricular mass, and incident heart failure: Multi-Ethnic Study of Atherosclerosis. *Circ Heart Fail*. 2012;5:727–734. doi: 10.1161/CIRCHEARTFAILURE.112.968701
45. Lam CS, Lyass A, Kraigher-Krainer E, Massaro JM, Lee DS, Ho JE, Levy D, Redfield MM, Pieske BM, Benjamin EJ, Vasan RS. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. *Circulation*. 2011;124:24–30. doi: 10.1161/CIRCULATIONAHA.110.979203
46. Kane GC, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC Jr, Jacobsen SJ, Rodeheffer RJ. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA*. 2011;306:856–863. doi: 10.1001/jama.2011.1201
47. Yeboah J, Rodriguez CJ, Stacey B, Lima JA, Liu S, Carr JJ, Hundley WG, Herrington DM. Prognosis of individuals with asymptomatic left ventricular systolic dysfunction in the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2012;126:2713–2719. doi: 10.1161/CIRCULATIONAHA.112.112201
48. Mehta H, Armstrong A, Swett K, Shah SJ, Allison MA, Hurwitz B, Bangdiwala S, Dadhania R, Kitzman DW, Arguelles W, Lima J, Youngblood M, Schneiderman N, Daviglus ML, Spevack D, Talavera GA, Raisinghani A, Kaplan R, Rodriguez CJ. Burden of systolic and diastolic left ventricular dysfunction among Hispanics in the United States: insights from the Echocardiographic Study of Latinos. *Circ Heart Fail*. 2016;9:e002733. doi: 10.1161/CIRCHEARTFAILURE.115.002733
49. Vasan RS, Xanthakis V, Lyass A, Andersson C, Tsao C, Cheng S, Aragam J, Benjamin EJ, Larson MG. Epidemiology of left ventricular systolic dysfunction and heart failure in the Framingham Study: an echocardiographic study over 3 decades. *JACC Cardiovasc Imaging*. 2018;11:1–11. doi: 10.1016/j.jcmg.2017.08.007
50. Centers for Disease Control and Prevention, National Center for Health Statistics website. 2010 National Ambulatory Medical Care Survey and 2010 National Hospital Ambulatory Medical Care Survey. For methodology, see National Center for Health Statistics, Public Use Data File Documentation: 2010 National Ambulatory Medical Care Survey and Public Use Data File Documentation: 2010 National Hospital Ambulatory

Medical Care Survey. http://www.cdc.gov/nchs/ahcd/ahcd_questionnaires.htm. Accessed July 17, 2013.
51. Centers for Disease Control and Prevention website. National Ambulatory Medical Care Survey: 2015 State and National Summary Tables. https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2015_namcs_web_tables.pdf. Accessed June 14, 2018.
52. Centers for Disease Control and Prevention website. National Hospital Ambulatory Medical Care Survey: 2015 Emergency Department Summary Tables. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2015_ed_web_tables.pdf. Accessed June 14, 2018.
53. Dunlay SM, Redfield MM, Weston SA, Therneau TM, Hall Long K, Shah ND, Roger VL. Hospitalizations after heart failure diagnosis: a community perspective. *J Am Coll Cardiol*. 2009;54:1695–1702. doi: 10.1016/j.jacc.2009.08.019
54. van den Broek KC, Defilippi CR, Christenson RH, Seliger SL, Gottdiener JS, Kop WJ. Predictive value of depressive symptoms and B-type natriuretic peptide for new-onset heart failure and mortality. *Am J Cardiol*. 2011;107:723–729. doi: 10.1016/j.amjcard.2010.10.055
55. Golwala H, Pandey A, Ju C, Butler J, Yancy C, Bhatt DL, Hernandez AF, Fonarow GC. Temporal trends and factors associated with cardiac rehabilitation referral among patients hospitalized with heart failure: findings from Get With The Guidelines-Heart Failure Registry. *J Am Coll Cardiol*. 2015;66:917–926. doi: 10.1016/j.jacc.2015.06.1089
56. Sueta CA, Rodgers JE, Chang PP, Zhou L, Thudium EM, Kucharska-Newton AM, Stearns SC. Medication adherence based on part D claims for patients with heart failure after hospitalization (from the Atherosclerosis Risk in Communities Study). *Am J Cardiol*. 2015;116:413–419. doi: 10.1016/j.amjcard.2015.04.058
57. Bello NA, Claggett B, Desai AS, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Pfeffer MA, Solomon SD. Influence of previous heart failure hospitalization on cardiovascular events in patients with reduced and preserved ejection fraction. *Circ Heart Fail*. 2014;7:590–595. doi: 10.1161/CIRCHEARTFAILURE.113.001281
58. Vivo RP, Krim SR, Krim NR, Zhao X, Hernandez AF, Peterson ED, Piña IL, Bhatt DL, Schwamm LH, Fonarow GC. Care and outcomes of Hispanic patients admitted with heart failure with preserved or reduced ejection fraction: findings from Get With The Guidelines-Heart Failure. *Circ Heart Fail*. 2012;5:167–175. doi: 10.1161/CIRCHEARTFAILURE.111.963546
59. Chang PP, Chambless LE, Shahar E, Bertoni AG, Russell SD, Ni H, He M, Mosley TH, Wagenknecht LE, Samdarshi TE, Wruck LM, Rosamond WD. Incidence and survival of hospitalized acute decompensated heart failure in four US communities (from the Atherosclerosis Risk in Communities Study). *Am J Cardiol*. 2014;113:504–510. doi: 10.1016/j.amjcard.2013.10.032
60. Dupre ME, Curtis LH, Peterson ED. Racial and ethnic differences in trajectories of hospitalizations in US men and women with heart failure. *J Am Heart Assoc*. 6e006290:1–11. doi: 10.1161/jaha.117.006290
61. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005–1011. doi: 10.1016/S0140-6736(06)69208-8
61a. Chen J, Normand S-LT, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998–2008. *JAMA*. 2011;306:1669–1678. doi: 10.1001/jama.2011.1474
62. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol*. 2008;101:1016–1022. doi: 10.1016/j.amjcard.2007.11.061
63. Merlo M, Pivetta A, Pinamonti B, Stolfo D, Zecchin M, Barbati G, Di Lenarda A, Sinagra G. Long-term prognostic impact of therapeutic strategies in patients with idiopathic dilated cardiomyopathy: changing mortality over the last 30 years. *Eur J Heart Fail*. 2014;16:317–324. doi: 10.1002/ejhf.16
64. Allen LA, Fonarow GC, Liang L, Schulte PJ, Masoudi FA, Rumsfeld JS, Ho PM, Eapen ZJ, Hernandez AF, Heidenreich PA, Bhatt DL, Peterson ED, Krumholz HM; on behalf of the American Heart Association's Get With The Guidelines Heart Failure (GWTG-HF) Investigators. Medication initiation burden required to comply with heart failure guideline recommendations and hospital quality measures. *Circulation*. 2015;132:1347–1353. doi: 10.1161/CIRCULATIONAHA.115.014281
65. Alehagen U, Benson L, Edner M, Dahlström U, Lund LH. Association between use of statins and mortality in patients with heart failure and ejection fraction of ≥50. *Circ Heart Fail*. 2015;8:862–870. doi: 10.1161/CIRCHEARTFAILURE.115.002143
66. Gerber Y, Weston SA, Enriquez-Sarano M, Berardi C, Chamberlain AM, Manemann SM, Jiang R, Dunlay SM, Roger VL. Mortality associated with heart failure after myocardial infarction: a contemporary community perspective. *Circ Heart Fail*. 2016;9:e002460. doi: 10.1161/CIRCHEARTFAILURE.115.002460
67. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. *JAMA*. 2004;292:344–350. doi: 10.1001/jama.292.3.344
68. National Center for Health Statistics. Centers for Disease Control and Prevention website. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2016. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed May 21, 2018.
69. Bilchick KC, Stukenborg GJ, Kamath S, Cheng A. Prediction of mortality in clinical practice for Medicare patients undergoing defibrillator implantation for primary prevention of sudden cardiac death. *J Am Coll Cardiol*. 2012;60:1647–1655. doi: 10.1016/j.jacc.2012.07.028
70. Heidenreich PA, Tsai V, Curtis J, Wang Y, Turakhia MP, Masoudi FA, Varosy PD, Goldstein MK. A validated risk model for 1-year mortality after primary prevention implantable cardioverter defibrillator placement. *Am Heart J*. 2015;170:281–289.e2. doi: 10.1016/j.ahj.2014.12.013
71. Nandi D, Rossano JW. Epidemiology and cost of heart failure in children. *Cardiol Young*. 2015;25:1460–1468. doi: 10.1017/S1047951115002280
72. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, Miller MA, Baldwin JT, Young JB. Seventh INTERMACS annual report: 15,000 patients and counting. *J Heart Lung Transplant*. 2015;34:1495–1504. doi: 10.1016/j.healun.2015.10.003
73. Shah N, Agarwal V, Patel N, Deshmukh A, Chothani A, Garg J, Badheka A, Martinez M, Islam N, Freudenberger R. National trends in utilization, mortality, complications, and cost of care after left ventricular assist device implantation from 2005 to 2011. *Ann Thorac Surg*. 2016;101:1477–1484. doi: 10.1016/j.athoracsur.2015.09.013
74. Khazanie P, Hammill BG, Patel CB, Eapen ZJ, Peterson ED, Rogers JG, Milano CA, Curtis LH, Hernandez AF. Trends in the use and outcomes of ventricular assist devices among Medicare beneficiaries, 2006 through 2011. *J Am Coll Cardiol*. 2014;63:1395–1404. doi: 10.1016/j.jacc.2013.12.020
75. Miller LW, Guglin M, Rogers J. Cost of ventricular assist devices: can we afford the progress? *Circulation*. 2013;127:743–748. doi: 10.1161/CIRCULATIONAHA.112.139824
76. Theochari CA, Michalopoulos G, Oikonomou EK, Giannopoulos S, Doulamis IP, Villela MA, Kokkinidis DG. Heart transplantation versus left ventricular assist devices as destination therapy or bridge to transplantation for 1-year mortality: a systematic review and meta-analysis. *Ann Cardiothorac Surg*. 2018;7:3–11. doi: 10.21037/acs.2017.09.18
77. Alba AC, Alba LF, Delgado DH, Rao V, Ross HJ, Goeree R. Cost-effectiveness of ventricular assist device therapy as a bridge to transplantation compared with nonbridged cardiac recipients. *Circulation*. 2013;127:2424–2435. doi: 10.1161/CIRCULATIONAHA.112.000194
78. Marasco SF, Summerhayes R, Quayle M, McGiffin D, Luthe M. Cost comparison of heart transplant vs. left ventricular assist device therapy at one year. *Clin Transplant*. 2016;30:598–605. doi: 10.1111/ctr.12725
79. Kilic A, Higgins RS, Whitson BA, Kilic A. Racial disparities in outcomes of adult heart transplantation. *Circulation*. 2015;131:882–889. doi: 10.1161/CIRCULATIONAHA.114.011676
80. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. *Nat Rev Cardiol*. 2013;10:531–547. doi: 10.1038/nrcardio.2013.105
81. Hershberger RE, Siegfried JD. Update 2011: clinical and genetic issues in familial dilated cardiomyopathy. *J Am Coll Cardiol*. 2011;57:1641–1649. doi: 10.1016/j.jacc.2011.01.015
82. Page SP, Kounas S, Syrris P, Christiansen M, Frank-Hansen R, Andersen PS, Elliott PM, McKenna WJ. Cardiac myosin binding protein-C mutations in families with hypertrophic cardiomyopathy: disease expression in relation to age, gender, and long term outcome. *Circ Cardiovasc Genet*. 2012;5:156–166. doi: 10.1161/CIRCGENETICS.111.960831
83. Marian AJ, Yu QT, Mares A Jr, Hill R, Roberts R, Perryman MB. Detection of a new mutation in the beta-myosin heavy chain gene in an individual with hypertrophic cardiomyopathy. *J Clin Invest*. 1992;90:2156–2165. doi: 10.1172/JCI116101
84. Perryman MB, Yu QT, Marian AJ, Mares A Jr, Czernuszewicz G, Ifegwu J, Hill R, Roberts R. Expression of a missense mutation in the messenger RNA for beta-myosin heavy chain in myocardial tissue in hypertrophic cardiomyopathy. *J Clin Invest*. 1992;90:271–277. doi: 10.1172/JCI115848

85. Cahill TJ, Ashrafian H, Watkins H. Genetic cardiomyopathies causing heart failure. *Circ Res*. 2013;113:660–675. doi: 10.1161/CIRCRESAHA.113.300282
86. Tayal U, Prasad S, Cook SA. Genetics and genomics of dilated cardiomyopathy and systolic heart failure. *Genome Med*. 2017;9:20. doi: 10.1186/s13073-017-0410-8
87. Hastings R, de Villiers CP, Hooper C, Ormondroyd L, Pagnamenta A, Lise S, Salatino S, Knight SJ, Taylor JC, Thomson KL, Arnold L, Chatziefthimiou SD, Konarev PV, Wilmanns M, Ehler E, Ghisleni A, Gautel M, Blair E, Watkins H, Gehmlich K. Combination of whole genome sequencing, linkage, and functional studies implicates a missense mutation in titin as a cause of autosomal dominant cardiomyopathy with features of left ventricular noncompaction. *Circ Cardiovasc Genet*. 2016;9:426–435. doi: 10.1161/CIRCGENETICS.116.001431
88. Walsh R, Thomson KL, Ware JS, Funke BH, Woodley J, McGuire KJ, Mazzarotto F, Blair E, Seller A, Taylor JC, Minikel EV, Exome Aggregation Consortium, MacArthur DG, Farrall M, Cook SA, Watkins H. Reassessment of Mendelian gene pathogenicity using 7,855 cardiomyopathy cases and 60,706 reference samples. *Genet Med*. 2017;19:192–203. doi: 10.1038/gim.2016.90
89. Cappola TP, Li M, He J, Ky B, Gilmore J, Qu L, Keating B, Reilly M, Kim CE, Glessner J, Frackelton E, Hakonarson H, Syed F, Hindes A, Matkovich SJ, Cresci S, Dorn GW 2nd. Common variants in HSPB7 and FRMD4B associated with advanced heart failure. *Circ Cardiovasc Genet*. 2010;3:147–154. doi: 10.1161/CIRCGENETICS.109.898395
90. Matkovich SJ, Van Booven DJ, Hindes A, Kang MY, Druley TE, Vallania FL, Mitra RD, Reilly MP, Cappola TP, Dorn GW 2nd. Cardiac signaling genes exhibit unexpected sequence diversity in sporadic cardiomyopathy, revealing HSPB7 polymorphisms associated with disease. *J Clin Invest*. 2010;120:280–289. doi: 10.1172/JCI39085
91. Stark K, Esslinger UB, Reinhard W, Petrov G, Winkler T, Komajda M, Isnard R, Charron P, Villard E, Cambien F, Tiret L, Aumont MC, Dubourg O, Trochu JN, Fauchier L, Degroote P, Richter A, Maisch B, Wichter T, Zollbrecht C, Grassl M, Schunkert H, Linsel-Nitschke P, Erdmann J, Baumert J, Illig T, Klopp N, Wichmann HE, Meisinger C, Koenig W, Lichtner P, Meitinger T, Schillert A, König IR, Hetzer R, Heid IM, Regitz-Zagrosek V, Hengstenberg C. Genetic association study identifies HSPB7 as a risk gene for idiopathic dilated cardiomyopathy. *PLoS Genet*. 2010;6:e1001167. doi: 10.1371/journal.pgen.1001167
92. Xu H, Dorn Ii GW, Shetty A, Parihar A, Dave T, Robinson SW, Gottlieb SS, Donahue MP, Tomaselli GF, Kraus WE, Mitchell BD, Liggett SB. A genome-wide association study of idiopathic dilated cardiomyopathy in African Americans. *J Pers Med*. 2018;8:E11. doi: 10.3390/jpm8010011
93. Smith NL, Felix JF, Morrison AC, Demissie S, Glazer NL, Loehr LR, Cupples LA, Dehghan A, Lumley T, Rosamond WD, Lieb W, Rivadeneira F, Bis JC, Folsom AR, Benjamin E, Aulchenko YS, Haritunians T, Couper D, Murabito J, Wang YA, Stricker BH, Gottdiener JS, Chang PP, Wang TJ, Rice KM, Hofman A, Heckbert SR, Fox ER, O'Donnell CJ, Uitterlinden AG, Rotter JI, Willerson JT, Levy D, van Duijn CM, Psaty BM, Witteman JC, Boerwinkle E, Vasan RS. Association of genome-wide variation with the risk of incident heart failure in adults of European and African ancestry: a prospective meta-analysis from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium. *Circ Cardiovasc Genet*. 2010;3:256–266. doi: 10.1161/CIRCGENETICS.109.895763
94. van der Harst P, van Setten J, Verweij N, Vogler G, Franke L, Maurano MT, Wang X, Mateo Leach I, Eijgelsheim M, Sotoodehnia N, Hayward C, Sorice R, Meirelles O, Lyytikäinen LP, Polašek O, Tanaka T, Arking DE, Ulivi S, Trompet S, Müller-Nurasyid M, Smith AV, Dörr M, Kerr KF, Magnani JW, Del Greco M F, Zhang W, Nolte IM, Silva CT, Padmanabhan S, Tragante V, Esko T, Abecasis GR, Adriaens ME, Andersen K, Barnett P, Bis JC, Bodmer R, Buckley BM, Campbell H, Cannon MV, Chakravarti A, Chen LY, Delitala A, Devereux RB, Doevendans PA, Dominiczak AF, Ferrucci L, Ford I, Gieger C, Harris TB, Haugen E, Heinig M, Hernandez DG, Hillege HL, Hirschhorn JN, Hofman A, Hubner N, Hwang SJ, Iorio A, Kähönen M, Kellis M, Kolcic I, Kooner IK, Kooner JS, Kors JA, Lakatta EG, Lage K, Launer LJ, Levy D, Lundby A, Macfarlane PW, May D, Meitinger T, Metspalu A, Nappo S, Naitza S, Neph S, Nord AS, Nutile T, Okin PM, Olsen JV, Oostra BA, Penninger JM, Pennacchio LA, Pers TH, Perz S, Peters A, Pinto YM, Pfeufer A, Pilia MG, Pramstaller PP, Prins BP, Raitakari OT, Raychaudhuri S, Rice KM, Rossin EJ, Rotter JI, Schafer S, Schlessinger D, Schmidt CO, Sehmi J, Silljé HHW, Sinagra G, Sinner MF, Slowikowski K, Soliman EZ, Spector TD, Spiering W, Stamatoyannopoulos JA, Stolk RP, Strauch K, Tan ST, Tarasov KV, Trinh B, Uitterlinden AG, van den Boogaard M, van Duijn CM, van Gilst WH, Viikari JS, Visscher PM, Vitart V, Völker U, Waldenberger M, Weichenberger CX, Westra HJ, Wijmenga C, Wolffenbuttel BH, Yang J, Bezzina CR, Munroe PB, Snieder H, Wright AF, Rudan I, Boyer LA, Asselbergs FW, van Veldhuisen DJ, Stricker BH, Psaty BM, Ciullo M, Sanna S, Lehtimäki T, Wilson JF, Bandinelli S, Alonso A, Gasparini P, Jukema JW, Kääb S, Gudnason V, Felix SB, Heckbert SR, de Boer RA, Newton-Cheh C, Hicks AA, Chambers JC, Jamshidi Y, Visel A, Christoffels VM, Isaacs A, Samani NJ, de Bakker PIW. 52 genetic loci influencing myocardial mass. *J Am Coll Cardiol*. 2016;68:1435–1448. doi: 10.1016/j.jacc.2016.07.729
95. Watkins H, Ashrafian H, Redwood C. Inherited cardiomyopathies. *N Engl J Med*. 2011;364:1643–1656. doi: 10.1056/NEJMra0902923
96. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP; Heart Rhythm Society (HRS); European Heart Rhythm Association (EHRA). HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) [published correction appears in *Europace*. 2012;14:277]. *Europace*. 2011;13:1077–1109. doi: 10.1093/europace/eur245
97. Sliwa K, Wilkinson D, Hansen C, Ntyintyane L, Tibazarwa K, Becker A, Stewart S. Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. *Lancet*. 2008;371:915–922. doi: 10.1016/S0140-6736(08)60417-1
98. Damasceno A, Mayosi BM, Sani M, Ogah OS, Mondo C, Ojji D, Dzudie A, Kouam CK, Suliman A, Schrueder N, Yonga G, Ba SA, Maru F, Alemayehu B, Edwards C, Davison BA, Cotter G, Sliwa K. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries. *Arch Intern Med*. 2012;172:1386–1394. doi: 10.1001/archinternmed.2012.3310
99. Sakata Y, Shimokawa H. Epidemiology of heart failure in Asia. *Circ J*. 2013;77:2209–2217.
100. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Flaxman A, Murray CJ, Naghavi M. The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study. *Circulation*. 2014;129:1493–1501. doi: 10.1161/CIRCULATIONAHA.113.004046
101. Khatibzadeh S, Farzadfar F, Oliver J, Ezzati M, Moran A. Worldwide risk factors for heart failure: a systematic review and pooled analysis. *Int J Cardiol*. 2013;168:1186–1194. doi: 10.1016/j.ijcard.2012.11.065
102. Dokainish H, Teo K, Zhu J, Roy A, Al-Habib K, ElSayed A, Palileo L, Jaramillo PL, Karaye K, Yusoff K, Orlandini A, Sliwa K, Mondo C, Lanas F, Dorairaj P, Huffman M, Badr A, Elmaghawry M, Damasceno A, Belley-Cote E, Harkness K, Grinvalds A, McKelvie R, Yusuf S. Heart failure in low- and middle-income countries: background, rationale, and design of the INTERnational Congestive Heart Failure Study (INTER-CHF). *Am Heart J*. 2015;170:627–634.e1. doi: 10.1016/j.ahj.2015.07.008
103. Blauwet LA, Cooper LT. Diagnosis and management of peripartum cardiomyopathy. *Heart*. 2011;97:1970–1981. doi: 10.1136/heartjnl-2011-300349

21. VALVULAR DISEASES

See Tables 21-1 through 21-3 and Charts 21-1 through 21-5

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Mortality and any-mention mortality in this section are for 2016. "Mortality" is the number of deaths in 2016 for the given underlying cause based on *ICD-10*. Prevalence data are for 2006 for US cohorts and 2016 and 2017 for European cohorts. Hospital discharge data are from HCUP, NIS, 2014; data included are for inpatients discharged alive, dead, or status unknown. Hospital discharge data for 2014 are based on *ICD-9* codes.

Abbreviations Used in Chapter 21

ACC	American College of Cardiology
AF	atrial fibrillation
AGES	Age, Gene/Environment Susceptibility
AHA	American Heart Association
APAC	Asia-Pacific
ARIC	Atherosclerosis Risk in Communities Study
BMI	body mass index
CABG	coronary artery bypass graft
CAD	coronary artery disease
CALA	Caribbean and Latin America
CARDIA	Coronary Artery Risk Development in Young Adults
CER	cost-effectiveness ratio
CHS	Cardiovascular Health Study
CI	confidence interval
DALY	disability-adjusted life-year
DCM	dilated cardiomyopathy
DM	diabetes mellitus
EF	ejection fraction
EVEREST	Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan
EVEREST II HRS	Endovascular Valve Edge-to-Edge Repair High-Risk Study
FHS	Framingham Heart Study
GBD	Global Burden of Disease
GWAS	genome-wide association study
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HF	heart failure
HR	hazard ratio
ICD	*International Classification of Diseases*
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
ICE-PCS	International Collaboration on Endocarditis–Prospective Cohort Study
ICE-PLUS	International Collaboration on Endocarditis–PLUS
IE	infective endocarditis
IHD	ischemic heart disease
IQR	interquartile range
LDL-C	low-density lipoprotein cholesterol
LV	left ventricular
LVEF	left ventricular ejection fraction
MI	myocardial infarction
MR	mitral regurgitation
NCHS	National Center for Health Statistics

(*Continued*)

Abbreviations Used in Chapter 21 Continued

NH	non-Hispanic
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
OR	odds ratio
PARTNER	Placement of Aortic Transcatheter Valve
QALY	quality-adjusted life-year
REMEDY	Global Rheumatic Heart Disease Registry
RR	relative risk
RV	right ventricular
SAVR	surgical aortic valve replacement
SD	standard deviation
SNP	single-nucleotide polymorphism
STS	Society of Thoracic Surgeons
SURTAVI	Surgical Replacement and Transcatheter Aortic Valve Implantation
TA	transapical
TAVR	transcatheter aortic valve replacement
TF	transfemoral
TIA	transient ischemic attack
TOF	tetralogy of Fallot
TVT	Transcatheter Valve Therapy

Valvular Heart Disease (See Table 21-1)

ICD-9 424; *ICD-10* I34 to I38.

2016: Mortality—24 902. Any-mention mortality—51 608.

2014: Hospital discharges—105 000.

Prevalence

- A large, population-based epidemiological study with systematic use of echocardiography on 16 501 participants from Olmsted County, MN, showed an overall age-adjusted prevalence of clinically diagnosed (moderate or greater) valvular HD of 1.8%.[1]
- Prevalence of any valve disease increased with age (P_{trend}<0.0001)[1]:
  - — 18 to 44 years: 0.3% (95% CI, 0.2%–0.3%)
  - — 45 to 54 years: 0.7% (95% CI, 0.6%–0.9%)
  - — 55 to 64 years: 1.6% (95% CI, 1.4%–1.9%)
  - — 65 to 74 years: 4.4% (95% CI, 3.9%–4.9%)
  - — ≥75 years: 11.7% (95% CI, 11.0%–12.5%)
- Pooled echocardiographic data from 11 911 participants from CARDIA (4351), ARIC (2435), and CHS (5125) demonstrated a similar increase in prevalence with advancing age (P_{trend}<0.0001; Table 21-1)[1]:
  - — 18 to 44 years: 0.7% (95% CI, 0.5%–1.0%)
  - — 45 to 54 years: 0.4% (95% CI, 0.1%–1.3%)
  - — 55 to 64 years: 1.9% (95% CI, 1.2%–2.8%)
  - — 65 to 74 years: 8.5% (95% CI, 7.6%–9.4%)
  - — ≥75 years: 13.2% (95% CI, 11.7%–15.0%)
- Adjusted to the entire 2000 US adult population, these data suggest that the prevalence of any valve disease is 2.5% (95% CI, 2.2%–2.7%), with no difference between males (2.4% [95%

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CI, 2.1%–2.8%]) and females (2.5% [95% CI, 2.1%–2.9%]).[1]

- In a recent report using the Swedish nationwide register to identify all patients with a first diagnosis of valvular HD at Swedish hospitals between 2003 and 2010 (N=10 164 211), the incidence of valvular HD was 63.9 per 100 000 person-years, with aortic stenosis (47.2%), MR (24.2%), and aortic regurgitation (18.0%) contributing most of the valvular diagnoses. The majority of valvulopathies were diagnosed in the elderly (68.9% in subjects aged ≥65 years). Incidences of aortic regurgitation, aortic stenosis, and MR were higher in males, who were also more frequently diagnosed at an earlier age. Mitral stenosis incidence was higher in females.[2]
- Previously undiagnosed, predominantly mild valvular HD was found in 51% of 2500 individuals aged ≥65 years from a primary care population screened using transthoracic echocardiography. The prevalence of undiagnosed moderate or severe valvular HD was 6.4%.[3]

Aortic Valve Disorders (See Table 21-1 and Chart 21-1) *ICD-9* 424.1; *ICD-10* I35.

2016: Mortality—17 046. Any-mention mortality 34 769.

2014: Hospital discharges—77 000.

Prevalence and Incidence

- On the basis of the CARDIA, ARIC, and CHS studies, the authors estimated an age- and sex-adjusted (2000 US adult population) prevalence of 0.4% (95% CI, 0.3%–0.5%) for aortic stenosis and 0.5% (95% CI, 0.3%–0.6%) for aortic regurgitation.[1]
- The prevalence of moderate or severe calcific aortic stenosis in patients ≥75 years old is 2.8% (95% CI, 2.1%–3.7%) based on pooled echocardiographic data from US cohorts including CARDIA, ARIC, and CHS (Table 21-1).[1]
- Prevalence of aortic stenosis by echocardiography is higher (4.3%) among individuals aged ≥70 years in the Icelandic AGES-Reykjavik cohort. In the Norwegian Tromsø study, the incidence of new aortic stenosis was 5 per 1000 per year, with the initial mean age of participants being 60 years.[4]
- In younger age groups, the most prevalent cause of aortic stenosis is bicuspid aortic valve, the most common form of congenital HD. In an Italian study of 817 primary school students, the prevalence of bicuspid aortic valve was 0.5% (95% CI, 0.13%–1.2%).[5]
- Nationally representative data from Sweden demonstrate a lower age-adjusted incidence of aortic stenosis, from 15.0 to 11.4 per 100 000 males and from 9.8 to 7.1 per 100 000 females, between the years 1989 to 1991 and 2007 to 2009.[6]
- The prevalence of moderate or severe aortic regurgitation in patients ≥75 years is 2.0% (95% CI, 1.4%–2.7%) based on pooled CARDIA, ARIC, and CHS data (Table 21-1).[1]

Lifetime Risk and Cumulative Risk

- The number of elderly patients with calcific aortic stenosis is projected to more than double by 2050 in both the United States and Europe based on a simulation model in 7 decision analysis studies. In the Icelandic AGES-Reykjavik study alone, projections suggest a doubling in prevalence among those with severe aortic stenosis aged ≥70 years by 2040 and a tripling by 2060.[7]

Mortality

- On the basis of *ICD-10* (with data coded from 1999 to 2009), there were 146 304 deaths in the aortic valve disease category in the United States. Of these, 82.7% were attributed to aortic stenosis, 4.0% to aortic insufficiency, and 0.6% to aortic stenosis with insufficiency, whereas 11.9% were unspecified or coded as attributed to other aortic valve disease and 0.7% to congenital aortic valve disease (assumed to be predominantly bicuspid aortic valve). The change in annual age- and sex-adjusted mortality rate over time was 1.016 (95% CI, 1.015–1.016; $P<0.001$) for nonrheumatic aortic valve disease.[8]
- A retrospective analysis of 3 different cohorts of consecutive patients with echocardiographic diagnosis of bicuspid aortic valve included the following: (1) a community cohort of 416 patients with bicuspid aortic valve diagnosed for the first time (aged 35±21 years, follow-up 16±7 years); (2) a tertiary care cohort of 2824 adults with bicuspid aortic valve (aged 51±16 years, follow-up 9±6 years); and (3) a cohort of 2242 adults with bicuspid aortic valve referred for aortic valve replacement (aged 62±14 years, follow-up 6±5 years).[9] In the community, morbidity related to bicuspid aortic valve was higher in males than in females, with a total combined risk of aortic regurgitation, surgery, and IE of 52±4% versus 35±6% in females ($P=0.01$).[9] Nevertheless, females had a significantly higher RR of death in tertiary and surgical referral cohorts, with an age-adjusted relative death risk of 1.63 (95% CI, 1.40–1.89) for females versus 1.34 (95% CI, 1.22–1.47) for males ($P=0.026$).[9] The risk of death was independently associated with aortic regurgitation ($P\leq0.04$).

Complications

- In a cohort of 416 community-based participants from Olmsted County, MN with bicuspid aortic valve followed up for a mean (SD) of 16 (7) years, the incidence of aortic dissection in individuals ≥50 years of age at baseline was 17.4 (95% CI, 2.9–53.6) cases per 10 000 patient-years. For patients aged ≥50 years with a bicuspid valve and a baseline aortic aneurysm, the incidence of aortic dissection was 44.9 (95% CI, 7.5–138.5) cases per 10 000 patient-years. In the remaining participants without baseline aortic aneurysm, the incidence of aneurysm was 84.9 (95% CI, 63.3–110.9) cases per 10 000 patient-years, for an age-adjusted RR of 86.2 (95% CI, 65.1–114) compared with the general population.[10]

Risk Factors

- Several prospective and retrospective series have attempted to identify risk factors for progression of aortic stenosis.[11–15] Among the highlighted factors were baseline valve area, degree of valve calcification, CAD, older age, male sex, bicuspid versus tricuspid involvement, mitral annular calcification, hypercholesterolemia, higher BMI, renal insufficiency, hypercalcemia, smoking, metabolic syndrome, and DM.[16–18]
- In a retrospective analysis of predictors of cardiac outcomes in 227 ambulatory adults with bicuspid aortic valve, independent predictors of the composite end point (need for surgery, death, aortic dissection, endocarditis, HF, arrhythmias, or IHD) were baseline moderate to severe aortic valve dysfunction (HR, 3.19 [95% CI, 1.35–7.54]; *P*<0.01) and aortic valve leaflet calcification (HR, 4.72 [95% CI, 1.91–11.64]; *P*<0.005).[19]

Genetics and Family History

- A GWAS in 6942 individuals identified an SNP located in an intron of the lipoprotein(a) gene that was significantly associated with the presence of aortic calcification (OR per allele, 2.05), circulating lipoprotein(a) levels, and the development of aortic stenosis.[20]
- Multiple SNPs that encode for LDL-C have been combined to form a genetic risk score that has been associated with prevalent aortic valve calcification (OR, 1.38 [95% CI, 1.09–1.74] per genetic risk score increment) and incident aortic valve stenosis (HR, 2.78 [95% CI, 1.22–6.37] per genetic risk score increment) by use of a mendelian randomization design.[21]
- The heritability of bicuspid aortic valve has been estimated at 89% (0.89±0.06; *P*<0.001), which suggests that most cases are familial.[22] Bicuspid aortic valve has been linked to mutations of *NOTCH1*, *GATA5*, and more recently *GATA4*.[23–25]
- GWAS of aortic valve stenosis have identified several loci, including *LPA*, *PALMD*, and *TEX41*.[20,26]
- In a nationwide Swedish study comprising 6 117 263 siblings (13 442 with aortic stenosis), having at least 1 sibling with aortic stenosis was associated with an HR of 3.41 (95% CI, 2.23–5.21) to be diagnosed with aortic stenosis. These findings indicate an overall familial aggregation of this disease beyond bicuspid aortic valve alone.[27]

Awareness, Treatment, and Control

- Before US Food and Drug Administration approval of TAVR for patients with severe aortic stenosis at high surgical risk in 2011, ≈50% of patients with severe aortic stenosis were referred for cardiothoracic surgery and ≈40% underwent aortic valve replacement, according to data from 10 US centers of various sizes and geographic distribution. Reasons for not undergoing aortic valve replacement included high perioperative risk, age, lack of symptoms, and patient or family refusal.[28]
- Two trials using 2 different devices (PARTNER 1A and US CoreValve High Risk) have shown that TAVR is able to compete in terms of mortality with SAVR in high-risk patients at 1, 2, and 5 years.[29–31]
- From 2011 through 2014, the STS/ACC TVT Registry recorded 26 414 TAVR procedures performed at 348 centers in 48 US states.[32] Sixty-eight percent of patients were ≥80 years of age, and preoperative risk was high; in 2014, median STS risk was 6.7%, and 95% of patients were deemed to be at extreme or high risk. The number of patients receiving commercially approved devices from 2012 through 2015 increased to 54 782 in a recent report from the same registry.[33]
- In Germany, the number of TAVR procedures increased from 144 in 2007 to 9147 in 2013. In the same study, the number of SAVR procedures decreased from 8622 to 7048 (Chart 21-1).[34]
- A recent meta-analysis identified 50 studies enrolling 44 247 patients with a mean follow-up of 21.4 months that compared TAVR to SAVR for patients at high surgical risk. No difference was found in intermediate-term (mean follow-up 21.4 months) all-cause mortality (3980 of 11 728 deaths [33.9%] in the TAVR group compared with 5811 of 32 366 deaths [17.9%] in the SAVR group; RR, 1.06 [95% CI, 0.91–1.22]). There was a significant difference favoring TAVR in the incidence of stroke (348 of 7079 [4.9%] compared with 389 of 6974 [5.5%] in the SAVR group; RR, 0.82 [95% CI, 0.71–0.94]), AF (371 of 3509 [10.5%] versus 1017 of 3589 [28.3%] in patients treated with SAVR; RR, 0.43 [95% CI, 0.33–0.54]), acute kidney injury (404 of 6065 [6.6%] versus 544 of 6103 [8.9%] in the SAVR

group; RR, 0.70 [95% CI, 0.53–0.92]), and major bleeding (607 of 4863 [12.4%] versus 1454 of 5078 [28.6%] in the SAVR group; RR, 0.57 [95% CI, 0.40–0.81]). TAVR resulted in a significantly higher incidence of vascular complications (392 of 4995 [7.8%] compared with 143 of 5084 [2.8%] in the SAVR group; RR, 2.90 [95% CI, 1.87–4.49]), moderate to severe aortic regurgitation (377 of 5548 [6.7%] versus 47 of 5531 [0.8%] in patients treated with SAVR; RR, 7.00 [95% CI, 5.27–9.30]), and pacemaker implantation (872 of 6157 [14.1%] compared with 456 of 6257 [7.2%] in the SAVR group; RR, 2.02 [95% CI, 1.51–2.68]).[35]
- The 54 782 patients with TAVR who entered the STS/ACC TVT Registry between 2012 and 2015 demonstrated decreases in expected risk of 30-day operative mortality (STS Predicted Risk of Mortality score) from 7% to 6% and in TVT Registry predicted risk of mortality from 4% to 3% (both *P*<0.0001) from 2012 to 2015. Observed in-hospital mortality decreased from 5.7% to 2.9%, and 1-year mortality decreased from 25.8% to 21.6%. However, 30-day postprocedure pacemaker insertion increased from 8.8% in 2013 to 12.0% in 2015.[33]
- In a cohort of 1746 patients with severe aortic stenosis at intermediate surgical risk in the SURTAVI trial, the estimated incidence of the primary end point (death attributable to any cause or debilitating stroke) was 12.6% in the TAVR group and 14.0% in the SAVR group (95% credible interval [bayesian analysis] for difference, −5.2 to 2.3%; posterior probability of noninferiority, >0.999) at 24 months. In the PARTNER 2 trial, the Kaplan-Meier event rates of the same end point were 19.3% in the TAVR group and 21.1% in the surgery group (HR in the TAVR group, 0.89 [95% CI, 0.73–1.09]; *P*=0.25) at 2-year follow-up. These findings demonstrate that TAVR is a noninferior alternative to SAVR in patients with severe aortic stenosis at intermediate surgical risk.[36,37]

Cost

- Initial length of stay was an average of 4.4 days shorter for patients treated with TAVR than for those who underwent surgical valve replacement. TAVR also reduced the need for rehabilitation services at discharge and was associated with improved 1-month quality of life. TAVR had higher index admission and projected lifetime costs than SAVR (differences of $11 260 and $17 849 per patient, respectively). However, TAVR was estimated to provide a lifetime gain of 0.32 QALYs (0.41) with 3% discounting. Lifetime incremental CERs were $55 090 per QALY gained and $43 114 per life-year gained. On the basis of sensitivity analyses, a reduction in the initial cost of TAVR by ≈$1650 was expected to lead to an incremental CER of <$50 000 per QALY gained.[38]

Mitral Valve Disorders
ICD-9 424.0; *ICD-10* I34.

2016: Mortality—2596. Any-mention mortality—5885. 2014: Hospital discharges—26 000.

Prevalence
(See Table 21-1)

- In pooled data from CARDIA, ARIC, and CHS, mitral valve disease was the most common valvular lesion. At least moderate MR occurred at a frequency of 1.7% as adjusted to the US adult population in 2000, increasing from 0.5% in participants aged 18 to 44 years to 9.3% in participants aged ≥75 years.[1] In the same pooled sample, mitral stenosis (commonly related to rheumatic involvement) was rare, with a frequency of 0.1% (Table 21-1).
- A systematic review by de Marchena and colleagues[39] found that in the US population, the prevalence of MR according to the Carpentier functional classification system was as follows:
  - — Type I (congenital MR [<10 per million] and endocarditis [3–7 per million]): <20 per 1 million
  - — Type II (myxomatous MR): 15 170.5 per 1 million
  - — Type IIIa (rheumatic HD, systemic lupus erythematosus, antiphospholipid syndrome, and rare diseases): 10 520 per 1 million
  - — Type IIIb (ischemic MR, LV dysfunction, DCM): 16 250 per 1 million
  - — Unclassified: 9530 per 1 million
- In a retrospective investigation of 134 874 individuals in China, 42.44%, 1.63%, and 1.44% had mild, moderate, and severe MR, respectively.[40] The prevalence of MR increased with advancing age. In individuals with severely reduced systolic function (LVEF <30%), the prevalence of severe MR was 22.14%, whereas in individuals with LVEF that was moderately depressed (LVEF 30%–44%), the prevalence was 13.0%. Similarly, the prevalence of severe MR was higher with higher mean LV end-systolic diameter: 15.74% at 50 to 59 mm and 27.28% at ≥60 mm. The authors reported the cause of severe MR in 1948 individuals. About half had secondary MR (N=976) and half had primary causes, including 55 with rheumatic HD, 96 with IE, 141 with papillary muscle dysfunction, and 608 with mitral valve prolapse.

Lifetime Risk and Cumulative Risk

- Because of the associations between MR and advancing age and between functional MR and HF, an increase in prevalence of MR is expected over the coming decades, although no population-based lifetime risk estimations of MR are available in the literature.[41]

Complications

- In the Olmsted County, MN, population, characterized by a mixed spectrum of community-dwelling and referred patients, females were diagnosed with mitral valve prolapse more often than males and at a younger age[42]; however, females had fewer complications (flail leaflet occurred in 2% versus 8% in males and severe regurgitation in 10% versus 23%; all *P*<0.001). At 15 years of follow-up, females with no or mild MR had better survival than males (87% versus 77%; adjusted RR, 0.82 [95% CI, 0.76–0.89]). In contrast, in individuals with severe MR, females had worse survival than males (60% versus 68%; adjusted RR, 1.13 [95% CI, 1.01–1.26]). Survival 10 years after surgery was similar in females and males (77% versus 79%; *P*=0.14).[43]

Risk Factors

- In a community-based study of 833 individuals diagnosed with asymptomatic mitral valve prolapse and followed up longitudinally in Olmsted County, MN, cardiac mortality was best predicted by the presence of MR and LV systolic dysfunction at the time of diagnosis. Risk factors for cardiovascular morbidity (defined as the occurrence of HF, thromboembolic events, endocarditis, AF, or need for cardiac surgery) included age ≥50 years, left atrial enlargement, MR, presence of a flail leaflet, and prevalent AF at the time of the baseline echocardiogram.[43]

Subclinical Disease

- Milder, nondiagnostic forms of mitral valve prolapse, first described in the familial context, are also present in the community and are associated with higher likelihood of mitral valve prolapse in offspring (OR, 2.52 [95% CI, 1.25–5.10]; *P*=0.01). Up to 80% of nondiagnostic morphologies can progress to diagnostic mitral valve prolapse.[44–46]

Genetics and Family History

- Among 3679 generation 3 participants in the FHS (53% female; mean age 40±9 years) with available parental data, 49 (1%) had mitral valve prolapse. Parental mitral valve prolapse was associated with a higher prevalence of mitral valve prolapse in offspring (10/186 [5.4%]) compared with no parental mitral valve prolapse (39/3493 [1.1%]; adjusted OR, 4.51 [95% CI, 2.13–9.54]; *P*<0.0001).[47] A number of genetic variants have been identified for the rare X-linked valvular dystrophy and the most common form of autosomal dominant mitral valve prolapse through pedigree investigations and GWASs. Genes implicated in mitral valve prolapse include *FLNA* (encoding for the filamin A protein), *DCHS1*, *TNS1*, and *LMCD1*.[48–50]
- Familial clustering exists across different MR subtypes including both primary (ie, related to mitral valve prolapse) and nonprimary MR. In a recent study, heritability of MR in the FHS was estimated at 0.15% (95% CI, 7%–23%), 12% (95% CI, 4%–20%) excluding mitral valve prolapse, and 44% (95% CI, 15%–73%) for moderate or greater MR only (all *P*<0.05). In Sweden, sibling MR was associated with an HR of 3.57 (95% CI, 2.21–5.76; *P*<0.001) for development of MR.[51]

Awareness, Treatment, and Control (See Chart 21-2)

- The treatment of mitral valve prolapse remains largely surgical and based on valve repair. Nevertheless, percutaneous mitral valve repair techniques are becoming a common treatment option for high-risk patients not deemed candidates for surgical repair. Data from the STS/ACC TVT Registry on patients commercially treated with the MitraClip percutaneous mitral valve repair device showed the following: of 564 patients (56% male, median age 83 years), 473 (86%) were severely symptomatic. The median STS predicted risk of mortality scores for mitral valve repair and replacement were 7.9% (IQR, 4.7%–12.2%) and 10% (IQR, 6.3%–14.5%), respectively.[52] Most of the transcatheter mitral valve repair patients (90.8%) had degenerative disease, and the procedure was successful in reducing the MR to moderate levels in 93% of cases. In-hospital mortality was 2.3%, and 30-day mortality was 5.8%. Events occurring in the first 30 days included stroke (1.8%), bleeding (2.6%), and device-related complications (1.4%). Most patients (84%) were discharged to home after a 3-day median hospital length (IQR, 1–6 days). The authors reported a procedural success rate of 91%. However, based on the EVEREST II trial, mitral valve dysfunction is more common with percutaneous mitral valve repair than with surgical repair (20% versus 2%).[53]
- Worldwide, the number of MitraClip procedures has increased progressively since 2008, especially in Western Europe. In the United States, the commercial use of the MitraClip started in 2014, with

a steadily growing number of procedures performed (Chart 21-2).[54]

- In patients with severe chronic MR secondary to ischemic cardiomyopathy undergoing CABG surgery, survival rates were not significantly different after bypass alone compared with bypass combined with mitral valve repair (1-, 5-, and 10-year survival of 88%, 75%, and 47% versus 92%, 74%, and 39%, respectively; *P*=0.6).[55] In patients with moderate secondary MR, the rate of death was 6.7% in the combined-surgery group and 7.3% in the CABG-alone group (HR with mitral valve repair, 0.90 [95% CI, 0.38 to 2.12]; *P*=0.81).[56]

Cost

- Lifetime costs, life-years, QALYs, and incremental cost per life-year and QALY gained were estimated for patients receiving MitraClip therapy compared with standard of care.[57] The EVEREST II HRS provided data on treatment-specific overall survival, risk of clinical events, quality of life, and resource utilization. The published literature was reviewed to obtain health utility and unit costs (Canadian 2013 dollars). The incremental cost per QALY gained was $23 433. On the basis of sensitivity analysis, MitraClip therapy had a 92% chance of being cost-effective compared with standard of care at a $50 000 per QALY willingness-to-pay threshold.

Pulmonary Valve Disorders *ICD-9* 424.3; *ICD-10* I37.

2016: Mortality—16. Any-mention mortality—54.

- Pulmonic valve stenosis is a relatively common congenital defect, occurring in ≈10% of children with congenital HD.[58] It is slightly more prevalent in females, and familial occurrence has been reported in 2% of cases.[59] Pulmonic stenosis is usually associated with a benign clinical course. In a 2-center consecutive series of 85 children and adolescents followed up for up to 10 years, reintervention occurred in 11% who received repeat balloon dilation and 5% who required surgical intervention for subvalvular or supravalvular stenosis.[60] Although residual pulmonary regurgitation was noted in the majority of patients, it was predominantly mild.
- Trivial or mild pulmonic valve regurgitation is commonly found in normal hearts on color Doppler echocardiography.[61] The most common cause of severe pulmonic regurgitation is iatrogenic, caused by surgical valvotomy/valvectomy or balloon pulmonary valvuloplasty performed for RV outflow tract obstruction as part of TOF repair.[62,63] Percutaneous pulmonic valve implantation of either a Melody or a SAPIEN valve is an option in patients with prosthetic pulmonic valve regurgitation, including those with a pulmonary artery conduit with regurgitant prosthetic valve.[64] Surgical pulmonary valve replacement is preferred for native pulmonic valve regurgitation (caused by endocarditis, carcinoid, etc) and is associated with <1% periprocedural mortality and excellent long-term outcome, with >60% freedom from reoperation at 10 years.[65]

Tricuspid Valve Disorders *ICD-9* 424.2; *ICD-10* I36.

2016: Mortality—36. Any-mention mortality—152.

Tricuspid valve stenosis is an uncommon valvular abnormality usually seen in patients with rheumatic HD.[66]

- Abnormal degrees of tricuspid regurgitation in adults are largely functional (ie, related to tricuspid annular dilation or leaflet tethering in the setting of RV pressure or volume overload) and much less often caused by primary disorders of the valve apparatus (endocarditis, Ebstein anomaly, rheumatic, carcinoid, prolapse, or direct valve injury from a permanent pacemaker or implantable cardioverter-defibrillator lead placement).[66]
- The frequency of tricuspid regurgitation and valvular pathology was evaluated in a study of 5223 adults (predominantly males, with a mean age of 67 years) who underwent echocardiography at 3 Veterans Affairs medical centers.[67] Moderate to severe tricuspid regurgitation was present in 819 (16%), but only 8% had primary tricuspid valve pathology. In the same study, moderate or greater tricuspid regurgitation was associated with increased mortality regardless of pulmonary artery systolic pressure (HR, 1.31 [95% CI, 1.16–1.49] for pulmonary artery systolic pressure >40 mm Hg; HR, 1.32 [95% CI, 1.05–1.62] for pulmonary artery systolic pressure ≤40 mm Hg) and LVEF (HR, 1.49 [95% CI, 1.34–1.66] for EF <50%; HR, 1.54 [95% CI, 1.37–1.71] for EF ≥50%).[67]
- Tricuspid valve surgery is recommended for patients with severe tricuspid regurgitation undergoing surgery for left-sided valve disease. A weaker recommendation for tricuspid valve surgery exists for patients with severe primary tricuspid regurgitation with symptoms unresponsive to medical therapy.[68]
- An analysis of the NIS demonstrated an increase in the number of isolated tricuspid valve surgeries performed over a 10-year period, from 290 in 2004 to 780 in 2013. In-hospital mortality was consistent over this time period at 8.8%.[69]

- In a cohort of 64 consecutive patients (mean age 76.6±10 years) at excessive surgical risk who underwent compassionate MitraClip treatment of chronic, severe tricuspid regurgitation, tricuspid regurgitation was reduced by at least 1 grade in 91% of the patients at a mean of 14±18 days. There were no intraprocedural deaths, cardiac tamponade, emergency surgery, stroke, MI, or major vascular complications. There was a significant improvement of New York Heart Association class (*P*<0.001) and 6-minute walking distance (177.4±103.0 m versus 193.5±115.9 m; *P*=0.007).[70]

Rheumatic Fever/Rheumatic HD (See Table 21-2 and Charts 21-3 through 21-5) *ICD-9* 390 to 398; *ICD-10* I00 to I09.

2016: Mortality—3553. Any-mention mortality—6622. 2014: Hospital discharges—26 000.

Prevalence

- Rheumatic HD is uncommon in high-income countries such as the United States but remains endemic in some low- and middle-income countries.[71]

Mortality

- In the United States in 2016, mortality attributable to rheumatic fever/rheumatic HD was 3553 for all ages (2345 females and 1208 males; Table 21-2).
- Mortality attributable to rheumatic HD varies widely across the United States, with the highest rates clustered in Alaska, Mississippi, Alabama, Kentucky, and Utah, where age-standardized mortality rates were estimated to be 5 to 10 per 100 000 population in 2014.[72]
- In 1950, ≈15 000 Americans (adjusted for changes in *ICD* codes) died of rheumatic fever/rheumatic HD compared with ≈3400 annually in the present era (NCHS/NHLBI) (Table 21-2). Recent declines in mortality have been slowest in the South compared with other regions.[72]

Complications

- People living with rheumatic HD experience high rates of morbid complications. In REMEDY, 33% had HF, 22% had AF, 7% had prior stroke, and 4% had prior endocarditis at baseline.[73] After 2 years of follow-up, the incidence of new events was 38 per 1000 patient-years for HF, 8.5 per 1000 patient-years for stroke or TIA, and 3.7 per 1000 patient-years for endocarditis.[74] Rates may be even higher in lower-income countries of sub-Saharan Africa such as Uganda, where patients tend to present with advanced disease.[75]
- Prognosis after development of complications is also worse for people living with rheumatic HD. In Thailand, patients with rheumatic mitral valve disease who had ischemic stroke had a higher risk of cardiac arrest (OR, 2.1), shock (OR, 2.1), arrhythmias (OR, 1.7), respiratory failure (OR, 2.1), pneumonia (OR, 2.0), and sepsis (OR, 1.4) after controlling for age, sex, and other comorbid chronic diseases.[76]

Subclinical Disease

- The prevalence of subclinical or latent rheumatic HD among children has been estimated by echocardiography using published guidelines[77] and can be classified as definite or borderline. The prevalence of combined definite and borderline disease ranges between 10 and 45 per 1000 in recent studies from endemic countries (eg, Nepal, Brazil, and Uganda) compared with <8 per 1000 in low-risk populations.[78–81]
- The natural history of latent rheumatic HD detected by echocardiography is not clear. Emerging data suggest that up to 20% of children with definite rheumatic HD may progress to severe disease that requires valve surgery over a median follow-up of 7.5 years[82]; however, many with borderline disease will remain stable, and 30% to 50% will regress to normal over 2 to 5 years of follow-up.[83,84]
- In the largest prospective registry of latent rheumatic HD published to date, 26% of children with definite rheumatic HD progressed over a median follow-up of 2.6 years. Younger age at diagnosis and presence of morphologic mitral valve changes were independent predictors of progression.[85]

Awareness, Treatment, and Control

- The REMEDY study highlighted consistently poor access to recommended therapies among people living with rheumatic HD: only 55% were taking penicillin prophylaxis, and only 3.6% of females of childbearing age were using contraception. Although 70% of those with indications (mechanical valve, AF, or severe mitral stenosis) were appropriately prescribed anticoagulant drugs, only a quarter of these had therapeutic international normalized ratios.[73]
- Underrecognition of acute rheumatic fever can contribute to delayed presentation of disease and poor outcomes. Of the REMEDY participants from low-income countries, only 22% reported a history of prior acute rheumatic fever.[73]
- In Uganda, retention in care over time is poor (56.9% [95% CI, 54.1–59.7%] seen in clinic in the past 12 months), but among those retained in care, optimal adherence to benzathine penicillin G is high (91.4% [95% CI, 88.7–93.5%]).[86]

Global Burden of Rheumatic HD (See Charts 21-3 and 21-5)

- In 2015, 33.4 million people were estimated to be living with rheumatic HD around the world, with sub-Saharan Africa and Oceania having the highest concentration of DALYs attributable to rheumatic HD.[71]
- Unfortunately, estimates of the global burden of rheumatic HD are hampered by a lack of data from endemic areas, which increases uncertainty of the estimates.[71]
- Globally, age-standardized mortality from rheumatic HD was estimated to have declined 47.8% from 1990 to 2015; however, the prevalence of HF attributable to rheumatic HD increased by 88% in the same time period.[71]
- The REMEDY study is a prospective registry of 3343 patients with rheumatic HD from 25 hospitals in 12 African countries, India, and Yemen (Chart 21-3). The age and sex distribution of the subjects is shown in Chart 21-3.[74] Rheumatic HD was twice as common among females, a finding consistent with prior studies across a variety of populations.[73]
- Mortality attributable to rheumatic HD remains exceptionally high in endemic settings. In a study from Fiji of 2619 people followed up during 2008 to 2012, the age-standardized death rate was 9.9 (95% CI, 9.8–10.0) per 100 000, or more than twice the GBD estimates.[87] Prognosis is exceptionally poor in sub-Saharan Africa, as highlighted by a follow-up study of REMEDY, which had a mortality rate of 116 per 1000 patient-years in the first year and 65 per 1000 patient-years in the second year.[74]
- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories.[88]
  - Age-standardized mortality attributable to rheumatic HD is highest in Southeast and South Asia, sub-Saharan Africa, and the Pacific Islands (Chart 21-4).
  - Rheumatic HD prevalence is highest in central sub-Saharan Africa, South Asia, and the Pacific Island Countries (Chart 21-5).

Infective Endocarditis (See Table 21-3) *ICD-9* 421.0; *ICD-10* I33.0.

2016: Mortality—1414. Any-mention mortality—3060.

2014: Hospital discharges—11 000, primary plus secondary diagnoses.

Prevalence and Incidence

- In 2011, there were 47 134 cases of IE and valve replacement in the United States (Table 21-3).[89]
- According to the 2015 GBD study, the age-standardized death rate attributable to IE in 2015 was 1.3 per 100 000.[90]
- Although the absolute risk for acquiring IE from a dental procedure is impossible to measure precisely, the best available estimates are as follows: If dental treatment causes 1% of all cases of viridans group streptococcal IE annually in the United States, the overall risk in the general population is estimated to be as low as 1 case of IE per 14 million dental procedures. The estimated absolute risk rates for acquiring IE from a dental procedure in patients with underlying cardiac conditions are as follows[91]:
  - Mitral valve prolapse: 1 per 1.1 million procedures
  - Congenital HD: 1 per 475 000
  - Rheumatic HD: 1 per 142 000
  - Presence of a prosthetic cardiac valve: 1 per 114 000
  - Previous IE: 1 per 95 000 dental procedures
- Data collected between 2004 and 2010 from the Pediatric Health Information System database from 37 centers that included 1033 cases of IE demonstrated a mortality rate of 6.7% (N=45) and 3.5% (N=13) among children (0–19 years old) with and without congenital HD, respectively.[92]
- Data from the NIS (2000–2011)[89] suggested no change in temporal trends in the incidence of IE before and after publication of the 2007 AHA guideline for antibiotic prophylaxis before dental procedures.[91] These findings from referral centers were corroborated by a community-based review of adults in Olmsted County, MN.[93] In the Olmsted County study, age- and sex-adjusted incidence of IE was 7.4 (95% CI, 5.3–9.4) cases per 100 000 person-years. In addition, these guideline changes do not appear to have altered rates of pediatric endocarditis. Using 2003 to 2010 data from 37 centers in the Pediatric Health Information Systems Database, Pasquali and colleagues[94] did not demonstrate a significant difference in the number of IE hospitalizations after the guidelines were implemented in 2007 (1.6% difference after versus before guideline implementation [95% CI, −6.4% to 10.3%]; *P*=0.7).
- A systematic review that included 160 studies and 27 083 patients from 1960 to 2011 demonstrated that in hospital-based studies (142 studies; 23 606 patients), staphylococcal endocarditis has increased over time (coagulase-negative *Staphylococcus* 2% to 10%, *P*<0.001), with recent increases in *S aureus* IE (21% to 30%,

P<0.05) and enterococcal IE (6.8% to 10.5%, *P*<0.001) over the past decade and a corresponding decrease in streptococcal endocarditis (32% to 17%) over the same time period.[95]

Complications

- Among 162 cases of left-sided native-valve *S aureus* IE retrospectively identified among 1254 patients hospitalized between 1990 and 2010 for IE, *Staphylococcus* represented 18% of all IE cases and 23% of native-valve IE cases. HF occurred in 45% of IE cases, acute renal failure in 23%, sepsis in 29%, neurological events in 36%, systemic embolic events in 55%, and in-hospital mortality in 25%. The risk of in-hospital mortality was higher in patients with HF (OR, 2.5; *P*=0.04) and sepsis (OR, 5.3; *P*=0.001). Long-term 5-year survival was 49.6±4.9%. There was higher long-term risk of death among individuals with HF (OR, 1.7; *P*=0.03), sepsis (OR, 3.0; *P*=0.0001), and delayed surgery (OR, 0.43; *P*=0.003). When the authors compared 2 study periods, 1990 to 2000 and 2001 to 2010, there was a significant increase in bivalvular involvement, valvular insufficiency, and acute renal failure from 2001 to 2010. In-hospital mortality rates and long-term 5-year survival were not significantly different between the 2 study periods (28.1% versus 23.5%; *P*=0.58).[96]

Risk Factors

- The 15-year cohort risk (through 2006) of IE after diagnosis of mitral valve prolapse (between 1989 to 1998) among Olmsted County, MN, residents was 1.1±0.4% (incidence, 86.6 cases per 100 000 person-years [95% CI, 43.3–173.2 cases per 100 000 person-years]); there was a higher age- and sex-adjusted risk of IE in patients with mitral valve prolapse (RR, 8.1 [95% CI, 3.6–18.0]) compared with the general population of Olmsted County (*P*<0.001). No IE cases were identified among patients without previously diagnosed MR. Conversely, there was a higher incidence of IE in patients with mitral valve prolapse and moderate, moderate-severe, or severe MR (289.5 cases per 100 000 person-years [95% CI, 108.7–771.2 cases per 100 000 person-years]; *P*=0.02 compared with trivial, mild, or mild-moderate MR) and in patients with a flail mitral leaflet (715.5 cases per 100 000 person-years [95% CI, 178.9–2861.0 cases per 100 000 person-years]; *P*=0.02 compared with no flail mitral leaflet).[97]
- Admissions for endocarditis related to injection drug use have risen in recent years in parallel with the opioid drug crisis. The prevalence of documented intravenous drug use among patients admitted for endocarditis in the NIS rose from 4.3% in 2008 to 10% in 2014. This trend was accentuated among the young (<30 years old) and among whites (compared with blacks and other races).[98]
- Cardiac device IE appears to be present in 6.4% (95% CI, 5.5%–7.4%) of patients with definite IE, according to data from ICE-PCS (2000–2006). Nearly half (45.8% [95% CI, 38.3%–53.4%]) of such cases were related to healthcare-associated infection. In-hospital and 1-year mortality rates for these patients were 14.7% (26 of 177 [95% CI, 9.8%–20.8%]) and 23.2% (41 of 177 [95% CI, 17.2%–30.1%]), respectively. Although not based on randomized data, compared with individuals without initial hospitalization device removal, there appeared to be a 1-year survival benefit in individuals undergoing device explantation during the index hospitalization (HR, 0.42 [95% CI, 0.22–0.82]).[99]
- Prosthetic valve IE continues to be associated with high in-hospital and 1-year mortality, although early surgery is associated with improved outcomes compared with medical therapy alone (1-year mortality 22% versus 27%; HR, 0.68 [95% CI, 0.53–0.87]), even in propensity-adjusted analyses (HR, 0.57 [95% CI, 0.49–0.67]).[51]

Awareness, Treatment, and Control

- Surgery was performed in 47% of cases of definite left-sided, non–cardiac device-related IE in the ICE-PLUS registry of 1296 patients from 16 countries.[100]

Heart Valve Procedure Costs

- In 2013, for heart valve procedures[101]:
  - The mean inflation-adjusted cost per hospitalization in 2013 dollars was $51 415, compared with $53 711 in 2005 and $43 829 in 2000.
  - The number of discharges for which heart valve surgery was the principal operating room procedure was 102 425, which was an increase from 93 802 in 2005 and 79 719 in 2000.
- Total inflation-adjusted national cost in 2013 dollars (in millions) was $5264, which was an increase from the mean cost (in millions) of $5058 in 2005 and $3488 in 2000.[101]

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Table 21-1. Pooled Prevalence of Valvular Heart Disease From CARDIA, ARIC, and CHS Cohorts

	Age, y					P Value for Trend	Frequency Adjusted to 2000 US Adult Population
	18–44	45–54	55–64	65–74	≥75		
Participants, N	4351	696	1240	3879	1745	…	209 128 094
Male	1959 (45)	258 (37)	415 (33)	1586 (41)	826 (47)	…	100 994 367 (48)
Mitral regurgitation (n=449)	23 (0.5)	1 (0.1)	12 (1.0)	250 (6.4)	163 (9.3)	<0.0001	1.7% (95% CI, 1.5%–1.9%)
Mitral stenosis (n=15)	0 (0)	1 (0.1)	3 (0.2)	7 (0.2)	4 (0.2)	0.006	0.1% (95% CI, 0.02%–0.2%)
Aortic regurgitation (n=90)	10 (0.2)	1 (0.1)	8 (0.7)	37 (1.0)	34 (2.0)	<0.0001	0.5% (95% CI, 0.3%–0.6%)
Aortic stenosis (n=102)	1 (0.02)	1 (0.1)	2 (0.2)	50 (1.3)	48 (2.8)	<0.0001	0.4% (95% CI, 0.3%–0.5%)
Any valve disease	…	…	…	…	…	…	…
Overall (N=615)	31 (0.7)	3 (0.4)	23 (1.9)	328 (8.5)	230 (13.2)	<0.0001	2.5% (95% CI, 2.2%–2.7%)
Female (n=356)	19 (0.8)	1 (0.2)	13 (1.6)	208 (9.1)	115 (12.6)	<0.0001	2.4% (95% CI, 2.1%–2.8%)
Male (n=259)	12 (0.6)	2 (0.8)	10 (2.4)	120 (7.6)	115 (14.0)	<0.0001	2.5% (95% CI, 2.1%–2.9%)

Values are n (%) unless otherwise indicated. ARIC indicates Atherosclerosis Risk in Communities study; CARDIA, Coronary Artery Risk Development in Young Adults; CHS, Cardiovascular Health Study; and ellipses (…), not applicable.

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Table 21-2. Rheumatic Fever/Rheumatic Heart Disease

Population Group	Mortality,2016: All Ages*	Hospital Discharges, 2014: All Ages
Both sexes	3553	26 000
Males	1208 (33.2%)†	12 000
Females	2345 (66.8%)†	14 000
NH white males	985	…
NH white females	1916	…
NH black males	100	…
NH black females	185	…
Hispanic males	77	…
Hispanic females	138	…
NH Asian or Pacific Islander males	37‡	…
NH Asian or Pacific Islander females	82‡	…
NH American Indian or Alaska Native	23	…

Ellipses (…) indicate data not available; and NH, non-Hispanic.

*Mortality for American Indian or Alaska Native and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total mortality that is for males vs females.

‡Includes Chinese, Filipino, Hawaiian, Japanese, and Other Asian or Pacific Islander.

Sources: Mortality: Centers for Disease Control and Prevention/National Center for Health Statistics, 2016 Mortality Multiple Cause-of-Death–United States; data represent underlying cause of death only. Hospital discharges: Healthcare Cost and Utilization Project, Hospital Discharges, 2014; data include those inpatients discharged alive, dead, or of unknown status.

Table 21-3. Incidence of IE and Valve Replacement From 2000 to 2011

Year	Total IE Cases	IE Incidence per 100 000	Valve Replacement per 1000 IE Cases
2000	29 820	11	14
2001	31 526	11	16
2002	32 229	11	19
2003	35 190	12	18
2004	36 660	13	19
2005	37 508	13	23
2006	40 573	14	23
2007	38 207	12	30
2008	41 143	14	19
2009	43 502	14	27
2010	43 560	14	27
2011	47 134	15	26

IE indicates infective endocarditis.

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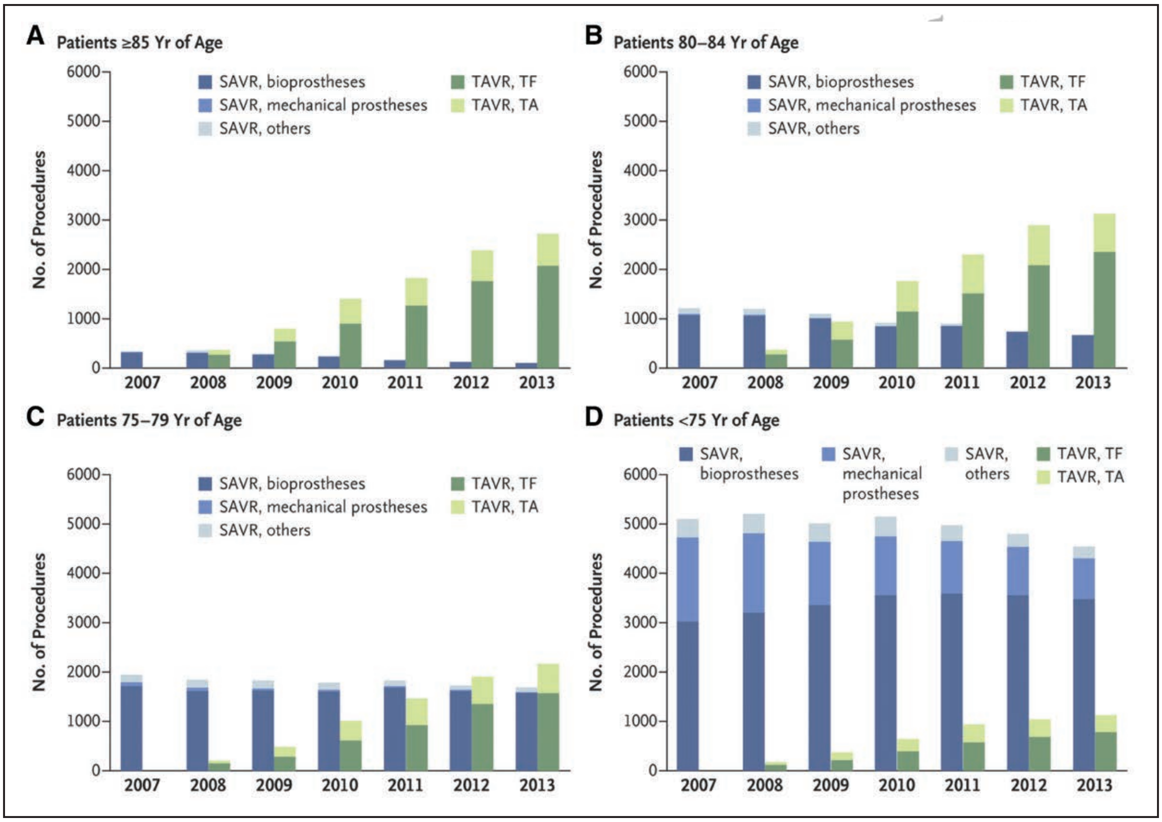

Chart 21-1. Number of TAVR and SAVR procedures performed according to type of procedure and age group, 2007 to 2013.
SAVR indicates surgical aortic valve replacement; TA, transapical; TAVR, transcatheter aortic valve replacement; and TF, transfemoral.
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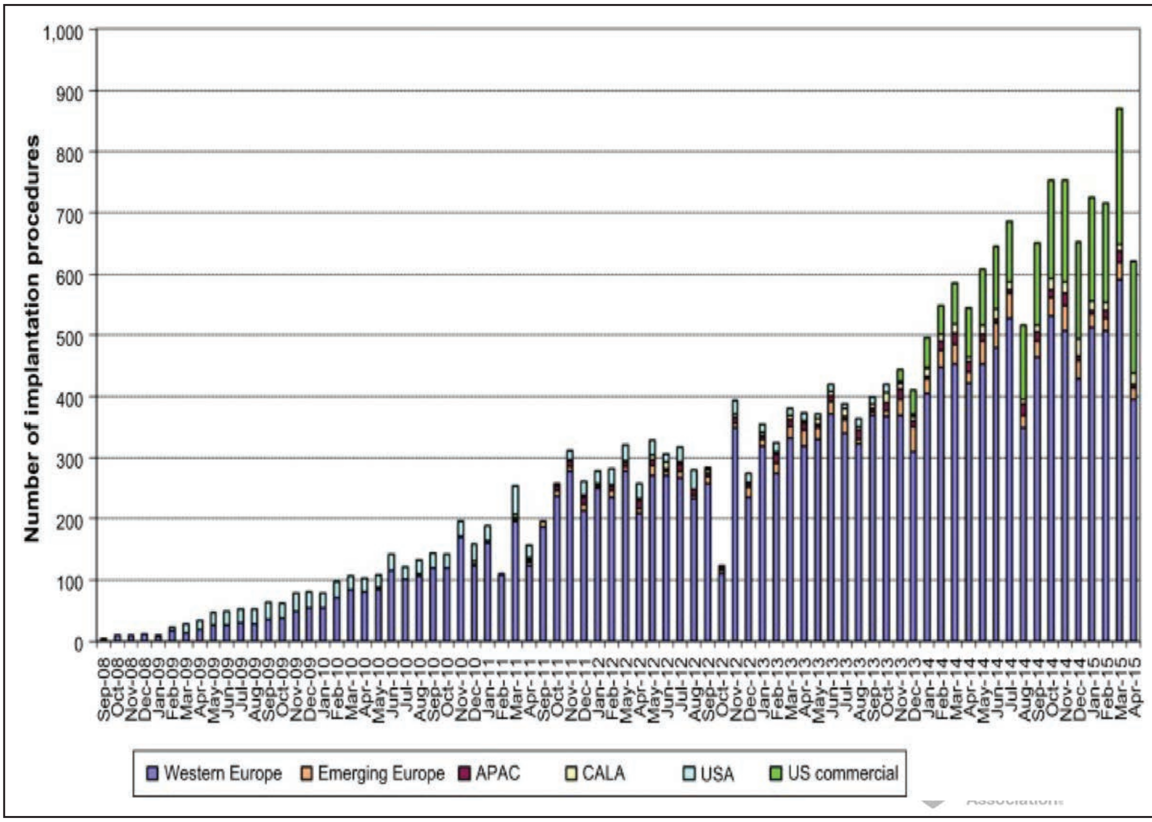

Chart 21-2. Worldwide experience with the MitraClip procedure from September 2008 until April 2015.
APAC indicates Asia-Pacific; and CALA, Caribbean and Latin America.
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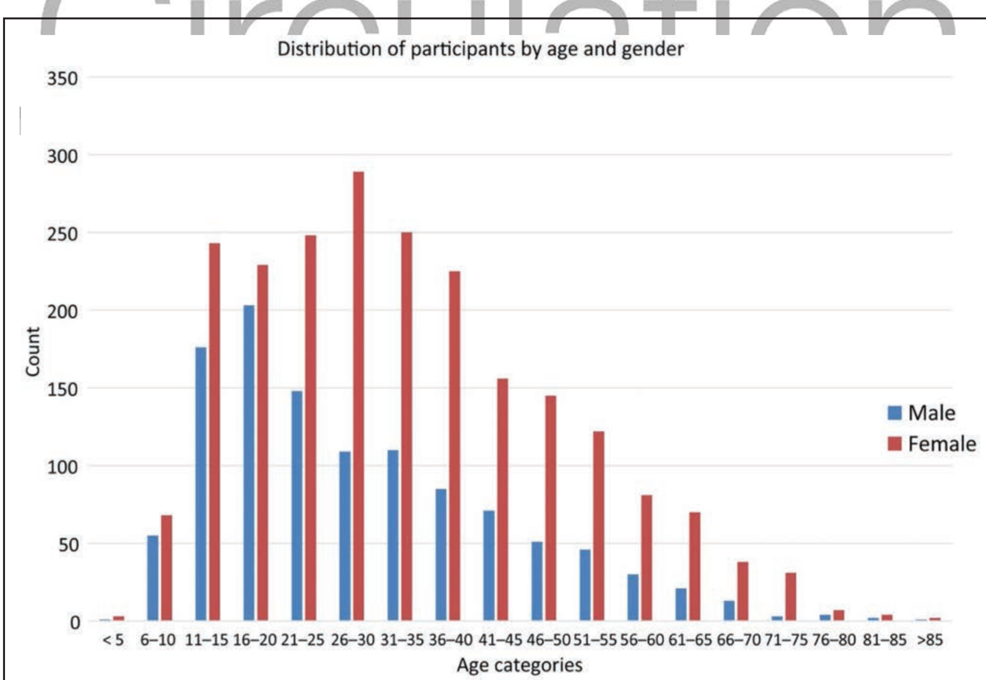

Chart 21-3. Age and sex distribution of 3343 subjects with rheumatic heart disease participating in the REMEDY study.
REMEDY indicates Global Rheumatic Heart Disease Registry.
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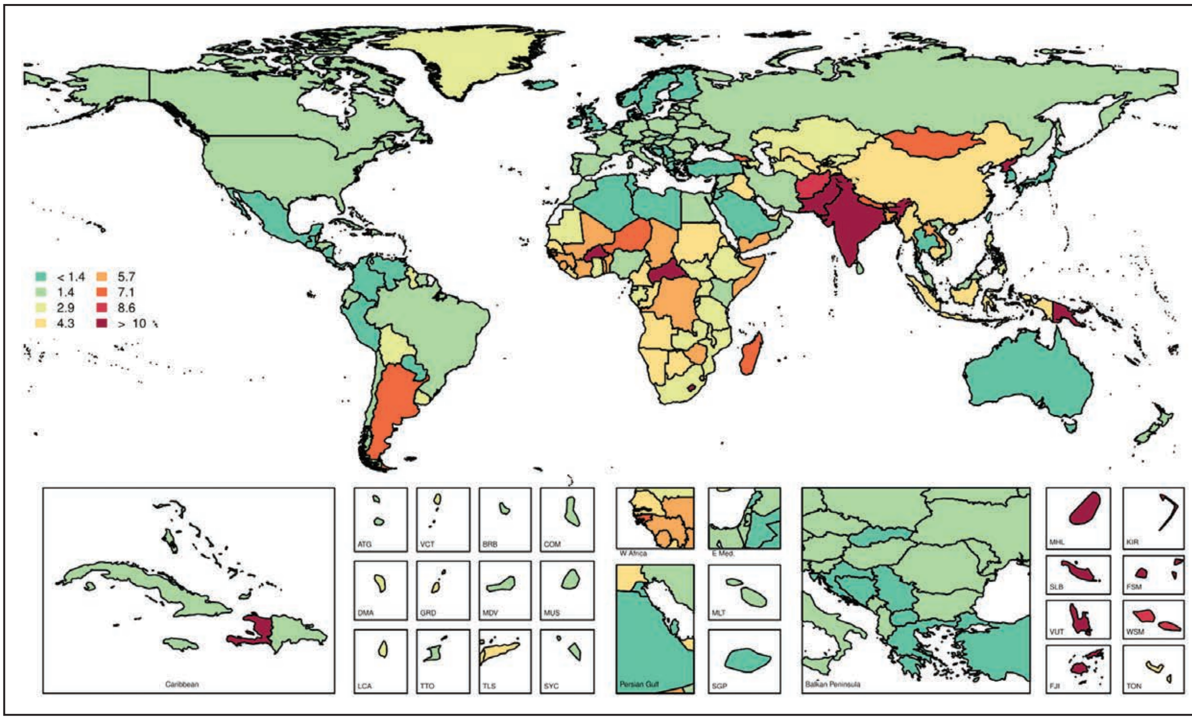

Chart 21-4. Age-standardized global mortality rates of rheumatic heart disease per 100 000, both sexes, 2016..
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[88] Printed with permission. Copyright © 2017, University of Washington.

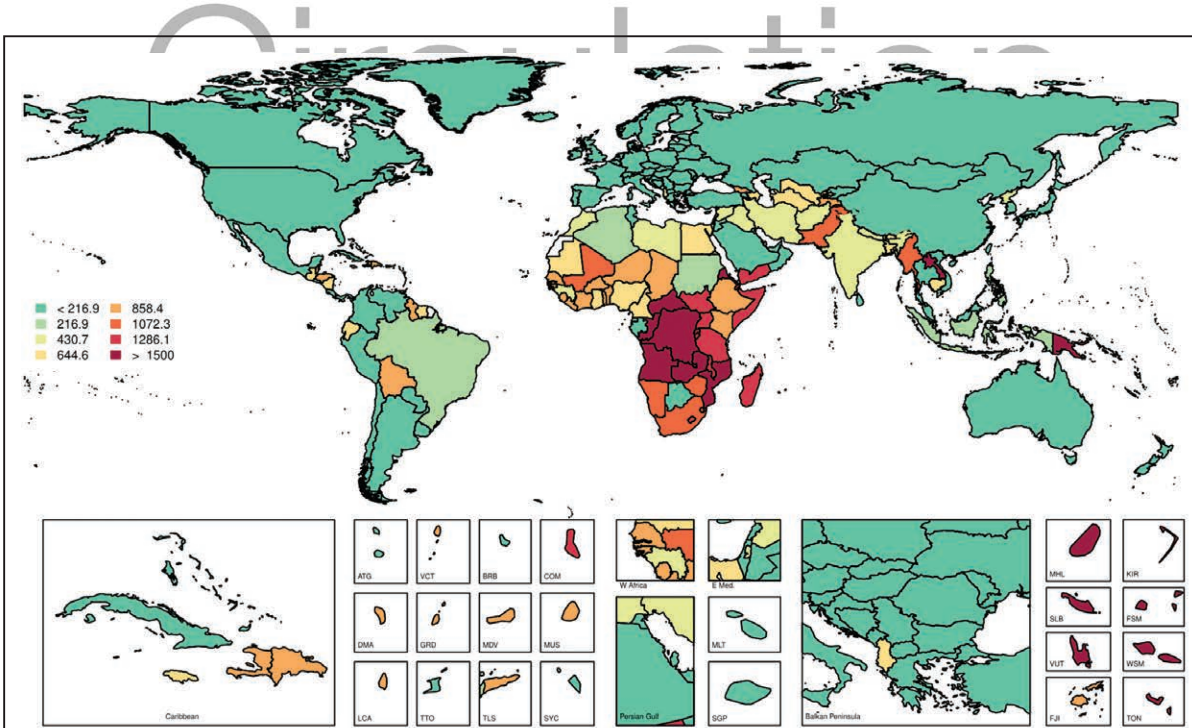

Chart 21-5. Age-standardized global prevalence rates of rheumatic heart disease per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[88] Printed with permission. Copyright © 2017, University of Washington.

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005–1011. doi: 10.1016/S0140-6736(06)69208-8
2. Andell P, Li X, Martinsson A, Andersson C, Stagmo M, Zöller B, Sundquist K, Smith JG. Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. *Heart*. 2017;103:1696–1703. doi: 10.1136/heartjnl-2016-310894
3. d'Arcy JL, Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J, Frangou E, Farmer AJ, Mant D, Wilson J, Myerson SG, Prendergast BD. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. *Eur Heart J*. 2016;37:3515–3522. doi: 10.1093/eurheartj/ehw229
4. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvular aortic stenosis: the Tromsø study. *Heart*. 2013;99:396–400. doi: 10.1136/heartjnl-2012-302265
5. Basso C, Boschello M, Perrone C, Mecenero A, Cera A, Bicego D, Thiene G, De Dominicis E. An echocardiographic survey of primary school children for bicuspid aortic valve. *Am J Cardiol*. 2004;93:661–663. doi: 10.1016/j.amjcard.2003.11.031
6. Martinsson A, Li X, Andersson C, Nilsson J, Smith JG, Sundquist K. Temporal trends in the incidence and prognosis of aortic stenosis: a nationwide study of the Swedish population. *Circulation*. 2015;131:988–994. doi: 10.1161/CIRCULATIONAHA.114.012906
7. Danielsen R, Aspelund T, Harris TB, Gudnason V. The prevalence of aortic stenosis in the elderly in Iceland and predictions for the coming decades: the AGES-Reykjavík study. *Int J Cardiol*. 2014;176:916–922. doi: 10.1016/j.ijcard.2014.08.053
8. Coffey S, Cox B, Williams MJ. Lack of progress in valvular heart disease in the pre-transcatheter aortic valve replacement era: increasing deaths and minimal change in mortality rate over the past three decades. *Am Heart J*. 2014;167:562–567.e2. doi: 10.1016/j.ahj.2013.12.030
9. Michelena HI, Suri RM, Katan O, Eleid MF, Clavel MA, Maurer MJ, Pellikka PA, Mahoney D, Enriquez-Sarano M. Sex differences and survival in adults with bicuspid aortic valves: verification in 3 contemporary echocardiographic cohorts. *J Am Heart Assoc*. 2016;5:e004211. doi: 10.1161/jaha.116.004211
10. Michelena HI, Khanna AD, Mahoney D, Margaryan E, Topilsky Y, Suri RM, Eidem B, Edwards WD, Sundt TM 3rd, Enriquez-Sarano M. Incidence of aortic complications in patients with bicuspid aortic valves. *JAMA*. 2011;306:1104–1112. doi: 10.1001/jama.2011.1286
11. Aronow WS, Schwartz KS, Koenigsberg M. Correlation of serum lipids, calcium, and phosphorus, diabetes mellitus and history of systemic hypertension with presence or absence of calcified or thickened aortic cusps or root in elderly patients. *Am J Cardiol*. 1987;59:998–999.
12. Mohler ER, Sheridan MJ, Nichols R, Harvey WP, Waller BF. Development and progression of aortic valve stenosis: atherosclerosis risk factors: a causal relationship? A clinical morphologic study. *Clin Cardiol*. 1991;14:995–999.
13. Lindroos M, Kupari M, Valvanne J, Strandberg T, Heikkilä J, Tilvis R. Factors associated with calcific aortic valve degeneration in the elderly. *Eur Heart J*. 1994;15:865–870.
14. Boon A, Cheriex E, Lodder J, Kessels F. Cardiac valve calcification: characteristics of patients with calcification of the mitral annulus or aortic valve. *Heart*. 1997;78:472–474.
15. Peltier M, Trojette F, Sarano ME, Grigioni F, Slama MA, Tribouilloy CM. Relation between cardiovascular risk factors and nonrheumatic severe calcific aortic stenosis among patients with a three-cuspid aortic valve. *Am J Cardiol*. 2003;91:97–99.
16. Yan AT, Koh M, Chan KK, Guo H, Alter DA, Austin PC, Tu JV, Wijeysundera HC, Ko DT. Association between cardiovascular risk factors and aortic stenosis: the CANHEART Aortic Stenosis study. *J Am Coll Cardiol*. 2017;69:1523–1532. doi: 10.1016/j.jacc.2017.01.025
17. Freeman RV, Otto CM. Spectrum of calcific aortic valve disease: pathogenesis, disease progression, and treatment strategies. *Circulation*. 2005;111:3316–3326. doi: 10.1161/CIRCULATIONAHA.104.486738
18. Capoulade R, Clavel MA, Dumesnil JG, Chan KL, Teo KK, Tam JW, Côté N, Mathieu P, Després JP, Pibarot P; ASTRONOMER Investigators. Impact of metabolic syndrome on progression of aortic stenosis: influence of age and statin therapy. *J Am Coll Cardiol*. 2012;60:216–223. doi: 10.1016/j.jacc.2012.03.052
19. Rodrigues I, Agapito AF, de Sousa L, Oliveira JA, Branco LM, Galrinho A, Abreu J, Timóteo AT, Rosa SA, Ferreira RC. Bicuspid aortic valve outcomes. *Cardiol Young*. 2017;27:518–529. doi: 10.1017/S1047951116002560
20. Thanassoulis G, Campbell CY, Owens DS, Smith JG, Smith AV, Peloso GM, Kerr KF, Pechlivanis S, Budoff MJ, Harris TB, Malhotra R, O'Brien KD, Kamstrup PR, Nordestgaard BG, Tybjaerg-Hansen A, Allison MA, Aspelund T, Criqui MH, Heckbert SR, Hwang SJ, Liu Y, Sjogren M, van der Pals J, Kälsch H, Mühleisen TW, Nöthen MM, Cupples LA, Caslake M, Di Angelantonio E, Danesh J, Rotter JI, Sigurdsson S, Wong Q, Erbel R, Kathiresan S, Melander O, Gudnason V, O'Donnell CJ, Post WS; CHARGE Extracoronary Calcium Working Group. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med*. 2013;368:503–512. doi: 10.1056/NEJMoa1109034
21. Smith JG, Luk K, Schulz CA, Engert JC, Do R, Hindy G, Rukh G, Dufresne L, Almgren P, Owens DS, Harris TB, Peloso GM, Kerr KF, Wong Q, Smith AV, Budoff MJ, Rotter JI, Cupples LA, Rich S, Kathiresan S, Orho-Melander M, Gudnason V, O'Donnell CJ, Post WS, Thanassoulis G; Cohorts for Heart and Aging Research in Genetic Epidemiology (CHARGE) Extracoronary Calcium Working Group. Association of low-density lipoprotein cholesterol-related genetic variants with aortic valve calcium and incident aortic stenosis. *JAMA*. 2014;312:1764–1771. doi: 10.1001/jama.2014.13959
22. Cripe L, Andelfinger G, Martin LJ, Shooner K, Benson DW. Bicuspid aortic valve is heritable. *J Am Coll Cardiol*. 2004;44:138–143. doi: 10.1016/j.jacc.2004.03.050
23. Garg V, Muth AN, Ransom JF, Schluterman MK, Barnes R, King IN, Grossfeld PD, Srivastava D. Mutations in NOTCH1 cause aortic valve disease. *Nature*. 2005;437:270–274. doi: 10.1038/nature03940
24. Padang R, Bagnall RD, Richmond DR, Bannon PG, Semsarian C. Rare non-synonymous variations in the transcriptional activation domains of GATA5 in bicuspid aortic valve disease. *J Mol Cell Cardiol*. 2012;53:277–281. doi: 10.1016/j.yjmcc.2012.05.009
25. Yang B, Zhou W, Jiao J, Nielsen JB, Mathis MR, Heydarpour M, Lettre G, Folkersen L, Prakash S, Schurmann C, Fritsche L, Farnum GA, Lin M, Othman M, Hornsby W, Driscoll A, Levasseur A, Thomas M, Farhat L, Dubé MP, Isselbacher EM, Franco-Cereceda A, Guo DC, Bottinger EP, Deeb GM, Booher A, Kheterpal S, Chen YE, Kang HM, Kitzman J, Cordell HJ, Keavney BD, Goodship JA, Ganesh SK, Abecasis G, Eagle KA, Boyle AP, Loos RJF, Eriksson P, Tardif JC, Brummett CM, Milewicz DM, Body SC, Willer CJ. Protein-altering and regulatory genetic variants near GATA4 implicated in bicuspid aortic valve. *Nat Commun*. 2017;8:15481. doi: 10.1038/ncomms15481
26. Helgadottir A, Thorleifsson G, Gretarsdottir S, Stefansson OA, Tragante V, Thorolfsdottir RB, Jonsdottir I, Bjornsson T, Steinthorsdottir V, Verweij N, Nielsen JB, Zhou W, Folkersen L, Martinsson A, Heydarpour M, Prakash S, Oskarsson G, Gudbjartsson T, Geirsson A, Olafsson I, Sigurdsson EL, Almgren P, Melander O, Franco-Cereceda A, Hamsten A, Fritsche L, Lin M, Yang B, Hornsby W, Guo D, Brummett CM, Abecasis G, Mathis M, Milewicz D, Body SC, Eriksson P, Willer CJ, Hveem K, Newton-Cheh C, Smith JG, Danielsen R, Thorgeirsson G, Thorsteinsdottir U, Gudbjartsson DF, Holm H, Stefansson K. Genome-wide analysis yields new loci associating with aortic valve stenosis. *Nat Commun*. 2018;9:987. doi: 10.1038/s41467-018-03252-6
27. Martinsson A, Li X, Zoller B, Andell P, Andersson C, Sundquist K, Smith JG. Familial aggregation of aortic valvular stenosis: a nationwide study of sibling risk. *Circ Cardiovasc Genet*. 2017;10:e001742. doi: 10.1161/circgenetics.117.001742
28. Bach DS. Prevalence and characteristics of unoperated patients with severe aortic stenosis. *J Heart Valve Dis*. 2011;20:284–291.
29. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ, Svensson LG; PARTNER 1 Trial Investigators. 5-Year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477–2484. doi: 10.1016/S0140-6736(15)60308-7
30. Kapadia SR, Leon MB, Makkar RR, Tuzcu EM, Svensson LG, Kodali S, Webb JG, Mack MJ, Douglas PS, Thourani VH, Babaliaros VC, Herrmann HC, Szeto WY, Pichard AD, Williams MR, Fontana GP, Miller DC, Anderson WN, Akin JJ, Davidson MJ, Smith CR; PARTNER Trial Investigators. 5-Year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2485–2491. doi: 10.1016/S0140-6736(15)60290-2

31. Adams DH, Popma JJ, Reardon MJ. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;371:967–968. doi: 10.1056/NEJMc1408396
32. Holmes DR Jr, Nishimura RA, Grover FL, Brindis RG, Carroll JD, Edwards FH, Peterson ED, Rumsfeld JS, Shahian DM, Thourani VH, Tuzcu EM, Vemulapalli S, Hewitt K, Michaels J, Fitzgerald S, Mack MJ; STS/ACC TVT Registry. Annual outcomes with transcatheter valve therapy: from the STS/ACC TVT Registry. *J Am Coll Cardiol*. 2015;66:2813–2823. doi: 10.1016/j.jacc.2015.10.021
33. Grover FL, Vemulapalli S, Carroll JD, Edwards FH, Mack MJ, Thourani VH, Brindis RG, Shahian DM, Ruiz CE, Jacobs JP, Hanzel G, Bavaria JE, Tuzcu EM, Peterson ED, Fitzgerald S, Kourtis M, Michaels J, Christensen B, Seward WF, Hewitt K, Holmes DR Jr; STS/ACC TVT Registry. 2016 annual report of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. *J Am Coll Cardiol*. 2017;69:1215–1230. doi: 10.1016/j.jacc.2016.11.033
34. Reinöhl J, Kaier K, Reinecke H, Schmoor C, Frankenstein L, Vach W, Cribier A, Beyersdorf F, Bode C, Zehender M. Effect of availability of transcatheter aortic-valve replacement on clinical practice. *N Engl J Med*. 2015;373:2438–2447. doi: 10.1056/NEJMoa1500893
35. Villablanca PA, Mathew V, Thourani VH, Rodés-Cabau J, Bangalore S, Makkiya M, Vlismas P, Briceno DF, Slovut DP, Taub CC, McCarthy PM, Augoustides JG, Ramakrishna H. A meta-analysis and meta-regression of long-term outcomes of transcatheter versus surgical aortic valve replacement for severe aortic stenosis. *Int J Cardiol*. 2016;225:234–243. doi: 10.1016/j.ijcard.2016.10.003
36. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PW, Kappetein AP; SURTAVI Investigators. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376:1321–1331. doi: 10.1056/NEJMoa1700456
37. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG; PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609–1620. doi: 10.1056/NEJMoa1514616
38. Reynolds MR, Lei Y, Wang K, Chinnakondepalli K, Vilain KA, Magnuson EA, Galper BZ, Meduri CU, Arnold SV, Baron SJ, Reardon MJ, Adams DH, Popma JJ, Cohen DJ; CoreValve US High Risk Pivotal Trial Investigators. Cost-effectiveness of transcatheter aortic valve replacement with a self-expanding prosthesis versus surgical aortic valve replacement. *J Am Coll Cardiol*. 2016;67:29–38. doi: 10.1016/j.jacc.2015.10.046
39. de Marchena E, Badiye A, Robalino G, Junttila J, Atapattu S, Nakamura M, De Canniere D, Salerno T. Respective prevalence of the different Carpentier classes of mitral regurgitation: a stepping stone for future therapeutic research and development. *J Card Surg*. 2011;26:385–392. doi: 10.1111/j.1540-8191.2011.01274.x
40. Li J, Pan W, Yin Y, Cheng L, Shu X. Prevalence and correlates of mitral regurgitation in the current era: an echocardiography study of a Chinese patient population. *Acta Cardiol*. 2016;71:55–60. doi: 10.2143/AC.71.1.3132098
41. Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol*. 1999;83:897–902.
42. Avierinos JF, Inamo J, Grigioni F, Gersh B, Shub C, Enriquez-Sarano M. Sex differences in morphology and outcomes of mitral valve prolapse. *Ann Intern Med*. 2008;149:787–795.
43. Avierinos JF, Gersh BJ, Melton LJ 3rd, Bailey KR, Shub C, Nishimura RA, Tajik AJ, Enriquez-Sarano M. Natural history of asymptomatic mitral valve prolapse in the community. *Circulation*. 2002;106:1355–1361.
44. Delling FN, Gona P, Larson MG, Lehman B, Manning WJ, Levine RA, Benjamin EJ, Vasan RS. Mild expression of mitral valve prolapse in the Framingham offspring: expanding the phenotypic spectrum. *J Am Soc Echocardiogr*. 2014;27:17–23. doi: 10.1016/j.echo.2013.09.015
45. Delling FN, Rong J, Larson MG, Lehman B, Fuller D, Osypiuk E, Stantchev P, Hackman B, Manning WJ, Benjamin EJ, Levine RA, Vasan RS. Evolution of mitral valve prolapse: insights from the Framingham Heart Study. *Circulation*. 2016;133:1688–1695. doi: 10.1161/circulationaha.115.020621
46. Nesta F, Leyne M, Yosefy C, Simpson C, Dai D, Marshall JE, Hung J, Slaugenhaupt SA, Levine RA. New locus for autosomal dominant mitral valve prolapse on chromosome 13: clinical insights from genetic studies. *Circulation*. 2005;112:2022–2030. doi: 10.1161/circulationaha.104.516930
47. Delling FN, Rong J, Larson MG, Lehman B, Osypiuk E, Stantchev P, Slaugenhaupt SA, Benjamin EJ, Levine RA, Vasan RS. Familial clustering of mitral valve prolapse in the community. *Circulation*. 2015;131:263–268. doi: 10.1161/circulationaha.114.012594
48. Kyndt F, Gueffet JP, Probst V, Jaafar P, Legendre A, Le Bouffant F, Toquet C, Roy E, McGregor L, Lynch SA, Newbury-Ecob R, Tran V, Young I, Trochu JN, Le Marec H, Schott JJ. Mutations in the gene encoding filamin A as a cause for familial cardiac valvular dystrophy. *Circulation*. 2007;115:40–49. doi: 10.1161/circulationaha.106.622621
49. Dina C, Bouatia-Naji N, Tucker N, Delling FN, Toomer K, Durst R, Perrocheau M, Fernandez-Friera L, Solis J, Le Tourneau T, Chen MH, Probst V, Bosse Y, Pibarot P, Zelenika D, Lathrop M, Hercberg S, Roussel R, Benjamin EJ, Bonnet F, Lo SH, Dolmatova E, Simonet F, Lecointe S, Kyndt F, Redon R, Le Marec H, Froguel P, Ellinor PT, Vasan RS, Bruneval P, Markwald RR, Norris RA, Milan DJ, Slaugenhaupt SA, Levine RA, Schott JJ, Hagege AA, Jeunemaitre X; PROMESA investigators; MVP-France; Leducq Transatlantic MITRAL Network. Genetic association analyses highlight biological pathways underlying mitral valve prolapse. *Nat Genet*. 2015;47:1206–1211. doi: 10.1038/ng.3383
50. Durst R, Sauls K, Peal DS, deVlaming A, Toomer K, Leyne M, Salani M, Talkowski ME, Brand H, Perrocheau M, Simpson C, Jett C, Stone MR, Charles F, Chiang C, Lynch SN, Bouatia-Naji N, Delling FN, Freed LA, Tribouilloy C, Le Tourneau T, LeMarec H, Fernandez-Friera L, Solis J, Trujillano D, Ossowski S, Estivill X, Dina C, Bruneval P, Chester A, Schott JJ, Irvine KD, Mao Y, Wessels A, Motiwala T, Puceat M, Tsukasaki Y, Menick DR, Kasiganesan H, Nie X, Broome AM, Williams K, Johnson A, Markwald RR, Jeunemaitre X, Hagege A, Levine RA, Milan DJ, Norris RA, Slaugenhaupt SA. Mutations in DCHS1 cause mitral valve prolapse. *Nature*. 2015;525:109–113. doi: 10.1038/nature14670
51. Lalani T, Chu VH, Park LP, Cecchi E, Corey GR, Durante-Mangoni E, Fowler VG Jr, Gordon D, Grossi P, Hannan M, Hoen B, Muñoz P, Rizk H, Kanj SS, Selton-Suty C, Sexton DJ, Spelman D, Ravasio V, Tripodi MF, Wang A; International Collaboration on Endocarditis–Prospective Cohort Study Investigators. In-hospital and 1-year mortality in patients undergoing early surgery for prosthetic valve endocarditis. *JAMA Intern Med*. 2013;173:1495–1504. doi: 10.1001/jamainternmed.2013.8203
52. Sorajja P, Mack M, Vemulapalli S, Holmes DR Jr, Stebbins A, Kar S, Lim DS, Thourani V, McCarthy P, Kapadia S, Grayburn P, Pedersen WA, Ailawadi G. Initial experience with commercial transcatheter mitral valve repair in the United States. *J Am Coll Cardiol*. 2016;67:1129–1140. doi: 10.1016/j.jacc.2015.12.054
53. Feldman T, Foster E, Glower DD, Glower DG, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engeron E, Loghin C, Trento A, Skipper ER, Fudge T, Letsou GV, Massaro JM, Mauri L; EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med*. 2011;364:1395–1406. doi: 10.1056/NEJMoa1009355
54. Deuschl F, Schofer N, Lubos E, Blankenberg S, Schäfer U. Critical evaluation of the MitraClip system in the management of mitral regurgitation. *Vasc Health Risk Manag*. 2016;12:1–8. doi: 10.2147/VHRM.S65185
55. Mihaljevic T, Lam BK, Rajeswaran J, Takagaki M, Lauer MS, Gillinov AM, Blackstone EH, Lytle BW. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. *J Am Coll Cardiol*. 2007;49:2191–2201. doi: 10.1016/j.jacc.2007.02.043
56. Smith PK, Puskas JD, Ascheim DD, Voisine P, Gelijns AC, Moskowitz AJ, Hung JW, Parides MK, Ailawadi G, Perrault LP, Acker MA, Argenziano M, Thourani V, Gammie JS, Miller MA, Pagé P, Overbey JR, Bagiella E, Dagenais F, Blackstone EH, Kron IL, Goldstein DJ, Rose EA, Moquete EG, Jeffries N, Gardner TJ, O'Gara PT, Alexander JH, Michler RE; Cardiothoracic Surgical Trials Network Investigators. Surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med*. 2014;371:2178–2188. doi: 10.1056/NEJMoa1410490
57. Cameron HL, Bernard LM, Garmo VS, Hernandez JB, Asgar AW. A Canadian cost-effectiveness analysis of transcatheter mitral valve repair with the MitraClip system in high surgical risk patients with significant mitral regurgitation. *J Med Econ*. 2014;17:599–615. doi: 10.3111/13696998.2014.923892

58. Allen HD,Shaddy RE, Penny DJ, Feltes TF, Cetta F. *Moss & Adams' Heart Disease in Infants, Children, and Adolescents, Including the Fetus and Young Adult*. Vol 1. 9th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2016.
59. Mutlak D, Lessick J, Reisner SA, Aronson D, Dabbah S, Agmon Y. Echocardiography-based spectrum of severe tricuspid regurgitation: the frequency of apparently idiopathic tricuspid regurgitation. *J Am Soc Echocardiogr*. 2007;20:405–408. doi: 10.1016/j.echo.2006.09.013
60. Rao PS, Galal O, Patnana M, Buck SH, Wilson AD. Results of three to 10 year follow up of balloon dilatation of the pulmonary valve. *Heart*. 1998;80:591–595.
61. Klein AL, Burstow DJ, Tajik AJ, Zachariah PK, Taliercio CP, Taylor CL, Bailey KR, Seward JB. Age-related prevalence of valvular regurgitation in normal subjects: a comprehensive color flow examination of 118 volunteers. *J Am Soc Echocardiogr*. 1990;3:54–63.
62. O'Connor BK, Beekman RH, Lindauer A, Rocchini A. Intermediate-term outcome after pulmonary balloon valvuloplasty: comparison with a matched surgical control group. *J Am Coll Cardiol*. 1992;20:169–173.
63. Hayes CJ, Gersony WM, Driscoll DJ, Keane JF, Kidd L, O'Fallon WM, Pieroni DR, Wolfe RR, Weidman WH. Second natural history study of congenital heart defects: results of treatment of patients with pulmonary valvar stenosis. *Circulation*. 1993;87(suppl):I28–I37.
64. Gillespie MJ, Rome JJ, Levi DS, Williams RJ, Rhodes JF, Cheatham JP, Hellenbrand WE, Jones TK, Vincent JA, Zahn EM, McElhinney DB. Melody valve implant within failed bioprosthetic valves in the pulmonary position: a multicenter experience. *Circ Cardiovasc Interv*. 2012;5:862–870. doi: 10.1161/CIRCINTERVENTIONS.112.972216
65. Lee C, Kim YM, Lee CH, Kwak JG, Park CS, Song JY, Shim WS, Choi EY, Lee SY, Baek JS. Outcomes of pulmonary valve replacement in 170 patients with chronic pulmonary regurgitation after relief of right ventricular outflow tract obstruction: implications for optimal timing of pulmonary valve replacement. *J Am Coll Cardiol*. 2012;60:1005–1014. doi: 10.1016/j.jacc.2012.03.077
66. Hauck AJ, Freeman DP, Ackermann DM, Danielson GK, Edwards WD. Surgical pathology of the tricuspid valve: a study of 363 cases spanning 25 years. *Mayo Clin Proc*. 1988;63:851–863.
67. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol*. 2004;43:405–409. doi: 10.1016/j.jacc.2003.09.036
68. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:e521–e643. doi: 10.1161/CIR.0000000000000031
69. Zack CJ, Fender EA, Chandrashekar P, Reddy YNV, Bennett CE, Stulak JM, Miller VM, Nishimura RA. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol*. 2017;70:2953–2960. doi: 10.1016/j.jacc.2017.10.039
70. Nickenig G, Kowalski M, Hausleiter J, Braun D, Schofer J, Yzeiraj E, Rudolph V, Friedrichs K, Maisano F, Taramasso M, Fam N, Bianchi G, Bedogni F, Denti P, Alfieri O, Latib A, Colombo A, Hammerstingl C, Schueler R. Transcatheter treatment of severe tricuspid regurgitation with the edge-to-edge MitraClip technique. *Circulation*. 2017;135:1802–1814. doi: 10.1161/CIRCULATIONAHA.116.024848
71. Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, Forouzanfar MH, Longenecker CT, Mayosi BM, Mensah GA, Nascimento BR, Ribeiro ALP, Sable CA, Steer AC, Naghavi M, Mokdad AH, Murray CJL, Vos T, Carapetis JR, Roth GA. Global, regional, and national burden of rheumatic heart disease, 1990-2015. *N Engl J Med*. 2017;377:713–722. doi: 10.1056/NEJMoa1603693
72. Roth GA, Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, Morozoff C, Naghavi M, Mokdad AH, Murray CJL. Trends and patterns of geographic variation in cardiovascular mortality among US counties, 1980-2014. *JAMA*. 2017;317:1976–1992. doi: 10.1001/jama.2017.4150
73. Zühlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B, Mauff K, Islam S, Joachim A, Daniels R, Francis V, Ogendo S, Gitura B, Mondo C, Okello E, Lwabi P, Al-Kebsi MM, Hugo-Hamman C, Sheta SS, Haileamlak A, Daniel W, Goshu DY, Abdissa SG, Desta AG, Shasho BA, Begna DM, ElSayed A, Ibrahim AS, Musuku J, Bode-Thomas F, Okeahialam BN, Ige O, Sutton C, Misra R, Abul Fadl A, Kennedy N, Damasceno A, Sani M, Ogah OS, Olunuga T, Elhassan HH, Mocumbi AO, Adeoye AM, Mntla P, Ojji D, Mucumbitsi J, Teo K, Yusuf S, Mayosi BM. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J*. 2015;36:1115–122a. doi: 10.1093/eurheartj/ehu449
74. Zühlke L, Karthikeyan G, Engel ME, Rangarajan S, Mackie P, Cupido-Katya Mauff B, Islam S, Daniels R, Francis V, Ogendo S, Gitura B, Mondo C, Okello E, Lwabi P, Al-Kebsi MM, Hugo-Hamman C, Sheta SS, Haileamlak A, Daniel W, Goshu DY, Abdissa SG, Desta AG, Shasho BA, Begna DM, ElSayed A, Ibrahim AS, Musuku J, Bode-Thomas F, Yilgwan CC, Amusa GA, Ige O, Okeahialam B, Sutton C, Misra R, Abul Fadl A, Kennedy N, Damasceno A, Sani MU, Ogah OS, Elhassan TO, Mocumbi AO, Adeoye AM, Mntla P, Ojji D, Mucumbitsi J, Teo K, Yusuf S, Mayosi BM. Clinical outcomes in 3343 children and adults with rheumatic heart disease from 14 low- and middle-income countries: two-year follow-up of the Global Rheumatic Heart Disease Registry (the REMEDY Study). *Circulation*. 2016;134:1456–1466. doi: 10.1161/CIRCULATIONAHA.116.024769
75. Okello E, Longenecker CT, Beaton A, Kamya MR, Lwabi P. Rheumatic heart disease in Uganda: predictors of morbidity and mortality one year after presentation. *BMC Cardiovasc Disord*. 2017;17:20. doi: 10.1186/s12872-016-0451-8
76. Wood AD, Mannu GS, Clark AB, Tiamkao S, Kongbunkiat K, Bettencourt-Silva JH, Sawanyawisuth K, Kasemsap N, Barlas RS, Mamas M, Myint PK. Rheumatic mitral valve disease is associated with worse outcomes in stroke: a Thailand National Database study. *Stroke*. 2016;47:2695–2701. doi: 10.1161/STROKEAHA.116.014512
77. Reményi B, Wilson N, Steer A, Ferreira B, Kado J, Kumar K, Lawrenson J, Maguire G, Marijon E, Mirabel M, Mocumbi AO, Mota C, Paar J, Saxena A, Scheel J, Stirling J, Viali S, Balekundri VI, Wheaton G, Zühlke L, Carapetis J. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease: an evidence-based guideline. *Nat Rev Cardiol*. 2012;9:297–309. doi: 10.1038/nrcardio.2012.7
78. Nascimento BR, Beaton AZ, Nunes MC, Diamantino AC, Carmo GA, Oliveira KK, Oliveira CM, Meira ZM, Castilho SR, Lopes EL, Castro IM, Rezende VM, Chequer G, Landay T, Tompsett A, Ribeiro AL, Sable C; PROVAR (Programa de RastreamentO da VAlvopatia Reumática) investigators. Echocardiographic prevalence of rheumatic heart disease in Brazilian schoolchildren: data from the PROVAR study. *Int J Cardiol*. 2016;219:439–445. doi: 10.1016/j.ijcard.2016.06.088
79. Ploutz M, Lu JC, Scheel J, Webb C, Ensing GJ, Aliku T, Lwabi P, Sable C, Beaton A. Handheld echocardiographic screening for rheumatic heart disease by non-experts. *Heart*. 2016;102:35–39. doi: 10.1136/heartjnl-2015-308236
80. Shrestha NR, Karki P, Mahto R, Gurung K, Pandey N, Agrawal K, Rothenbühler M, Urban P, Jüni P, Pilgrim T. Prevalence of subclinical rheumatic heart disease in eastern Nepal: a school-based cross-sectional study. *JAMA Cardiol*. 2016;1:89–96. doi: 10.1001/jamacardio.2015.0292
81. Clark BC, Krishnan A, McCarter R, Scheel J, Sable C, Beaton A. Using a low-risk population to estimate the specificity of the World Heart Federation criteria for the diagnosis of rheumatic heart disease. *J Am Soc Echocardiogr*. 2016;29:253–258. doi: 10.1016/j.echo.2015.11.013
82. Engelman D, Wheaton GR, Mataika RL, Kado JH, Colquhoun SM, Remenyi B, Steer AC. Screening-detected rheumatic heart disease can progress to severe disease. *Heart Asia*. 2016;8:67–73. doi: 10.1136/heartasia-2016-010847
83. Bertaina G, Rouchon B, Huon B, Guillot N, Robillard C, Noël B, Nadra M, Tribouilloy C, Marijon E, Jouven X, Mirabel M. Outcomes of borderline rheumatic heart disease: a prospective cohort study. *Int J Cardiol*. 2017;228:661–665. doi: 10.1016/j.ijcard.2016.11.234
84. Zühlke L, Engel ME, Lemmer CE, van de Wall M, Nkepu S, Meiring A, Bestawros M, Mayosi BM. The natural history of latent rheumatic heart disease in a 5 year follow-up study: a prospective observational study. *BMC Cardiovasc Disord*. 2016;16:46. doi: 10.1186/s12872-016-0225-3
85. Beaton A, Aliku T, Dewyer A, Jacobs M, Jiang J, Longenecker CT, Lubega S, McCarter R, Mirabel M, Mirembe G, Namuyonga J, Okello E, Scheel A, Tenywa E, Sable C, Lwabi P. Latent rheumatic heart disease: identifying the children at highest risk of unfavorable outcome. *Circulation*. 2017;136:2233–2244. doi: 10.1161/CIRCULATIONAHA.117.029936
86. Longenecker CT, Morris SR, Aliku TO, Beaton A,Costa MA, Kamya MR, Kityo C, Lwabi P Mirembe G, Nampijja D, Rwebembera J, Sable C, Salata RA, Scheel A, Simon DI, Ssinabulya I, Okello E. Rheumatic heart disease treatment cascade in Uganda. *Circ Cardiovasc Qual Outcomes*. 2017;10:e004037. doi: 10.1161/CIRCOUTCOMES.117.004037
87. Parks T, Kado J, Miller AE, Ward B, Heenan R, Colquhoun SM, Bärnighausen TW, Mirabel M, Bloom DE, Bailey RL, Tukana IN, Steer AC. Rheumatic heart disease-attributable mortality at ages 5-69 years in Fiji: a five-year, national, population-based record-linkage cohort study. *PLoS Negl Trop Dis*. 2015;9:e0004033. doi: 10.1371/journal.pntd.0004033

88. Global Burden of Disease Study 2016. Global Burden of Disease Study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed May 1, 2018.
89. Pant S, Patel NJ, Deshmukh A, Golwala H, Patel N, Badheka A, Hirsch GA, Mehta JL. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. *J Am Coll Cardiol*. 2015;65:2070–2076. doi: 10.1016/j.jacc.2015.03.518
90. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1459–1544. doi: 10.1016/S0140-6736(16)31012-1
91. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, Bolger A, Cabell CH, Takahashi M, Baltimore RS, Newburger JW, Strom BL, Tani LY, Gerber M, Bonow RO, Pallasch T, Shulman ST, Rowley AH, Burns JC, Ferrieri P, Gardner T, Goff D, Durack DT. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group [published correction appears in *Circulation*. 2007;116:e376–e377]. *Circulation*. 2007;116:1736–1754. doi: 10.1161/CIRCULATIONAHA.106.183095
92. Ware AL, Tani LY, Weng HY, Wilkes J, Menon SC. Resource utilization and outcomes of infective endocarditis in children. *J Pediatr*. 2014;165:807–812.e1. doi: 10.1016/j.jpeds.2014.06.026
93. DeSimone DC, Tleyjeh IM, Correa de Sa DD, Anavekar NS, Lahr BD, Sohail MR, Steckelberg JM, Wilson WR, Baddour LM. Temporal trends in infective endocarditis epidemiology from 2007 to 2013 in Olmsted County, MN. *Am Heart J*. 2015;170:830–836. doi: 10.1016/j.ahj.2015.07.007
94. Pasquali SK, He X, Mohamad Z, McCrindle BW, Newburger JW, Li JS, Shah SS. Trends in endocarditis hospitalizations at US children's hospitals: impact of the 2007 American Heart Association antibiotic prophylaxis guidelines. *Am Heart J*. 2012;163:894–899. doi: 10.1016/j.ahj.2012.03.002
95. Slipczuk L, Codolosa N, Carlos D, Romero-Corral A, Pressman G, Figueredo V. Systematic review & meta-analysis of infective endocarditis microbiology over 5 decades. *Circulation*. 2012;126(suppl 21):A15138. Abstract 15138.
96. Abdallah L, Remadi JP, Habib G, Salaun E, Casalta JP, Tribouilloy C. Long-term prognosis of left-sided native-valve *Staphylococcus aureus* endocarditis. *Arch Cardiovasc Dis*. 2016;109:260–267. doi: 10.1016/j.acvd.2015.11.012
97. Katan O, Michelena HI, Avierinos JF, Mahoney DW, DeSimone DC, Baddour LM, Suri RM, Enriquez-Sarano M. Incidence and predictors of infective endocarditis in mitral valve prolapse: a population-based study. *Mayo Clin Proc*. 2016;91:336–342. doi: 10.1016/j.mayocp.2015.12.006
98. Deo SV, Raza S, Kalra A, Deo VS, Altarabsheh SE, Zia A, Khan MS, Markowitz AH, Sabik JF 3rd, Park SJ. Admissions for infective endocarditis in intravenous drug users. *J Am Coll Cardiol*. 2018;71:1596–1597. doi: 10.1016/j.jacc.2018.02.011
99. Athan E, Chu VH, Tattevin P, Selton-Suty C, Jones P, Naber C, Miró JM, Ninot S, Fernández-Hidalgo N, Durante-Mangoni E, Spelman D, Hoen B, Lejko-Zupanc T, Cecchi E, Thuny F, Hannan MM, Pappas P, Henry M, Fowler VG Jr, Crowley AL, Wang A; ICE-PCS Investigators. Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices. *JAMA*. 2012;307:1727–1735. doi: 10.1001/jama.2012.497
100. Chu VH, Park LP, Athan E, Delahaye F, Freiberger T, Lamas C, Miro JM, Mudrick DW, Strahilevitz J, Tribouilloy C, Durante-Mangoni E, Pericas JM, Fernández-Hidalgo N, Nacinovich F, Rizk H, Krajinovic V, Giannitsioti E, Hurley JP, Hannan MM, Wang A; for the International Collaboration on Endocarditis (ICE) Investigators. Association between surgical indications, operative risk, and clinical outcome in infective endocarditis: a prospective study from the International Collaboration on Endocarditis. *Circulation*. 2015;131:131–140. doi: 10.1161/CIRCULATIONAHA.114.012461
101. National Center for Health Statistics. *Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities.* Hyattsville, MD: National Center for Health Statistics; 2016.

22. VENOUS THROMBOEMBOLISM (DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM), CHRONIC VENOUS INSUFFICIENCY, PULMONARY HYPERTENSION

See Charts 22-1 and 22-2

Click here to return to the Table of Contents

Pulmonary Embolism
ICD-9 415.1; *ICD-10* I26.

Mortality—8502. Any-mention mortality—33 987 (2016 NHLBI tabulation). Hospital discharges—178 000 (principal diagnosis), 339 000 (all-listed diagnoses) (2014 HCUP).

Deep Vein Thrombosis
ICD-9 451.1, 451.2, 451.81, 451.9, 453.0, 453.1 453.2, 453.3, 453.4, 453.5, 453.9; *ICD-10* I80.1, I80.2, I80.3, I80.9, I82.0, I82.1, I82.2, I82.3, I82.4, I82.5, I82.9.

Mortality—3187. Any-mention mortality—16 479 (2016 NHLBI tabulation). Hospital discharges—114 000 (principal diagnosis), 473 000 (all-listed diagnoses) (2014 HCUP).

Abbreviations Used in Chapter 22

BMI	body mass index
CI	confidence interval
CT	computed tomography
CTEPH	chronic thromboembolic pulmonary hypertension
CVI	chronic venous insufficiency
DM	diabetes mellitus
DVT	deep vein thrombosis
FHS	Framingham Heart Study
GWAS	genome-wide association study
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HF	heart failure
HIV	human immunodeficiency virus
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
ICU	intensive care unit
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
OR	odds ratio
PAH	pulmonary arterial hypertension
PE	pulmonary embolism
PH	pulmonary hypertension
PTS	postthrombotic syndrome
REVEAL	Registry to Evaluate Early and Long-term PAH Disease Management
RCT	randomized controlled trial
RR	relative risk
RV	right ventricular
VTE	venous thromboembolism
WHO	World Health Organization

Venous Thromboembolism

Incidence (Charts 22-1 and 22-2)

- VTE includes both DVT and PE. Information on VTE incidence in the United States is limited because there is no national surveillance system. The HCUP NIS (Charts 22-1 and 22-2) shows increasing rates of hospitalization cases for both PE from 1996 to 2014 and DVT from 2005 to 2014, with DVT trending down since 2012. Extrapolating from these data, if we assume 30% of DVTs were treated in the outpatient setting, we estimate that in 2014 there were ≈676 000 DVTs, ≈340 000 PEs and ≈1 016 000 total VTE events in the United States (US population was 319 million in 2014).[1]
- Interpretation of the HCUP NIS, and most other sources of VTE incidence data, should be viewed in light of secular trends and data characteristics that could have resulted in an increase in VTE diagnosis that might overstate changes in VTE incidence (eg, advances in PE imaging, which enable the detection of smaller PEs[2] increased use of full leg ultrasound, which detects distal DVT; the co-occurrence of codes for DVT and PE in the same patient) and other factors that could lead to underestimation of VTE incidence (eg, outpatient management of ≈35% of DVT cases[3] and a smaller portion of PE cases,[4,5] misdiagnosis of VTE events, and failure to ascertain fatal PEs because of low autopsy rates).
- A modeling study estimated VTE incidence in 6 countries in Europe (total population 310.4 million), accounting for missed diagnoses related to factors such as lack of routine autopsy, misdiagnosis, or underdiagnosis because of lack of symptom recognition.[6] The authors estimated there were 465 715 (404 664–538 189) cases of DVT, 295 982 (242 450–360 363) cases of PE, and 370 012 (300 193–483 108) VTE-related deaths annually. Of these deaths, only 7% were diagnosed antemortem; 34% were sudden fatal PE, and 59% followed undiagnosed PE.
- Using administrative data in the United States, the estimated admissions for PE increased from 23 per 100 000 in 1993 to 65 per 100 000 in 2012.[7] Trends in DVT incidence were not reported. The Danish National Cohort also reported that PE incidence increased from 45 to 83 per 100 000 from 2004 to 2014.[8]
- Regarding trends in total VTE incidence, the Tromsø Study in Norway reported that the VTE

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incidence rate increased from 158 per 100 000 in 1996 to 1997 to 201 per 100 000 in 2010 to 2011.[9] This trend was driven by increasing incidence of PE.

- VTE incidence varies by race/ethnicity.[10–13] Blacks appear to be at greatest risk, followed by Caucasians, Hispanics, and Asians, respectively.
- Incidence rates for PE and DVT increase exponentially with advancing age for both males and females.[11,14,15]

Lifetime Risk

- In 2 US cohorts including 19 599 males and females aged 45 to 99 years at baseline and followed up for 288 535 person-years, the remaining lifetime risk of VTE at age 45 years was 8.1% (95% CI, 7.1%–8.7%) overall, 11.5% in African Americans, 10.9% in those with obesity, 17.1% in individuals with the factor V Leiden genetic mutation, and 18.2% in people with sickle cell trait or disease.[16]

Mortality

- Using administrative data for first-time VTE in Quebec, Canada, from 2000 to 2009, 30-day case fatality was 10.6% and 1-year mortality was 23.0%. The 1-year survival rate was 47% (95% CI, 46%–48%) for cases with VTE and cancer, 93% (95% CI, 93%–94%) for cases with unprovoked VTE, and 84% (95% CI, 83%–84%) for those with provoked VTE.[17]
- Data from a Worcester, MA, surveillance study from 1999 to 2009 suggested a decline in 3-year mortality after VTE (from 41% to 26%).[18] Declines in VTE mortality rates have also been reported in the National Danish Cohort for the period from 2004 to 2014.[8] A decrease in mortality rates associated with VTE could be the result of several factors, including recognition of smaller PEs[2] and recent changes in treatment options.[19]

Recurrence

- VTE is a chronic disease with episodic recurrence; in the absence of long-term anticoagulation, ≈30% of patients develop recurrence within the next 10 years.[20–22]
- Independent predictors of recurrence within 180 days include active cancer and inadequate anticoagulation. Two-week case-fatality rates are 2% for recurrent DVT alone and 11% for recurrent PE with or without DVT.[23]

Complications

- Because of the use of anticoagulant therapy to treat VTE, bleeding is a major potential complication. Data from phase III RCTs suggest that use of direct oral anticoagulants, instead of warfarin, for VTE primary treatment could further reduce bleeding risk.[24]
- Postthrombotic syndrome/venous stasis syndrome and venous stasis ulcers are important complications of proximal lower-extremity DVT, which are discussed in greater depth in the Chronic Venous Insufficiency section of this chapter. After proximal lower-extremity DVT, the 20-year cumulative incidences of PTS/venous stasis syndrome and venous stasis ulcers are 30% and 3.7%, respectively.[25]
- CTEPH affects ≈4% of patients with PE within 2 years of their initial PE event.[26]

Costs

- A literature review estimated incremental direct medical costs (2014 US dollars) per case among 1-year survivors of acute VTE at $12 000 to $15 000 and the cost of complications, including recurrent VTE, PTS, CTEPH, and anticoagulation-related adverse events, at $18 000 to $23 000 per case. This review assumed 375 000 to 425 000 new cases in the United States annually and estimated the annual overall cost at $7 to 10 billion.[27]

Risk Factors

- Approximately 50% of VTEs are provoked because of immobilization, trauma, surgery, or hospitalization in the antecedent 3 months; 20% are associated with cancer; and 30% are unprovoked.[28–31]
- Independent VTE risk factors include increasing age, obesity, family history or personal history of thrombosis, recent surgery, trauma/fracture, hospitalization, prolonged immobility, nursing home residence, active cancer, indwelling central venous catheter or transvenous pacemaker, prior superficial vein thrombosis, infection, inherited or acquired thrombophilia, kidney disease, neurological disease with leg paresis, sickle cell anemia and sickle cell trait, long-distance travel, and among females, the use of estrogen-based contraceptives or hormone therapy, pregnancy, and the postpartum period.[20,32–34] Recently, autoimmune diseases, such as lupus and Sjögren syndrome, and acute infection have also been associated with elevated VTE risk.[35–38]
- Traditional atherosclerotic risk factors, including hypertension, hyperlipidemia, and DM, were not associated with VTE risk in a 2017 individual-level meta-analysis of >240 000 participants from 9 cohorts.[39] Cigarette smoking was associated with provoked but not with unprovoked VTE events.
- Among patients hospitalized for acute medical illness, independent risk factors for VTE include prior VTE, thrombophilia, cancer, age >60 years, leg paralysis, immobilization for 7 days, and admission to an ICU or coronary care unit.[40]

- Pregnancy-associated VTE has an incidence of 1 to 2 per 1000 person-years; compared with nonpregnant females of childbearing age, the RR for VTE is increased 4-fold.[41–43] VTE risk is higher for pregnancies after in vitro fertilization than for natural pregnancies,[44] and with multiple gestation, cesarean delivery, or other pregnancy complications.[45] Risk factors associated with VTE in the general population (eg, obesity) are also associated with pregnancy-associated VTE.
- VTE risk during the postpartum period is ≈5-fold higher than during pregnancy. Among females who are pregnant or postpartum, approximately one-third of the DVT events and one-half of the PE events occur after delivery,[46] with the RR being 21- to 84-fold increased within 6 weeks postpartum compared with females who are not pregnant or postpartum.[47]

Family History and Genetics

- VTE is highly heritable.[48,49]
- Factor V Leiden is a genetic variant responsible for ≈90% of cases of VTE caused by activated protein C resistance and is the most common genetic cause of VTE. Factor V Leiden increases risk of VTE 3- to 18-fold depending on the number of variants carried, and its presence can influence management.[50]
- More common genetic variants associated with VTE have a lesser risk of VTE than rare mutations and include non-O blood group, prothrombin 20210A, and sickle cell disease and trait.[51] GWASs have identified additional common genetic variants associated with VTE risk, including variants in *F5*, *F2*, *F11*, *FGG*, and *ZFPM2*.[52] These common variants individually increase the risk of VTE to a small extent, but genetic risk scores composed of a combination of these variants can increase the OR of VTE risk to up to 7.5.[53]

Treatment

- VTE is generally treated for 3 to 6 months with anticoagulation (primary treatment), at which point the risks and benefits of continued anticoagulation should be assessed (secondary prevention).[19] When oral anticoagulation is contraindicated or ineffective, inferior vena cava filters can be used.
- Current treatment guidelines consider anticoagulation with either warfarin or direct oral anticoagulant drugs (ie, apixaban, rivaroxaban, dabigatran, edoxaban) as the standard of care.[19] In phase III RCTs of VTE primary treatment,[54–57] the direct oral anticoagulant drugs were each shown to be as effective as warfarin in the prevention of recurrent VTE and VTE-related death. A meta-analysis[24] of these trials suggested that direct oral anticoagulant drugs have a lower risk of most bleeding complications than warfarin.

Chronic Venous Insufficiency *ICD-10* I87.2.

Mortality—46. Any-mention mortality—490 (2016 NHLBI tabulation).

Prevalence

- Varicose veins are a common manifestation of CVI, affecting 25 million US adults. More severe venous disease affects 6 million adults.[58]
- By way of international comparators, Zolotukhin and colleagues[59] described the prevalence of CVI (8.2%) and venous ulcers (1.1%) in a cohort of 703 people from central Russia.
- Functional chronic venous disease was recently reviewed by Serra and colleagues,[60] who described it as a complex syndrome that is as of now poorly understood.

Incidence

- The FHS reported an annual incidence of varicose veins of 2.6% in females and 1.9% in males.[61]

Complications

- More severe venous disease often includes manifestations such as hyperpigmentation, venous eczema, lipodermatosclerosis, atrophie blanche, and healed or active venous ulcers.[62]
- Analysis of NIS data for black and white Americans demonstrated declines in ulcer debridement, vein stripping, and sclerotherapy procedures from 1998 to 2011. Blacks presented at younger ages and more often had ulcer debridement and history of DVT than whites.[63]
- A recent publication that used a database of 300 patients treated for advanced CVI with radiofrequency ablation procedures showed that African-Americans presented with higher severity CVI and had less improvement with ablation.[64]
- A 2017 study reviewed the risk factors for PTS as well, finding age, sex, and prior DVT to be predictors, though nonmodifiable. Oral anticoagulation with warfarin or newer factor Xa inhibitors, along with catheter-directed thrombolysis, are suggested as potential therapeutic options.[65]

Cost

- Estimated cost in the United States to treat venous ulcers is $1 billion annually.[62]

Risk Factors

- The prevalence of moderate CVI increases with advancing age, family history, hernia surgery, obesity, number of births, and presence of flat feet in females and is less likely in those with hypertension; risk factors for more severe CVI include smoking in males and leg injury in females.[66] Blood coagulation disorders and inflammatory biomarkers that are related to DVT risk are also associated with an increased risk of CVI, consistent with the hypothesis that DVT predisposes to CVI.[67]

- PTS, a subset of CVI, has specific risk factors that can be identified at the time of or after DVT: recurrent ipsilateral DVT, obesity, more extensive DVT, poor quality of initial anticoagulation, ongoing symptoms or signs of DVT 1 month after diagnosis, and elevated D-dimer at 1 month.[68–70]
- Galanaud and colleagues[70] described the 2 most important predictors of PTS as an extensive proximal DVT and prior DVT in the same limb. PTS was reviewed by Rabinovich and Kahn,[71] who described prevention of DVT and appropriate anticoagulation of DVT once it occurs as the best means to prevent PTS.
- Varicose veins are more likely to occur in the setting of a positive family history, consistent with a heritable component. Although a number of genes are implicated, the genetic factors[72] predisposing to varicose veins have not been definitively identified.[73]
- Similarly, in the study by Zolotukhin et al,[59] family history was independently associated with chronic venous disease.

Pulmonary Hypertension
ICD-10 I27.0, I27.2.

Mortality—7313. Any-mention mortality—23 067 (2016 NHLBI tabulation).

Prevalence and Incidence

- In the United States, between 2001 and 2010, hospitalization rates for PH increased significantly, and among those aged ≥85 years, hospitalization rates nearly doubled.[74] In 2010, the age-adjusted rate of hospitalization associated with PH was 131 per 100 000 discharges overall and 1527 per 100 000 for those aged ≥85 years. There is also evidence of increasing mortality rates in both males and females; in 2010, the death rate for PH as any contributing cause of death was 6.5 per 100 000.[74]
- The WHO classifies PH into 5 groups (described below) according to underlying pathogenesis. Limited information is available on prevalence of PH subtypes in nonreferral settings. In one study conducted in Armadale, Australia, the most commonly identified PH subtypes were left-sided HD (WHO group 2: 68%), lung disease (WHO group 3: 9%), WHO group 1, underlying causes combined (3%), and CTEPH (WHO group 4: 2%); 15% were unclassifiable.[75]
- The prevalence of WHO group 1 PH (idiopathic, heritable, drug/toxin induced, or associated with other factors including connective tissue disease, infections [HIV, schistosomiasis], portal hypertension, and congenital HD) is estimated at 6.6 to 26.0 per million adults and the incidence at 1.1 to 7.6 per million adults annually.[76]
- WHO group 2 PH is attributable to left-sided HD. Estimates of the incidence and prevalence are difficult to ascertain but most likely would track with HF prevalence rates.[76]
- The prevalence and incidence of WHO group 3 PH (attributable to lung disease or hypoxia) is difficult to estimate but likely would track with lung disease prevalence.[76]
- The prevalence of WHO group 4 PH (CTEPH and other pulmonary obstructions) ranges from 1.0% to 8.8% among those with PE.[76] CTEPH incidence, however, may be underestimated based on general population data; in a 2017 modeling study, only 7% to 29% of CTEPH cases were diagnosed.[77]
- WHO group 5 PH has multifactorial mechanisms. When it accompanies sickle cell disease, the prevalence is 6% to 10% and increases with advancing age. When it accompanies thalassemia, the prevalence is 2.1%.[76,78]

Mortality

Mortality of PH depends on the cause and treatment.

- In the US-based REVEAL registry of patients with group 1 PH enrolled from 2006 to 2009, 5-year survival was 61.2% to 65.4%. Lower 5-year survival was strongly and directly associated with worse functional class at presentation.[79] In an earlier study from this registry, 6-minute walk distance was also shown to be a strong predictor, with 97%, 90%, and 68% 1-year survival for patients with >440, 165 to 440, and <165 meter walk distances, respectively. A decline of >15% over time also predicted a significantly worse outcome compared with a stable or improving 6-minute walk distance.[80]
- A German single-center registry study reported 5-year survival rates of 65.3% for patients with idiopathic PH, 50.9% for those with PH associated with connective tissue disease, 74.5% for those with PH caused by congenital HD, and 18.7% for those with pulmonary venous occlusive disease, respectively.[81]
- In a multicenter study of patients with PH caused by congenital HD with Eisenmenger syndrome, mortality was associated with age, pretricuspid

lesion, and the presence of a pericardial effusion and inversely associated with sinus rhythm and resting oxygen saturation.[82]

- In a French Registry study of 981 patients with idiopathic, heritable, or drug-induced PAH enrolled between 2006 and 2016, survival at 1 and 3 years was 90% and 73%, respectively.[83]
- In sickle cell disease–related PH, the 5-year survival rate in one study was 63% with and 83% without PH.[84]
- An international prospective registry that included 679 patients with CTEPH estimated that the 3-year survival was 89% with and 70% without pulmonary thromboendarterectomy.[85] Among the patients with CTEPH, treatments for PH did not affect survival. High New York Heart Association functional class, increased right atrial pressure, and history of cancer were associated with mortality regardless of surgery.

Risk Factors

- Risk factors are implicit in the WHO disease classification of the 5 mechanistic subtypes of PH described above. The most common risk factors are left-sided HD and lung disease.
- In a study of 772 consecutive PE patients without major comorbidities such as cancer, the risk factors for CTEPH were unprovoked PE, hypothyroidism, symptom onset >2 weeks before PE diagnosis, RV dysfunction on CT or echocardiography, DM, and thrombolytic therapy or embolectomy; a risk prediction score that included these factors was able to predict a group with a CTEPH incidence of 10% (95% CI, 6.5%–15%).[86] It is not clear to what extent these factors may be affected by the possibility that the index presentation was caused by worsening RV failure in the setting of CTEPH rather than acute PE. Higher BMI also has been associated with CTEPH risk after PE.[87]

Global Burden

- 80% of patients with PH live in developing countries, and the cause of their PH is primarily HD and lung disease, but schistosomiasis, rheumatic HD, HIV, and sickle cell disease remain prominent compared with developed countries. In these countries, younger people are more often affected (average age of onset <40 years).[76]
- In high-income countries, rates of CTEPH are believed to be lower in Japan than in the United States and Europe.[77]

Treatment

- Galiè and colleagues[88] performed a double-blind RCT of 500 treatment-naïve patients with WHO group 2 or 3 PH, randomizing them to ambrisentan, tadalafil, or both in combination. The combination group (versus the pooled monotherapy groups) was at lower risk for the composite primary end point of death, PAH hospitalization, or clinical disease progression (HR, 0.50 [95% CI, 0.35–0.72]).
- In a large, placebo-controlled, double-blind RCT of 1156 patients with PAH randomized to selexipag, an oral selective IP prostacyclin receptor agonist, versus placebo, Sitbon and colleagues[89] found a significant reduction in the primary composite end point of death attributable to any cause or PAH-related complication (HR, 0.60 [99% CI, 0.46–0.78]). This observed benefit was driven by differences in disease progression and hospitalization; no significant difference in mortality was seen between selexipag and placebo.
- Pulido and colleagues[90] performed a 250-patient RCT of 3 mg or 10 mg of macitentan, a dual endothelin receptor antagonist, versus placebo, with a primary end point composite of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of PAH. Macitentan was shown to have statistically and clinically significant benefit at either tested dose; the HR for 3 mg of macitentan versus placebo was 0.70 (97.5% CI, 0.52–0.96), and for 10 mg of macitentan versus placebo, the HR was 0.55 (97.5% CI, 0.39–0.76).[90]

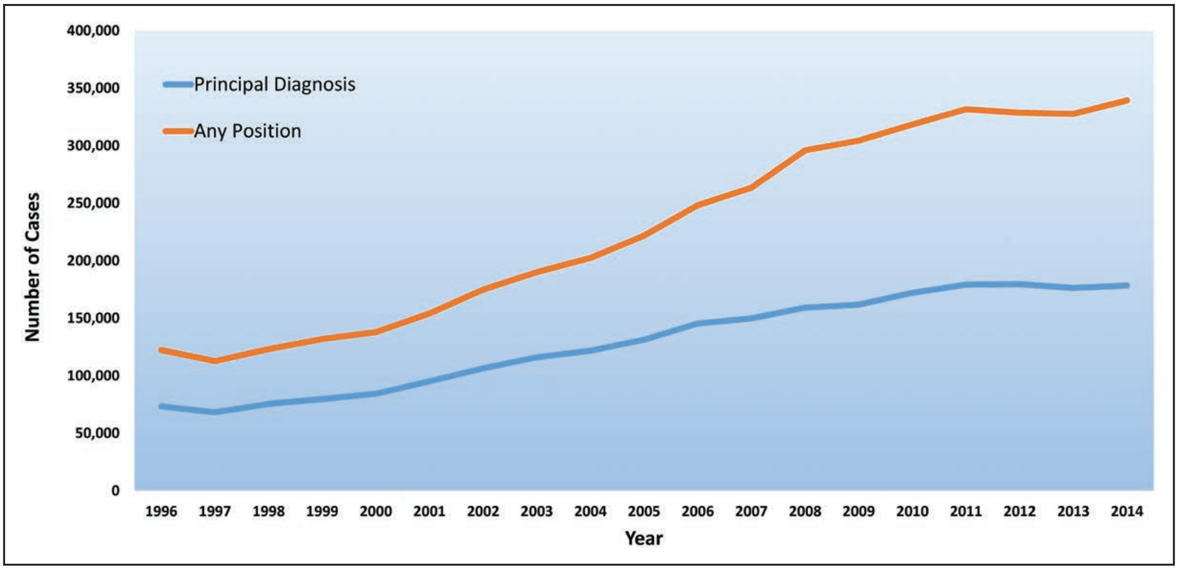

Chart 22-1. Trends in hospitalized pulmonary embolism, 1996 to 2014.
Source: Weighted national estimates from Healthcare Cost and Utilization Project National (Nationwide) Inpatient Sample, Agency for Healthcare Research and Quality, based on data collected by individual states.[1]

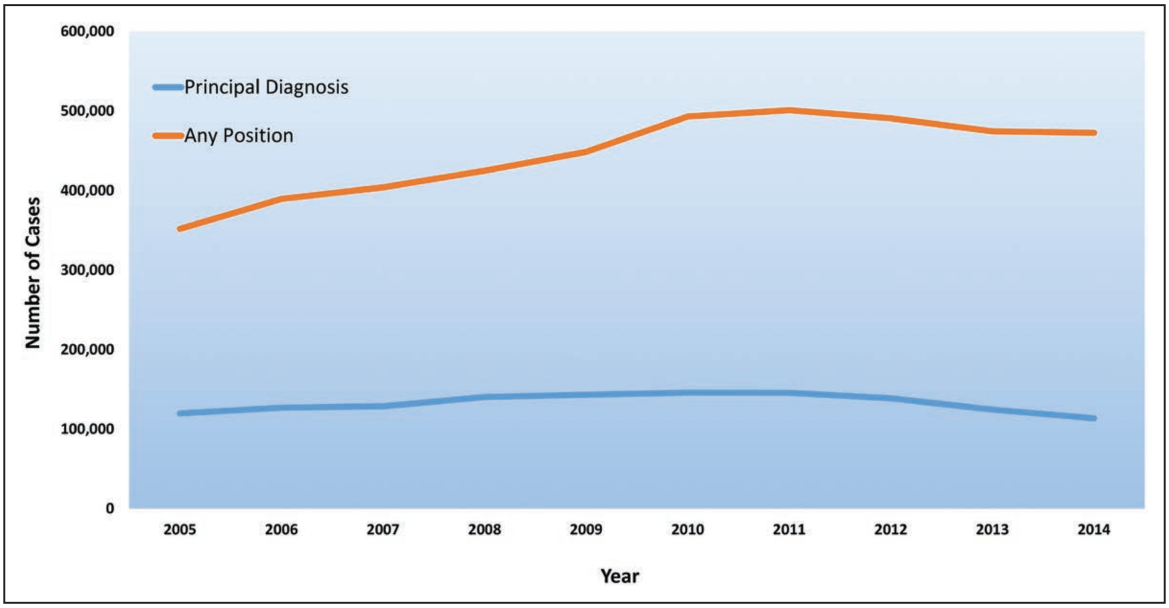

Chart 22-2. Trends in hospitalized deep vein thrombosis, 2005 to 2014.
Source: Weighted national estimates from Healthcare Cost and Utilization Project National (Nationwide) Inpatient Sample, Agency for Healthcare Research and Quality, based on data collected by individual states.[1]

REFERENCES

1. Weighted national estimates from HCUP National (Nationwide) Inpatient Sample (NIS), AHRQ, based on data collected by individual states. http://www.HCUP-US.AHRQ.gov. Accessed May 20, 2017.
2. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. *Arch Intern Med*. 2011;171:831–837. doi: 10.1001/archinternmed.2011.178
3. Stein PD, Matta F, Hughes MJ. Home treatment of deep venous thrombosis according to comorbid conditions. *Am J Med*. 2016;129:392–397. doi: 10.1016/j.amjmed.2015.10.022
4. Stein PD, Matta F, Hughes PG, Hourmouzis ZN, Hourmouzis NP, White RM, Ghiardi MM, Schwartz MA, Moore HL, Bach JA, Schweiss RE, Kazan VM, Kakish EJ, Keyes DC, Hughes MJ. Home treatment of pulmonary embolism in the era of novel oral anticoagulants. *Am J Med*. 2016;129:974–977. doi: 10.1016/j.amjmed.2016.03.035
5. Klil-Drori AJ, Coulombe J, Suissa S, Hirsch A, Tagalakis V. Temporal trends in outpatient management of incident pulmonary embolism and associated mortality. *Thromb Res*. 2018;161:111–116. doi: 10.1016/j.thromres.2017.10.026
6. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, Greer IA, Heit JA, Hutchinson JL, Kakkar AK, Mottier D, Oger E, Samama MM, Spannagl M; VTE Impact Assessment Group in Europe (VITAE). Venous thromboembolism (VTE) in Europe: the number of VTE events and associated morbidity and mortality. *Thromb Haemost*. 2007;98:756–764.
7. Smith SB, Geske JB, Kathuria P, Cuttica M, Schimmel DR, Courtney DM, Waterer GW, Wunderink RG. Analysis of national trends in admissions for pulmonary embolism. *Chest*. 2016;150:35–45. doi: 10.1016/j.chest.2016.02.638
8. Lehnert P, Lange T, Møller CH, Olsen PS, Carlsen J. Acute pulmonary embolism in a national Danish cohort: increasing incidence and decreasing mortality. *Thromb Haemost*. 2018;118:539–546. doi: 10.1160/TH17-08-0531
9. Arshad N, Isaksen T, Hansen JB, Brækkan SK. Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population. *Eur J Epidemiol*. 2017;32:299–305. doi: 10.1007/s10654-017-0238-y
10. White RH, Zhou H, Murin S, Harvey D. Effect of ethnicity and gender on the incidence of venous thromboembolism in a diverse population in California in 1996. *Thromb Haemost*. 2005;93:298–305. doi: 10.1160/TH04-08-0506
11. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, Folsom AR. Deep vein thrombosis and pulmonary embolism in two cohorts: the Longitudinal Investigation of Thromboembolism Etiology. *Am J Med*. 2004;117:19–25. doi: 10.1016/j.amjmed.2004.01.018
12. Klatsky AL, Armstrong MA, Poggi J. Risk of pulmonary embolism and/or deep venous thrombosis in Asian-Americans. *Am J Cardiol*. 2000;85:1334–1337.
13. Stein PD, Kayali F, Olson RE, Milford CE. Pulmonary thromboembolism in Asians/Pacific Islanders in the United States: analysis of data from the National Hospital Discharge Survey and the United States Bureau of the Census. *Am J Med*. 2004;116:435–442. doi: 10.1016/j.amjmed.2003.11.020
14. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med*. 1998;158:585–593.
15. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost*. 2007;5:692–699. doi: 10.1111/j.1538-7836.2007.02450.x
16. Bell EJ, Lutsey PL, Basu S, Cushman M, Heckbert SR, Lloyd-Jones DM, Folsom AR. Lifetime risk of venous thromboembolism in two cohort studies. *Am J Med*. 2016;129:339.e19–339.e26. doi: 10.1016/j.amjmed.2015.10.014
17. Tagalakis V, Patenaude V, Kahn SR, Suissa S. Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort. *Am J Med*. 2013;126:832.e13–832.e21. doi: 10.1016/j.amjmed.2013.02.024
18. Huang W, Goldberg RJ, Cohen AT, Anderson FA, Kiefe CI, Gore JM, Spencer FA. Declining long-term risk of adverse events after first-time community-presenting venous thromboembolism: the population-based Worcester VTE study (1999 to 2009). *Thromb Res*. 2015;135:1100–1106. doi: 10.1016/j.thromres.2015.04.007
19. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JRE, Wells P, Woller SC, Moores L. Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. *Chest*. 2016;149:315–352. doi: 10.1016/j.chest.2015.11.026
20. Heit JA. The epidemiology of venous thromboembolism in the community. *Arterioscler Thromb Vasc Biol*. 2008;28:370–372. doi: 10.1161/ATVBAHA.108.162545
21. Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, Iotti M, Tormene D, Simioni P, Pagnan A. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism: a prospective cohort study in 1,626 patients. *Haematologica*. 2007;92:199–205.
22. Lutsey PL, Virnig BA, Durham SB, Steffen LM, Hirsch AT, Jacobs DR Jr, Folsom AR. Correlates and consequences of venous thromboembolism: the Iowa Women's Health Study. *Am J Public Health*. 2010;100:1506–1513. doi: 10.2105/AJPH.2008.157776
23. Heit JA, Lahr BD, Petterson TM, Bailey KR, Ashrani AA, Melton LJ 3rd. Heparin and warfarin anticoagulation intensity as predictors of recurrence after deep vein thrombosis or pulmonary embolism: a population-based cohort study. *Blood*. 2011;118:4992–4999. doi: 10.1182/blood-2011-05-357343
24. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. *J Thromb Haemost*. 2014;12:320–328. doi: 10.1111/jth.12485
25. Mohr DN, Silverstein MD, Heit JA, Petterson TM, O'Fallon WM, Melton LJ. The venous stasis syndrome after deep venous thrombosis or pulmonary embolism: a population-based study. *Mayo Clin Proc*. 2000;75:1249–1256.
26. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, Albanese P, Biasiolo A, Pegoraro C, Iliceto S, Prandoni P; Thromboembolic Pulmonary Hypertension Study Group. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med*. 2004;350:2257–2264. doi: 10.1056/NEJMoa032274
27. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: a review of estimated attributable healthcare costs. *Thromb Res*. 2016;137:3–10. doi: 10.1016/j.thromres.2015.11.033
28. Connolly GC, Francis CW. Cancer-associated thrombosis. *Hematology Am Soc Hematol Educ Program*. 2013;2013:684–691. doi: 10.1182/asheducation-2013.1.684
29. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. *Blood*. 2013;122:1712–1723. doi: 10.1182/blood-2013-04-460121
30. Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. *J Clin Oncol*. 2009;27:4839–4847. doi: 10.1200/JCO.2009.22.3271
31. Ay C, Pabinger I, Cohen AT. Cancer-associated venous thromboembolism: burden, mechanisms, and management. *Thromb Haemost*. 2017;117:219–230. doi: 10.1160/TH16-08-0615
32. Folsom AR, Tang W, Roetker NS, Kshirsagar AV, Derebail VK, Lutsey PL, Naik R, Pankow JS, Grove ML, Basu S, Key NS, Cushman M. Prospective study of sickle cell trait and venous thromboembolism incidence. *J Thromb Haemost*. 2015;13:2–9. doi: 10.1111/jth.12787
33. Mahmoodi BK, Gansevoort RT, Næss IA, Lutsey PL, Brækkan SK, Veeger NJ, Brodin EE, Meijer K, Sang Y, Matsushita K, Hallan SI, Hammerstrøm J, Cannegieter SC, Astor BC, Coresh J, Folsom AR, Hansen JB, Cushman M. Association of mild to moderate chronic kidney disease with venous thromboembolism: pooled analysis of five prospective general population cohorts. *Circulation*. 2012;126:1964–1971. doi: 10.1161/CIRCULATIONAHA.112.113944
34. Parkin L, Sweetland S, Balkwill A, Green J, Reeves G, Beral V; for the Million Women Study Collaborators. Body mass index, surgery, and risk of venous thromboembolism in middle-aged women: a cohort study. *Circulation*. 2012;125:1897–1904. doi: 10.1161/CIRCULATIONAHA.111.063354
35. Ahlehoff O, Wu JJ, Raunsø J, Kristensen SL, Khalid U, Kofoed K, Gislason G. Cutaneous lupus erythematosus and the risk of deep venous thrombosis and pulmonary embolism: a Danish nationwide cohort study. *Lupus*. 2017;26:1435–1439. doi: 10.1177/0961203317716306
36. Annangi S, Dammalapati TR, Nutalapati S, Henriques King MN. Prevalence of pulmonary embolism among systemic lupus erythematosus discharges: a decade of analysis of the National Hospital Discharge Survey. *J Clin Rheumatol*. 2017;23:200–206. doi: 10.1097/RHU.0000000000000521

37. Aviña-Zubieta JA, Jansz M, Sayre EC, Choi HK. The risk of deep venous thrombosis and pulmonary embolism in primary Sjögren syndrome: a general population-based study. *J Rheumatol*. 2017;44:1184–1189. doi: 10.3899/jrheum.160185
38. Cohoon KP, Ashrani AA, Crusan DJ, Petterson TM, Bailey KR, Heit JA. Is infection an independent risk factor for venous thromboembolism? A population-based, case-control study. *Am J Med*. 2018;131:307–316.e2. doi: 10.1016/j.amjmed.2017.09.015
39. Mahmoodi BK, Cushman M, Anne Næss I, Allison MA, Bos WJ, Brækkan SK, Cannegieter SC, Gansevoort RT, Gona PN, Hammerstrøm J, Hansen JB, Heckbert S, Holst AG, Lakoski SG, Lutsey PL, Manson JE, Martin LW, Matsushita K, Meijer K, Overvad K, Prescott E, Puurunen M, Rossouw JE, Sang Y, Severinsen MT, Ten Berg J, Folsom AR, Zakai NA. Association of traditional cardiovascular risk factors with venous thromboembolism: an individual participant data meta-analysis of prospective studies. *Circulation*. 2017;135:7–16. doi: 10.1161/CIRCULATIONAHA.116.024507
40. Spyropoulos AC, Anderson FA Jr, FitzGerald G, Decousus H, Pini M, Chong BH, Zotz RB, Bergmann JF, Tapson V, Froehlich JB, Monreal M, Merli GJ, Pavanello R, Turpie AGG, Nakamura M, Piovella F, Kakkar AK, Spencer FA; IMPROVE Investigators. Predictive and associative models to identify hospitalized medical patients at risk for VTE. *Chest*. 2011;140:706–714. doi: 10.1378/chest.10-1944
41. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. *Am J Obstet Gynecol*. 2006;194:1311–1315. doi: 10.1016/j.ajog.2005.11.008
42. Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. *J Thromb Thrombolysis*. 2016;41:92–128. doi: 10.1007/s11239-015-1309-0
43. Greer IA. Thrombosis in pregnancy: updates in diagnosis and management. *Hematology Am Soc Hematol Educ Program*. 2012;2012:203–207. doi: 10.1182/asheducation-2012.1.203
44. Henriksson P, Westerlund E, Wallén H, Brandt L, Hovatta O, Ekbom A. Incidence of pulmonary and venous thromboembolism in pregnancies after *in vitro* fertilisation: cross sectional study. *BMJ*. 2013;346:e8632. doi: 10.1136/bmj.e8632
45. McLean K, Cushman M. Venous thromboembolism and stroke in pregnancy. *Hematology Am Soc Hematol Educ Program*. 2016;2016:243–250. doi: 10.1182/asheducation-2016.1.243
46. James AH. Venous thromboembolism in pregnancy. *Arterioscler Thromb Vasc Biol*. 2009;29:326–331. doi: 10.1161/ATVBAHA.109.184127
47. Jackson E, Curtis KM, Gaffield ME. Risk of venous thromboembolism during the postpartum period: a systematic review. *Obstet Gynecol*. 2011;117:691–703. doi: 10.1097/AOG.0b013e31820ce2db
48. Zöller B, Li X, Sundquist J, Sundquist K. A nationwide family study of pulmonary embolism: identification of high risk families with increased risk of hospitalized and fatal pulmonary embolism. *Thromb Res*. 2012;130:178–182. doi: 10.1016/j.thromres.2012.02.002
49. Zöller B, Ohlsson H, Sundquist J, Sundquist K. Familial risk of venous thromboembolism in first-, second- and third-degree relatives: a nationwide family study in Sweden. *Thromb Haemost*. 2013;109:458–463. doi: 10.1160/TH12-10-0743
50. Kujovich JL. Factor V Leiden thrombophilia. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, eds. GeneReviews [Internet]. Seattle, WA: University of Washington; 1993.
51. Morange PE, Suchon P, Trégouët DA. Genetics of venous thrombosis: update in 2015. *Thromb Haemost*. 2015;114:910–919. doi: 10.1160/TH15-05-0410
52. Klarin D, Emdin CA, Natarajan P, Conrad MF; and the INVENT Consortium, Kathiresan S. Genetic analysis of venous thromboembolism in UK Biobank identifies the ZFPM2 locus and implicates obesity as a causal risk factor. *Circ Cardiovasc Genet*. 2017;10:e001643. doi: 10.1161/CIRCGENETICS.116.001643
53. de Haan HG, Bezemer ID, Doggen CJ, Le Cessie S, Reitsma PH, Arellano AR, Tong CH, Devlin JJ, Bare LA, Rosendaal FR, Vossen CY. Multiple SNP testing improves risk prediction of first venous thrombosis. *Blood*. 2012;120:656–663. doi: 10.1182/blood-2011-12-397752
54. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361:2342–2352. doi: 10.1056/NEJMoa0906598
55. EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363:2499–2510. doi: 10.1056/NEJMoa1007903
56. Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369:1406–1415. doi: 10.1056/NEJMoa1306638
57. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI; for the AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369:799–808. doi: 10.1056/NEJMoa1302507
58. Beebe-Dimmer JL, Pfeifer JR, Engle JS, Schottenfeld D. The epidemiology of chronic venous insufficiency and varicose veins. *Ann Epidemiol*. 2005;15:175–184. doi: 10.1016/j.annepidem.2004.05.015
59. Zolotukhin IA, Seliverstov EI, Shevtsov YN, Avakiants IP, Nikishkov AS, Tatarintsev AM, Kirienko AI. Prevalence and risk factors for chronic venous disease in the general Russian population. *Eur J Vasc Endovasc Surg*. 2017;54:752–758. doi: 10.1016/j.ejvs.2017.08.033
60. Serra R, Andreucci M, De Caridi G, Massara M, Mastroroberto P, de Franciscis S. Functional chronic venous disease: a systematic review. *Phlebology*. 2017;32:588–592. doi: 10.1177/0268355516686451
61. Brand FN, Dannenberg AL, Abbott RD, Kannel WB. The epidemiology of varicose veins: the Framingham Study. *Am J Prev Med*. 1988;4:96–101.
62. Eberhardt RT, Raffetto JD. Chronic venous insufficiency. *Circulation*. 2014;130:333–346. doi: 10.1161/CIRCULATIONAHA.113.006898
63. Dua A, Desai SS, Heller JA. The impact of race on advanced chronic venous insufficiency. *Ann Vasc Surg*. 2016;34:152–156. doi: 10.1016/j.avsg.2016.01.020
64. Dua A, Heller JA. Advanced chronic venous insufficiency. *Vasc Endovascular Surg*. 2017;51:12–16. doi: 10.1177/1538574416682175
65. Strijkers RH, de Wolf MA, Wittens CH. Risk factors of postthrombotic syndrome before and after deep venous thrombosis treatment. *Phlebology*. 2017;32:384–389. doi: 10.1177/0268355516652010
66. Criqui MH, Denenberg JO, Bergan J, Langer RD, Fronek A. Risk factors for chronic venous disease: the San Diego Population Study. *J Vasc Surg*. 2007;46:331–337. doi: 10.1016/j.jvs.2007.03.052
67. Cushman M, Callas PW, Denenberg JO, Bovill EG, Criqui MH. Risk factors for peripheral venous disease resemble those for venous thrombosis: the San Diego Population Study. *J Thromb Haemost*. 2010;8:1730–1735. doi: 10.1111/j.1538-7836.2010.03924.x
68. Kahn SR, Comerota AJ, Cushman M, Evans NS, Ginsberg JS, Goldenberg NA, Gupta DK, Prandoni P, Vedantham S, Walsh ME, Weitz JI; on behalf of the American Heart Association Council on Peripheral Vascular Disease, Council on Clinical Cardiology, and Council on Cardiovascular and Stroke Nursing. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation*. 2014;130:1636–1661. doi: 10.1161/CIR.0000000000000130
69. Busuttil A, Lim CS, Davies AH. Post thrombotic syndrome. *Adv Exp Med Biol*. 2017;906:363–375. doi: 10.1007/5584_2016_126
70. Galanaud JP, Monreal M, Kahn SR. Epidemiology of the post-thrombotic syndrome. *Thromb Res*. 2018;164:100–109. doi: 10.1016/j.thromres.2017.07.026
71. Rabinovich A, Kahn SR. The postthrombotic syndrome: current evidence and future challenges. *J Thromb Haemost*. 2017;15:230–241. doi: 10.1111/jth.13569
72. Slonková V, Slonková V Jr, Vašků A, Vašků V. Genetic predisposition for chronic venous insufficiency in several genes for matrix metalloproteinases (MMP-2, MMP-9, MMP-12) and their inhibitor TIMP-2. *J Eur Acad Dermatol Venereol*. 2017;31:1746–1752. doi: 10.1111/jdv.14447
73. Anwar MA, Georgiadis KA, Shalhoub J, Lim CS, Gohel MS, Davies AH. A review of familial, genetic, and congenital aspects of primary varicose vein disease. *Circ Cardiovasc Genet*. 2012;5:460–466. doi: 10.1161/CIRCGENETICS.112.963439
74. George MG, Schieb LJ, Ayala C, Talwalkar A, Levant S. Pulmonary hypertension surveillance: United States, 2001 to 2010. *Chest*. 2014;146:476–495. doi: 10.1378/chest.14-0527
75. Strange G, Playford D, Stewart S, Deague JA, Nelson H, Kent A, Gabbay E. Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. *Heart*. 2012;98:1805–1811. doi: 10.1136/heartjnl-2012-301992
76. Hoeper MM, Humbert M, Souza R, Idrees M, Kawut SM, Sliwa-Hahnle K, Jing ZC, Gibbs JS. A global view of pulmonary hypertension. *Lancet Respir Med*. 2016;4:306–322. doi: 10.1016/S2213-2600(15)00543-3
77. Gall H, Hoeper MM, Richter MJ, Cacheris W, Hinzmann B, Mayer E. An epidemiological analysis of the burden of chronic thromboembolic pulmonary hypertension in the USA, Europe and Japan. *Eur Respir Rev*. 2017;26:160121. doi: 10.1183/16000617.0121-2016

78. Derchi G, Galanello R, Bina P, Cappellini MD, Piga A, Lai ME, Quarta A, Casu G, Perrotta S, Pinto V, Musallam KM, Forni GL; on behalf of the Webthal Pulmonary Arterial Hypertension Group. Prevalence and risk factors for pulmonary arterial hypertension in a large group of β-thalassemia patients using right heart catheterization: a Webthal study. *Circulation*. 2014;129:338–345. doi: 10.1161/CIRCULATIONAHA.113.002124
79. Farber HW, Miller DP, Poms AD, Badesch DB, Frost AE, Muros-Le Rouzic E, Romero AJ, Benton WW, Elliott CG, McGoon MD, Benza RL. Five-year outcomes of patients enrolled in the REVEAL Registry. *Chest*. 2015;148:1043–1054. doi: 10.1378/chest.15-0300
80. Farber HW, Miller DP, McGoon MD, Frost AE, Benton WW, Benza RL. Predicting outcomes in pulmonary arterial hypertension based on the 6-minute walk distance. *J Heart Lung Transplant*. 2015;34:362–368. doi: 10.1016/j.healun.2014.08.020
81. Gall H, Felix JF, Schneck FK, Milger K, Sommer N, Voswinckel R, Franco OH, Hofman A, Schermuly RT, Weissmann N, Grimminger F, Seeger W, Ghofrani HA. The Giessen Pulmonary Hypertension Registry: survival in pulmonary hypertension subgroups. *J Heart Lung Transplant*. 2017;36:957–967. doi: 10.1016/j.healun.2017.02.016
82. Kempny A, Hjortshøj CS, Gu H, Li W, Opotowsky AR, Landzberg MJ, Jensen AS, Søndergaard L, Estensen ME, Thilén U, Budts W, Mulder BJ, Blok I, Tomkiewicz-Pająk L, Szostek K, D'Alto M, Scognamiglio G, Prokšelj K, Diller GP, Dimopoulos K, Wort SJ, Gatzoulis MA. Predictors of death in contemporary adult patients with Eisenmenger syndrome: a multicenter study. *Circulation*. 2017;135:1432–1440. doi: 10.1161/CIRCULATIONAHA.116.023033
83. Weatherald J, Boucly A, Chemla D, Savale L, Peng M, Jevnikar M, Jaïs X, Taniguchi Y, O'Connell C, Parent F, Sattler C, Hervé P, Simonneau G, Montani D, Humbert M, Adir Y, Sitbon O. Prognostic value of follow-up hemodynamic variables after initial management in pulmonary arterial hypertension. *Circulation*. 2018;137:693–704. doi: 10.1161/CIRCULATIONAHA.117.029254
84. Mehari A, Alam S, Tian X, Cuttica MJ, Barnett CF, Miles G, Xu D, Seamon C, Adams-Graves P, Castro OL, Minniti CP, Sachdev V, Taylor JG 6th, Kato GJ, Machado RF. Hemodynamic predictors of mortality in adults with sickle cell disease. *Am J Respir Crit Care Med*. 2013;187:840–847. doi: 10.1164/rccm.201207-1222OC
85. Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, Bresser P, Torbicki A, Mellemkjaer S, Lewczuk J, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Jaïs X, Ambroz D, Treacy C, Morsolini M, Jenkins D, Lindner J, Dartevelle P, Mayer E, Simonneau G. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *Circulation*. 2016;133:859–871. doi: 10.1161/CIRCULATIONAHA.115.016522
86. Klok FA, Dzikowska-Diduch O, Kostrubiec M, Vliegen HW, Pruszczyk P, Hasenfuß G, Huisman MV, Konstantinides S, Lankeit M. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *J Thromb Haemost*. 2016;14:121–128. doi: 10.1111/jth.13175
87. Barros A, Baptista R, Nogueira A, Jorge E, Teixeira R, Castro G, Monteiro P, Providência LA. Predictors of pulmonary hypertension after intermediate-to-high risk pulmonary embolism. *Rev Port Cardiol*. 2013;32:857–864. doi: 10.1016/j.repc.2013.02.008
88. Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery JL, Grünig E, Oudiz RJ, Vonk-Noordegraaf A, White RJ, Blair C, Gillies H, Miller KL, Harris JH, Langley J, Rubin LJ; AMBITION Investigators. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med*. 2015;373:834–844. doi: 10.1056/NEJMoa1413687
89. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galiè N, Ghofrani HA, Hoeper MM, Lang IM, Preiss R, Rubin LJ, Di Scala L, Tapson V, Adzerikho I, Liu J, Moiseeva O, Zeng X, Simonneau G, McLaughlin VV; GRIPHON Investigators. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2015;373:2522–2533. doi: 10.1056/NEJMoa1503184
90. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani HA, Jansa P, Jing ZC, Le Brun FO, Mehta S, Mittelholzer CM, Perchenet L, Sastry BK, Sitbon O, Souza R, Torbicki A, Zeng X, Rubin LJ, Simonneau G; SERAPHIN Investigators. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369:809–818. doi: 10.1056/NEJMoa1213917

23. PERIPHERAL ARTERY DISEASE AND AORTIC DISEASES

***ICD-9* 440.20 to 440.24, 440.30 to 440.32, 440.4, 440.9, 443.9, 445.02; *ICD-10* I70.2, I70.9, I73.9, I74.3, I74.4. See Tables 23-1 through 23-3 and Charts 23-1 through 23-9**

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Peripheral Artery Disease

Prevalence and Incidence (See Table 23-1 and Charts 23-1 and 23-2)

- On the basis of data from several US cohorts during the 1970s to 2000s and the 2000 US Census, 6.5 million Americans aged ≥40 years (5.5%) are estimated to have low ABI (<0.9).[1] Of these, one-fourth have severe PAD (ABI <0.7).[1]
- Further accounting for PAD cases with ABI >0.9 (after revascularization or false-negative results with ABI), in 2000, PAD was estimated to affect ≈8.5 million Americans aged ≥40 years (7.2%).[2]
- Estimates of PAD prevalence in males and females by age and ethnicity are shown in Charts 23-1 and 23-2.[2]
- The highest prevalence of low ABI (<0.9) has been observed among older adults (22.7% among individuals aged ≥80 years versus 1.6% among those aged 40–49 years) and NH blacks (≈11.6% in NH blacks versus ≈5.5% in whites).[2] The prevalence of low ABI (<0.9) is similar between females (5.9%) and males (5.0%).
- Only ≈10% of people with PAD have the classic symptom of intermittent claudication. Approximately 40% do not complain of leg pain, whereas the remaining 50% have a variety of leg symptoms different from classic claudication (ie, exertional pain that either did not stop the individual from walking or did stop the individual from walking but did not involve the calves or did not resolve within 10 minutes of rest).[3,4]
- On the basis of *ICD* codes in nationwide claims data from large employers' health plans and from Medicare and Medicaid programs between 2003 and 2008, among adults aged >40 years, the annual incidence and prevalence of PAD were 2.69% and 12.02%, respectively.[5] The corresponding estimates for critical limb ischemia, the most severe form of PAD, were 0.35% and 1.33%, respectively.
- Data from the NIS demonstrate that admission rates because of critical limb ischemia remained constant from 2003 to 2011.[6]

Abbreviations Used in Chapter 23

AAA	abdominal aortic aneurysm
ABI	ankle-brachial index
ACC	American College of Cardiology
AHA	American Heart Association
Amer.	American
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
CORAL	Cardiovascular Outcomes in Renal Atherosclerotic Lesions
CVD	cardiovascular disease
DM	diabetes mellitus
ED	emergency department
GBD	Global Burden of Disease
GWAS	genome-wide association study
HCUP	Healthcare Cost and Utilization Project
HF	heart failure
HR	hazard ratio
ICD	*International Classification of Diseases*
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
IRAD	International Registry of Acute Aortic Dissection
JHS	Jackson Heart Study
KD	Kawasaki disease
LDL	low-density lipoprotein
MACE	major adverse cardiovascular event
MI	myocardial infarction
NAMCS	National Ambulatory Medical Care Survey
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHLBI	National Heart, Lung, and Blood Institute
NIS	Nationwide Inpatient Sample
OR	odds ratio
OVER	Open Versus Endovascular Repair
PA	physical activity
PAD	peripheral artery disease
RR	relative risk
SBP	systolic blood pressure
SES	socioeconomic status
SNP	single-nucleotide polymorphism

Mortality (See Table 23-1 and Chart 23-3)

- In 2016, the overall any-mention age-adjusted death rate for PAD was 14.8 per 100 000. Any-mention death rates in males were 18.2 for NH whites, 22.8 for NH blacks, 7.6 for NH Asians or Pacific Islanders, 17.5 for NH American Indians or Alaska Natives, and 14.1 for Hispanic males. In females, rates were 12.5 for NH whites, 15.7 for NH blacks, 5.9 for NH Asians or Pacific Islanders, 14.6 for NH American Indians or Alaska Natives, and 10.0 for Hispanic females.[7]
- In 2016, PAD was the underlying cause in 13 048 deaths. The number of any-mention deaths attributable to PAD was 56 923 in 2016 (NHLBI tabulation).[7]
- A 2008 meta-analysis of 24 955 males and 23 339 females from 16 cohorts demonstrated a reverse-J-shaped association between ABI and mortality in which participants with an ABI of 1.11 to 1.40 were at lowest risk for mortality (Chart 23-3). In

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males, low ABI (≤0.9) carried a 3-fold (RR, 3.33 [95% CI, 2.74–4.06]) risk of all-cause death compared with a normal ABI (1.11–1.40), and a similar risk was observed in females (RR, 2.71 [95% CI, 2.03–3.62]).[8] A similar reverse-J-shaped association between ABI was observed for cardiovascular mortality.

- In-hospital mortality was higher in females than males, regardless of disease severity or procedure performed, even after adjustment for age and baseline comorbidities: 0.5% versus 0.2% after percutaneous transluminal angioplasty or stenting for intermittent claudication; 1.0% versus 0.7% after open surgery for intermittent claudication; 2.3% versus 1.6% after percutaneous transluminal angioplasty or stenting for critical limb ischemia; and 2.7% versus 2.2% after open surgery for critical limb ischemia (*P*<0.01 for all comparisons).[9]
- Progression of PAD as measured by a decline in ABI also carries prognostic value beyond single measurements.[10] Among 508 patients (449 males) identified from 2 vascular laboratories in San Diego, CA, a decline in ABI of >0.15 within a 10-year period was associated with a subsequent increased risk of all-cause mortality (RR, 2.4 [95% CI, 1.2–4.8]) and CVD mortality (RR, 2.8 [95% CI, 1.3–6.0]) at 3 years' follow-up.[10]
- Among 400 patients with PAD confirmed with digital subtraction angiography, aortoiliac (proximal) disease was associated with an increased risk of mortality or cardiovascular events compared with infrailiac (distal) disease (adjusted HR, 3.28 [95% CI, 1.87–5.75]).[11] Compared with infrailiac PAD, aortoiliac PAD was associated with younger age, male sex, and smoking.

Complications

- PAD is a marker for systemic atherosclerotic disease, and thus, people with PAD are more likely to have atherosclerosis in other vascular beds (eg, coronary, carotid, and renal arteries and abdominal aorta).[12–15]
- Pooled data from 11 studies in 6 countries found that the pooled age-, sex-, risk factor–, and CVD-adjusted RRs in people with PAD (defined by ABI <0.9) versus those without were 1.45 (95% CI, 1.08–1.93) for CHD and 1.35 (95% CI, 1.10–1.65) for stroke.[16]
- From 2000 to 2008, the overall rate of lower-extremity amputation decreased significantly, from 7258 to 5790 per 100 000 Medicare beneficiaries with PAD. Patients with PAD who underwent major lower-extremity amputation were more likely to have DM (60.3% versus 35.7% with PAD without amputation; *P*<0.001). There was significant geographic variation in the rate of lower-extremity amputation, from 8400 amputations per 100 000 patients with PAD in the East South Central region to 5500 amputations per 100 000 patients with PAD in the Mountain region. After adjustment for clustering at the US Census Bureau level, geographic variation in lower-extremity amputations remained. Lower-extremity amputation was performed more often in the East South Central region (adjusted OR, 1.152 [95% CI, 1.131–1.174]; *P*<0.001) and West South Central region (adjusted OR, 1.115 [95% CI, 1.097–1.133]; *P*<0.001) and less often in the Middle Atlantic region (OR, 0.833 [95% CI, 0.820–0.847]; *P*<0.001) versus the South Atlantic reference region.[17]
- Among 186 338 older Medicare PAD patients undergoing major lower-extremity amputation, mortality was found to be 48.3% at 1 year.[18]
- A study of Medicare beneficiaries reported that between 2006 and 2011, 39 339 required revascularization for PAD, and the annual rate of peripheral vascular intervention increased slightly from 401.4 to 419.6 per 100 000 people.[19]
- People with PAD have impaired function and quality of life, regardless of whether or not they report leg symptoms. Furthermore, patients with PAD, including those who are asymptomatic, experience a significant decline in lower-extremity function over time.[20–22] A few recent studies have demonstrated that even individuals with low-normal ABI (0.91–0.99) have reduced physical function compared with those with normal ABI.[23]
- Among patients with established PAD, higher PA levels during daily life are associated with better overall survival rate, a lower risk of death because of CVD, and slower rates of functional decline.[24,25] In addition, better 6-minute walk performance and faster walking speed are associated with lower rates of all-cause mortality, cardiovascular mortality, and mobility loss.[26,27]

Interventions

- A 2011 systematic review evaluated lower-extremity aerobic exercise against usual care and demonstrated a range of benefits, including the following[28]:
  - Increased time to claudication by 71 seconds (79%) to 918 seconds (422%)
  - Increased distance before claudication by 15 m (5.6%) to 232 m (200%)
  - Increased walking distance/time by 67% to 101% after 40 minutes of walking 2 to 3 times per week
- Observational studies have found that the risk of death,[29] MI,[30] and amputation[29] are substantially

greater in individuals with PAD who continue to smoke than in those who have stopped smoking.

- The "2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease" noted that several randomized and observational studies demonstrated that statins reduced the risk of MACE and amputation among people with PAD.[31]
- A meta-analysis of 42 trials demonstrated that antiplatelet therapy reduces the odds of vascular events by 26% among patients with PAD.[32,33]
- A recent Danish trial in males aged 65 to 74 years reported that screening of PAD (with ABI), AAA (with abdominal ultrasound), and hypertension followed by optimal care resulted in 7% lower risk of 5-year mortality compared with no screening.[34]
- Data from the US Department of Veterans Affairs during 2013 to 2014 demonstrate that patients with PAD alone receive optimal medical therapy less frequently than patients with CHD (including those with concomitant PAD; statin use 59% versus 72% and antiplatelet use 66% versus 84%, respectively).[35]
- In a study that randomized patients with PAD to 3 groups (optimal medical care, supervised exercise training, and iliac artery stent placement), supervised exercise resulted in superior treadmill walking distance compared with stenting. Results in the exercise group and stent group were superior to optimal medical care alone.[36]
- In 2017, the Centers for Medicare & Medicaid Services decided to cover supervised exercise therapy (up to 36 sessions over 12 weeks) for eligible symptomatic PAD patients with intermittent claudication.[37]
- Endovascular therapies for critical limb ischemia are being used with greater frequency in the United States. From 2003 to 2011, there was a significant increase in endovascular treatment of critical limb ischemia (from 5.1% to 11.0%), which was accompanied by lower rates of in-hospital mortality and major amputation, as well as shorter length of stay.[6]

Hospital Discharges and Ambulatory Care Visits (See Table 23-1)

- Principal diagnosis discharges for PAD slightly decreased from 2004 to 2014, with first-listed discharges of 140 000 and 115 000, respectively (NHLBI tabulation).
- In 2015, there were 1 070 000 physician office visits and 22 000 ED visits with a primary diagnosis of PAD (NAMCS/NHAMCS, NHLBI tabulation).[38,39]

Risk Factors

- The risk factors for PAD are similar but not identical to those for CHD. Cigarette smoking is a stronger risk factor for PAD than for CHD.[40] Age- and sex-adjusted OR for heavy smoking was 3.94 for symptomatic PAD and 1.66 for CHD.[40]
- Among males in the Health Professionals Follow-up Study, smoking, type 2 DM, hypertension, and hypercholesterolemia accounted for 75% (95% CI, 64%–87%) of risk associated with development of clinical PAD.[41]
- In a meta-analysis of 34 studies from high-income countries and low- to middle-income countries, respectively, important risk factors for PAD included cigarette smoking (OR, 2.72 versus 1.42), DM (OR, 1.88 versus 1.47), hypertension (OR, 1.55 versus 1.36), and hypercholesterolemia (OR, 1.19 versus 1.14).[42]
- A study of 3.3 million people 40 to 99 years of age primarily self-referring for vascular screening tests in the United States showed that risk factor burden was associated with increased prevalence of PAD, and there was a graded association between the number of traditional risk factors and the prevalence of PAD.[43]
- Other risk factors for PAD include sedentary lifestyle, elevated inflammation markers, hypertension in pregnancy, and CKD.[43–46]
- African Americans have a 37% higher amputation risk than whites (HR, 1.37 [95% CI, 1.30–1.45]). Lower SES is an independent predictor for amputation (HR, 1.12 [95% CI, 1.06–1.17]).[47]
- A secondary analysis of a randomized feeding trial showed reduced risk of incident PAD with the Mediterranean diet compared with a control diet.[48]

Social Determinants

- In the JHS, the prevalence of PAD was higher among participants who did not graduate from high school than among participants with an associate's degree or higher.[49]

Awareness

- A cross-sectional, population-based telephone survey of >2500 adults ≥50 years of age, with oversampling of blacks and Hispanics, found that 26% expressed familiarity with PAD in contrast to >65% for CHD, stroke, and HF. Of these, half were not aware that DM and smoking increase the risk of PAD. One in 4 knew that PAD is associated with increased risk of MI and stroke, and only 14% were aware that PAD could lead to amputation. All knowledge domains were lower in individuals with lower income and education levels.[3]
- In data concerning people aged ≥70 years or those aged 50 to 69 years with a history of DM or smoking, as well as their physicians, 83% of patients with a prior diagnosis of PAD were aware

of the diagnosis, but only half of their physicians had recognized the diagnosis.[3]

Genetics of PAD

- Atherosclerotic PAD is heritable, even independent of risk factors for PAD which themselves are heritable.
- In the ethnically diverse San Diego Population Study, a family history of PAD was independently associated with a 1.83-fold higher odds of PAD.[50] In the Swedish Twin Registry, the OR of PAD in a monozygotic twin was 17.7 and 5.7 in dizygotic twins; estimated genetic effects accounted for 58% and nonshared environmental effects for 42% of the phenotypic variance between twins.[51] The NHLBI Twin Study found that 48% of the variability in ABI with similar environmental risk factors could be attributed to additive genetic effects.[52]
- There are monogenic (mendelian) diseases that result in PAD, including familial lipoprotein disorders such as chylomicronemia and familial hypercholesterolemia, hyperhomocysteinemia, and pseudoxanthoma elasticum.[53]
- GWASs have identified genetic loci associated with atherosclerotic PAD, including the CHD-associated chromosome 9p21 genetic locus, which has been shown to be associated with PAD, AAA, and intracranial aneurysm.[54] Other PAD-associated genetic loci found through GWASs include SNPs in the cholinergic receptor nicotinic α3 (*CHRNA3*), DAB2 interaction protein (*DAB21P*), and cytochrome B-245 α-chain (*CYBA*) genes.[55]
- GWASs have also identified genetic variants associated with inflammatory forms of PAD such as KD.[56]

Global Burden of PAD (See Table 23-2 and Charts 23-4 through 23-6)

- A systematic study of 34 studies reported that globally, 202 million people were living with PAD, and during the preceding decade, the number of people with PAD increased by 28.7% in low- to middle-income countries and by 13.1% in high-income countries (Chart 23-4).[42]
- Global mortality attributable to PAD and global prevalence of PAD by sex from the GBD 2016 Study are shown in Table 23-2.[57]
- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories.[57]
  - PAD mortality is high in Russia and in Central and Eastern Europe (Chart 23-5).
  - PAD prevalence is high in Southern and sub-Saharan Africa, North America, and Western and Northern Europe (Chart 23-6).

Aortic Diseases *ICD-9* 440, 441, 444, and 447; *ICD-10* I70, I71, I74, I77, and I79.

Aortic Aneurysm and Acute Aortic Dissection (See Charts 23-7 and 23-8) *ICD-9* 441; *ICD-10* I71.

Prevalence and Incidence

- The prevalence of AAAs that are 2.9 to 4.9 cm in diameter ranges from 1.3% in males 45 to 54 years of age to 12.5% in males 75 to 84 years of age. For females, the prevalence ranges from 0% in the youngest to 5.2% in the oldest age groups.[58]
- A meta-analysis of 15 475 individuals from 18 studies on small AAAs (3.0–5.4 cm) demonstrated that mean aneurysm growth rate was 2.21 mm per year and did not significantly vary by age and sex. Growth rates were higher in smokers versus former or never smokers (by 0.35 mm/y) and lower in people with DM than in those without DM (by 0.51 mm/y).[59]
- A study from Olmsted County, MN,[60] demonstrated annual age- and sex-adjusted incidences per 100 000 people of 3.5 (95% CI, 2.2–4.9) for thoracic aortic aneurysm rupture and 3.5 (95% CI, 2.4–4.6) for acute aortic dissection.

Mortality

2016: Mortality—9758. Any-mention mortality—16 458.

Complications

- Rates of rupture of small AAAs (3.0–5.4 cm in diameter) range from 0.71 to 11.03 per 1000 person-years, with higher rupture rates in smokers (pooled HR, 2.02 [95% CI, 1.33–3.06]) and females (pooled HR, 3.76 [95% CI, 2.58–5.47]; *P*<0.001).[59]
- There is a dose-response association between the diameter and the minimum and maximum risk of AAA rupture per year (Chart 23-7).[61]
- A 2015 systematic review that included 4 randomized trials of ultrasound screening demonstrated lower AAA-associated mortality, emergency operations, and rupture with screening, but with higher AAA-associated elective repair rates; however, there was no effect on all-cause mortality (Chart 23-8).[62] Similar results were reported in a systematic review report prepared for the US Preventive Services Task Force[63] and in a 2016

Swedish study evaluating a nationwide screening program targeting 65-year-old males.[64]

- Data from IRAD demonstrated that the rate of mesenteric malperfusion in 1809 patients with type A acute dissections was 3.7%, with a higher mortality rate than for patients without malperfusion (63.2% versus 23.8%; *P*<0.001).[65]
- Data from IRAD demonstrated that patients with acute type B aortic dissection have heterogeneous in-hospital outcomes. In-hospital mortality in patients with and without complications (such as mesenteric ischemia, renal failure, limb ischemia, or refractory pain) was 20.0% and 6.1%, respectively. In patients with complications, in-hospital mortality associated with surgical and endovascular repair was 28.6% and 10.1% (*P*=0.006), respectively.[66]

Hospital Discharges

- In 2014, there were 69 000 hospital discharges with aortic aneurysm as principal diagnoses, of which 50 000 were males and 19 000 were females (HCUP, NHLBI tabulation).

Interventions

- Results from 4 trials (N=3314 participants) evaluating the effect of open or endovascular repair of small AAAs (4.0–5.5 cm) did not demonstrate an advantage to earlier intervention compared with routine ultrasound surveillance.[67]
- Data from 23 838 patients with ruptured AAAs collected through the NIS (2005–2010) demonstrated in-hospital mortality of 53.1% (95% CI, 51.3%–54.9%), with 80.4% (95% CI, 79.0%–81.9%) undergoing intervention for repair. Of individuals who underwent repair, 20.9% (95% CI, 18.6%–23.2%) underwent endovascular repair, with a 26.8% (95% CI, 23.7%–30.0%) postintervention mortality rate, and 79.1% (95% CI, 76.8%–81.4%) underwent open repair, with a 45.6% (95% CI, 43.6%–47.5%) postintervention mortality rate.[68]
- Data from the NIS suggest that the use of endovascular repair of AAAs rose substantially between 2000 and 2010 (5% versus 74% of all AAA repairs, respectively), whereas the overall number of AAAs (≈45 000 per year) remained stable. In-hospital mortality and length of stay declined during this period, but costs rose.[69]
- At least for the first 3 years after elective repair of an AAA, individuals who have endovascular repair may have better outcomes than those who undergo open repair. After multivariable adjustment, Medicare patients who underwent open AAA repair had a higher risk of all-cause mortality (HR, 1.24 [95% CI, 1.05–1.47]), AAA-related mortality (HR, 4.37 [95% CI, 2.51–7.66]), and complications at 1 year than patients who underwent endovascular repair.[70] However, after 8 years of follow-up, survival in the open repair group was similar to that in the endovascular repair group. Of note, individuals in the endovascular repair group had a higher rate of eventual aneurysm rupture (5.4%) than patients who underwent open repair (1.4%).[71] Similar findings were observed in the OVER Veterans Affairs Cooperative trial, which compared open AAA repair to endovascular repair in 881 patients and demonstrated reductions in mortality from endovascular repair at 2 years (HR, 0.63 [95% CI, 0.40–0.98]) and 3 years (HR, 0.72 [95% CI, 0.51–1.00]).[72] However, there was no survival difference between open and endovascular repair in individuals followed up for up to 9 years (mean, 5 years; HR, 0.97 [95% CI, 0.77–1.22]).[72]
- In comparisons of the United States and the United Kingdom, the United States demonstrated a higher rate of AAA repair, smaller AAA diameter at the time of repair, and lower rates of AAA rupture and AAA-related death.[73]
- In ruptured AAAs, implementation of a contemporary endovascular-first protocol was associated with decreased perioperative morbidity and mortality, a higher likelihood of discharge to home, and improved long-term survival in a retrospective analysis of 88 consecutive patients seen at an academic medical center.[74]
- Perioperative mortality of endovascular aneurysm repair was not related to surgeon case volume but was lower in hospitals with higher volume (eg, 1.9% in hospitals with <10 cases a year versus 1.4% in those with 49–198 cases; *P*<0.01). Perioperative mortality after open repair was inversely related to both surgeon case volume (6.4% in ≤3 cases versus 3.8% in 14–62 cases; *P*<0.01) and hospital case volume (6.3% in ≤5 cases vs 3.8% in 14–62 cases; *P*<0.01).[75]
- The data for surgery in thoracic aortic aneurysms are more mixed between open and endovascular repair. A sample of 12 573 and 2732 Medicare patients who underwent open thoracic aortic aneurysm and endovascular repair from 1998 to 2007 demonstrated higher perioperative mortality for open repair in both intact (7.1% versus 6.1%; *P*=0.07) and ruptured (46% versus 28%; *P*<0.01) thoracic aortic aneurysms but higher 1-year (87% versus 82%; *P*=0.001) and 5-year (72% versus 62%; *P*=0.001) survival rates.[76] Perioperative mortality rates for open thoracic aortic aneurysms were higher for NH black Medicare patients than for white Medicare patients (18% versus 10%; *P*<0.001), but rates were similar for endovascular repair (8% versus 9%; *P*=0.56).[63] On the basis

of data from the NIS (N=1400), weekend repair for thoracic aortic aneurysm rupture (N=322) was associated with higher mortality than weekday repair (N=1078; OR, 2.55 [95% CI, 1.77–3.68]), likely because of delays in surgical intervention.[77]

- Seventeen-year trends in the IRAD database (1996–2013) demonstrate an increase in surgical repair of type A thoracic dissections (79%–90%) and a significant decrease in in-hospital and surgical mortality for type A dissections (31%–22% [*P*<0.001] and 25%–18% [*P*=0.003], respectively). Type B dissections were more likely to be treated with endovascular therapies, but no significant changes in mortality were observed.[78]

Risk Factors

- Many risk factors for atherosclerosis are also associated with increased risk for AAAs.[79] Of these, smoking is the most important modifiable risk factor for AAAs.[80]
- A 2014 systematic review of 17 community-based observational studies demonstrated a consistent, inverse association between DM and prevalent AAAs (OR, 0.80 [95% CI, 0.70–0.90]).[81]
- On the basis of nationally representative data from the United Kingdom, giant cell arteritis has been demonstrated to be associated with a 2-fold higher risk (sub-HR, 1.92 [95% CI, 1.52–2.41]) after adjustment for competing risks for developing an AAA. These data also demonstrate an inverse association between DM and AAAs.[82]

Genetics

- Monogenic diseases that cause thoracic aortic disease include Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, arterial tortuosity syndrome, and familial thoracic aortic aneurysm disease. Mutations in the genes causing these disorders significantly increase the risk of developing vascular aneurysms. If these disorders are suspected, referral to a specialty clinic for genetic testing can be useful for diagnosis, treatment, and cascade screening in family members.
- GWASs have identified genetic variants associated with nonfamilial forms of thoracic aortic aneurysm/dissection, including common variants in the fibrillin gene (*FBN1*; rare mutations in this gene cause Marfan syndrome) and variants in the LDL receptor protein–related 1 (*LRP1*) and unc-51–like kinase 4 (*ULK4*) genes.[83,84]
- AAA is heritable; a family history of AAA is a risk factor for AAA, particularly in male siblings of male patients, for whom the RR for AAA is as high as 18.[85,86]
- GWASs and other studies have identified genetic variants associated with AAA, including a locus on chromosome 3p12.3 and SNPs in *DAB2IP*, *LDLR*, *LRP1*, *MMP3*, *TGFβR2*, and *SORT1*.[87,88]
- A GWAS has also identified common genetic variants for intracranial aneurysms.[89] In addition, rare variants in *ANGPTL6* are associated with increased risk of intracranial aneurysms.[90]
- Despite the co-occurrence of different types of aneurysms, a meta-analysis has found no shared genetic variants for intracranial, thoracic, and aortic aneurysms.[85]
- Nonatherosclerotic forms of arterial disease such as fibromuscular dysplasia and spontaneous coronary artery dissection are more difficult to evaluate for genetic components given their lesser prevalence and heterogeneous nature, but studies of these diseases are ongoing. A recent study has identified a noncoding SNP in the phosphatase and actin regulator 1 (*PHACTR1*) gene as being associated with fibromuscular dysplasia.[91]

Global Burden of Aortic Aneurysm
(See Table 23-3 and Chart 23-9)

- Global mortality attributable to and prevalence of aortic aneurysm by sex are shown in Table 23-3.[57]
- The GBD 2016 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 315 diseases and injuries in 195 countries and territories. The highest age-standardized mortality rates attributable to aortic aneurysm are estimated for Northern and Eastern Europe, southern and tropical Latin America, and Oceania (Chart 23-9).[57]

Atherosclerotic Renal Artery Stenosis *ICD-9* 440.1; *ICD-10* I70.1.

Prevalence and Incidence

- A US community-based cohort of older adults (≥65 years old) reported the prevalence of renal artery disease as 6.8%.[92] Among those with renal artery stenosis, 88% were unilateral and 12% were bilateral.
- A US study using Medicare data reported that the incidence rate of renal artery stenosis was 3.1 per 1000 patient-years.[93] The incidence of renal artery stenosis increased by ≈5 fold from 1992 to 2004.

Complications

- Atherosclerotic renal artery stenosis is often a cause of drug-resistant hypertension.[94]
- An Irish study reported that among a total of 3987 patients undergoing coronary angiography, the presence of renal artery stenosis conferred 2 times higher mortality risk.[95]

Interventions

- The CORAL study compared medical therapy alone versus medical therapy plus renal artery stenting in patients with atherosclerotic renal artery stenosis and hypertension. Although there was a significant difference in SBP favoring the stent group (−2.3 mm Hg [95% CI, −4.4 to −0.2 mm Hg]), there was no difference in the primary end point of major cardiovascular or kidney event.[96]

Risk Factors

- Traditional atherosclerotic risk factors such as advanced age, DM, smoking, and hypertension are associated with higher prevalence of atherosclerotic renal artery stenosis.[94]

Table 23-1. Peripheral Artery Disease

Population Group	Prevalence, Age ≥40 y	Mortality, 2016, All Ages*	Hospital Discharges, 2014, All Ages
Both sexes	≥6.8 Million	13048	115000
Males	…	5888 (45.1%)†	69000
Females	…	7160 (54.9%)†	46000
NH white males	…	4689	…
NH white females	…	5677	…
NH black males	…	719	…
NH black females	…	938	…
Hispanic males	…	331	…
Hispanic females	…	377	…
NH Asian or Pacific Islander males	…	110‡	…
NH Asian or Pacific Islander females	…	110‡	…
NH American Indian/Alaska Native	…	70	…

Ellipses (…) indicate data not available; and NH, non-Hispanic.

*Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total mortality attributable to peripheral artery disease that is for males vs females.

‡Includes Chinese, Filipino, Hawaiian, Japanese, and Other Asian or Pacific Islander.

Sources: Prevalence: Data derived from Allison et al.[2] Prevalence of peripheral artery disease is based on an ankle-brachial index <0.9 or a previous revascularization for peripheral artery disease. Mortality: Centers for Disease Control and Prevention/National Center for Health Statistics, 2015 Mortality Multiple Cause-of-Death–United States.

Table 23-2. Global Mortality From and Prevalence of PAD by Sex

	Both Sexes Combined		Males		Females	
	Death	Prevalence	Death	Prevalence	Death	Prevalence
Total number (millions)	0.1 (0.0 to 0.1)	120.1 (105.6 to 137.7)	0.02 (0.02 to 0.04)	50.6 (44.4 to 58.3)	0.03 (0.02 to 0.06)	69.5 (61.3 to 79.7)
Percent change total number, 1990 to 2016	128.6 (92.1 to 173.3)	82.2 (80.3 to 84.2)	109.3 (84.5 to 167.4)	91.2 (88.8 to 93.7)	148.5 (61.9 to 199.6)	76.2 (74.2 to 78.3)
Percent change total number, 2006 to 2016	37.4 (26.0 to 51.3)	30.0 (29.0 to 31.0)	33.9 (21.7 to 49.5)	31.8 (30.6 to 33.0)	40.5 (22.7 to 59.0)	28.8 (27.7 to 29.9)
Rate per 100000	1.0 (0.8 to 1.5)	1805.2 (1588.5 to 2063.9)	1.1 (0.9 to 1.6)	1,657.6 (1456.5 to 1899.6)	0.9 (0.5 to 1.6)	1,929.8 (1702.0 to 2202.2)
Percent change rate, 1990 to 2016	2.0 (−16.0 to 19.6)	−8.0 (−8.8 to −7.2)	−7.2 (−18.6 to 16.0)	−6.5 (−7.5 to −5.6)	8.9 (−29.7 to 30.4)	−8.4 (−9.3 to −7.5)
Percent change rate, 2006 to 2016	−2.6 (−10.5 to 6.9)	−1.6 (−2.3 to −0.9)	−4.7 (−12.7 to 5.4)	−1.3 (−2.2 to −0.5)	−0.8 (−13.6 to 12.0)	−1.6 (−2.3 to −0.9)

PAD indicates peripheral artery disease.

Table 23-3. Global Mortality From and Prevalence of Aortic Aneurysm by Sex

	Both sexes	Males	Females
Total number (millions)	0.2 (0.2 to 0.2)	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)
Percent change total number, 1990 to 2016	61.7 (54.5 to 70.1)	55.3 (46.9 to 66.4)	73.4 (60.6 to 82.6)
Percent change total number, 2006 to 2016	20.5 (17.0 to 24.9)	18.3 (13.3 to 24.8)	24.4 (18.3 to 30.2)
Rate per 100 000	2.6 (2.6 to 2.7)	3.8 (3.6 to 3.9)	1.7 (1.7 to 1.8)
Percent change rate, 1990 to 2016	−20.5 (−23.7 to −16.7)	−26.2 (−29.9 to −21.6)	−15.0 (−20.9 to −10.7)
Percent change rate, 2006 to 2016	−10.1 (−12.6 to −7.0)	−13.0 (−16.4 to −8.4)	−7.4 (−11.9 to −3.2)

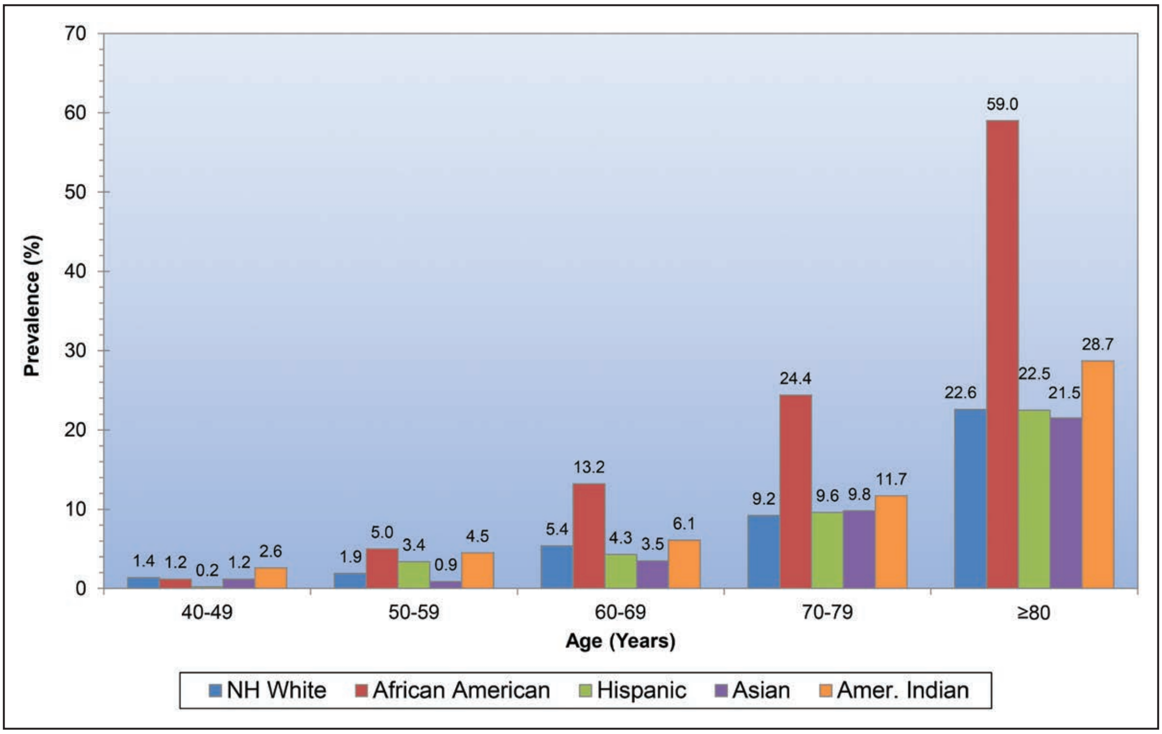

Chart 23-1. Estimates of prevalence of peripheral artery disease in males by age and ethnicity.
Amer. indicates American; and NH, non-Hispanic.
Data derived from Allison et al.[2]

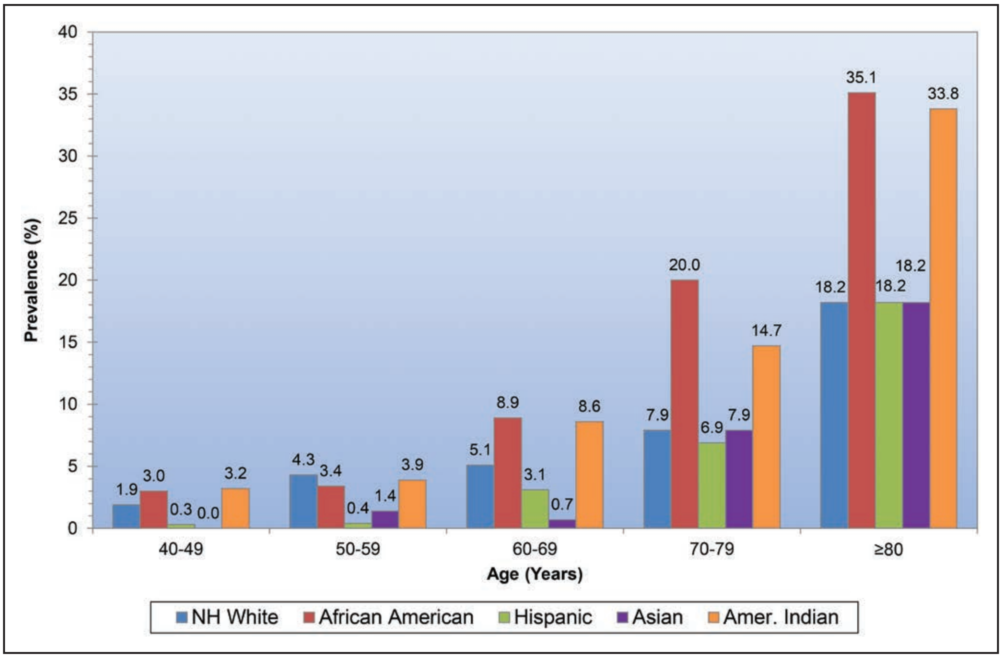

Chart 23-2. **Estimates of prevalence of peripheral artery disease in females by age and ethnicity.**
Amer. indicates American; and NH, non-Hispanic.
Data derived from Allison et al.[2]

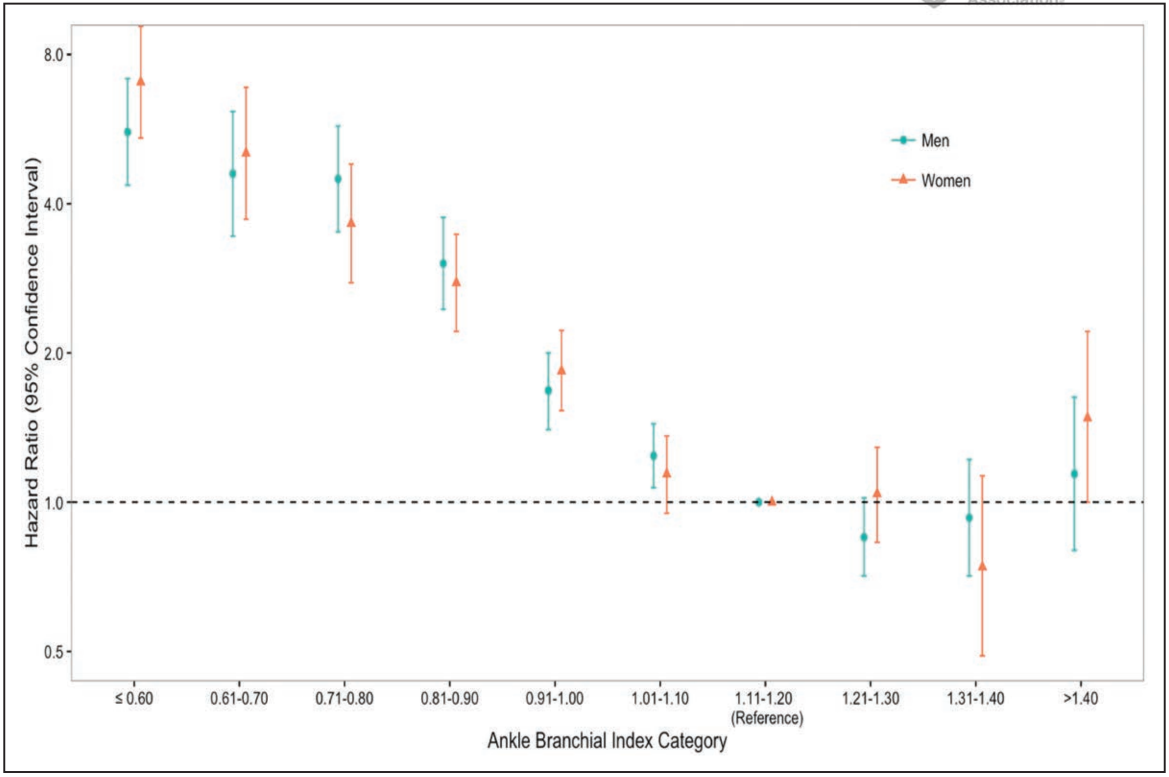

Chart 23-3. **Hazard ratios of cardiovascular mortality with 95% CI by ankle-brachial index categories.**
Data derived from Fowkes et al.[8]

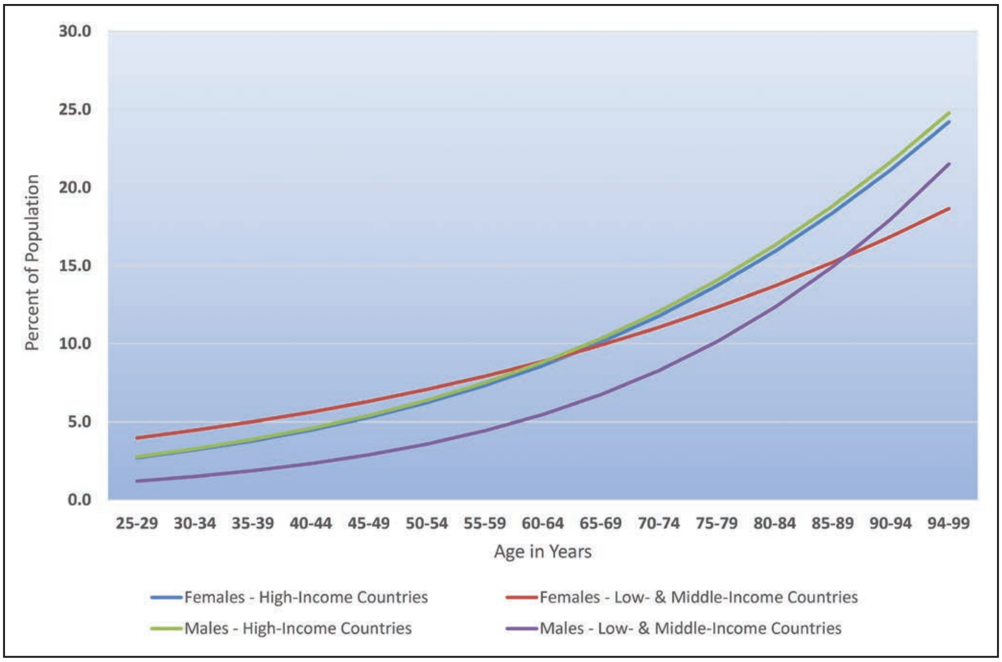

Chart 23-4. Prevalence of peripheral artery disease by age in males and females in high-income countries and low-income or middle-income countries.

Adapted from *The Lancet* (Fowkes et al[42]), with permission from Elsevier. Copyright © 2013, Elsevier Ltd.

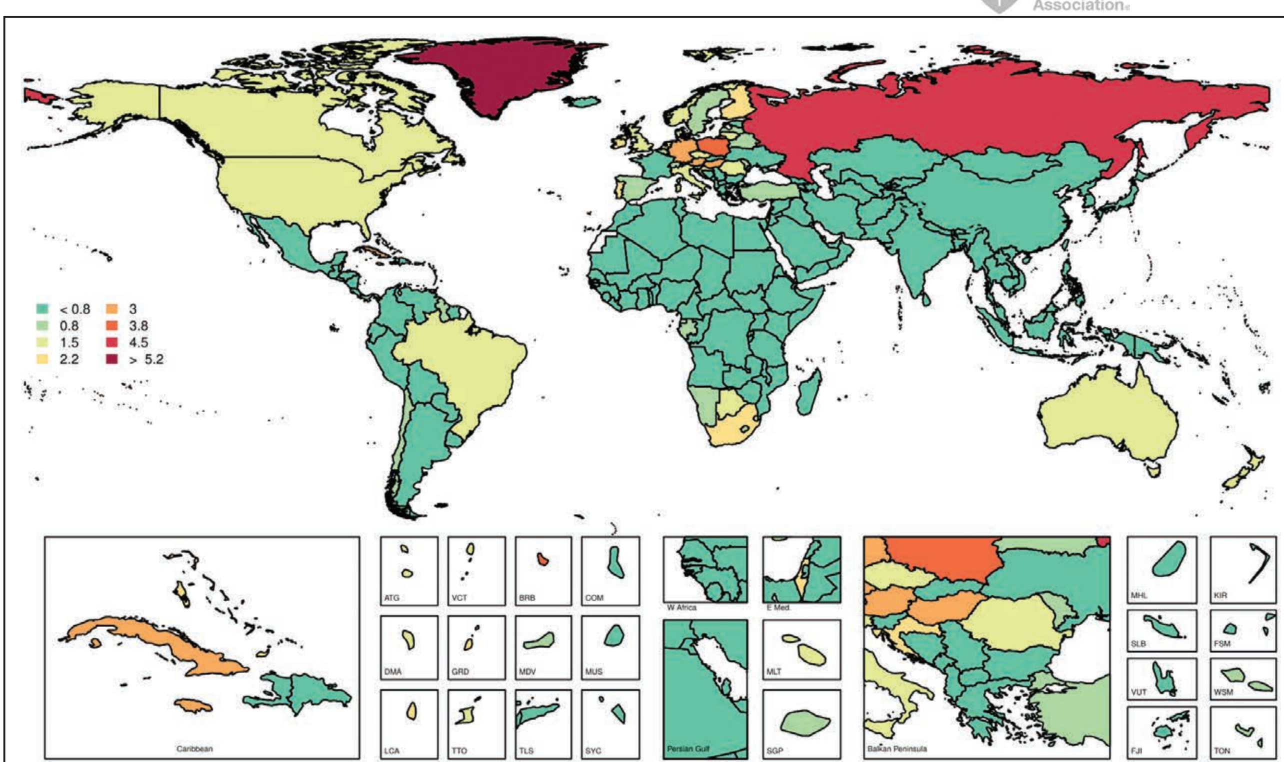

Chart 23-5. Age-standardized mortality rates of peripheral artery disease per 100 000, both sexes, 2016.

Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[57] Printed with permission. Copyright © 2017 University of Washington.

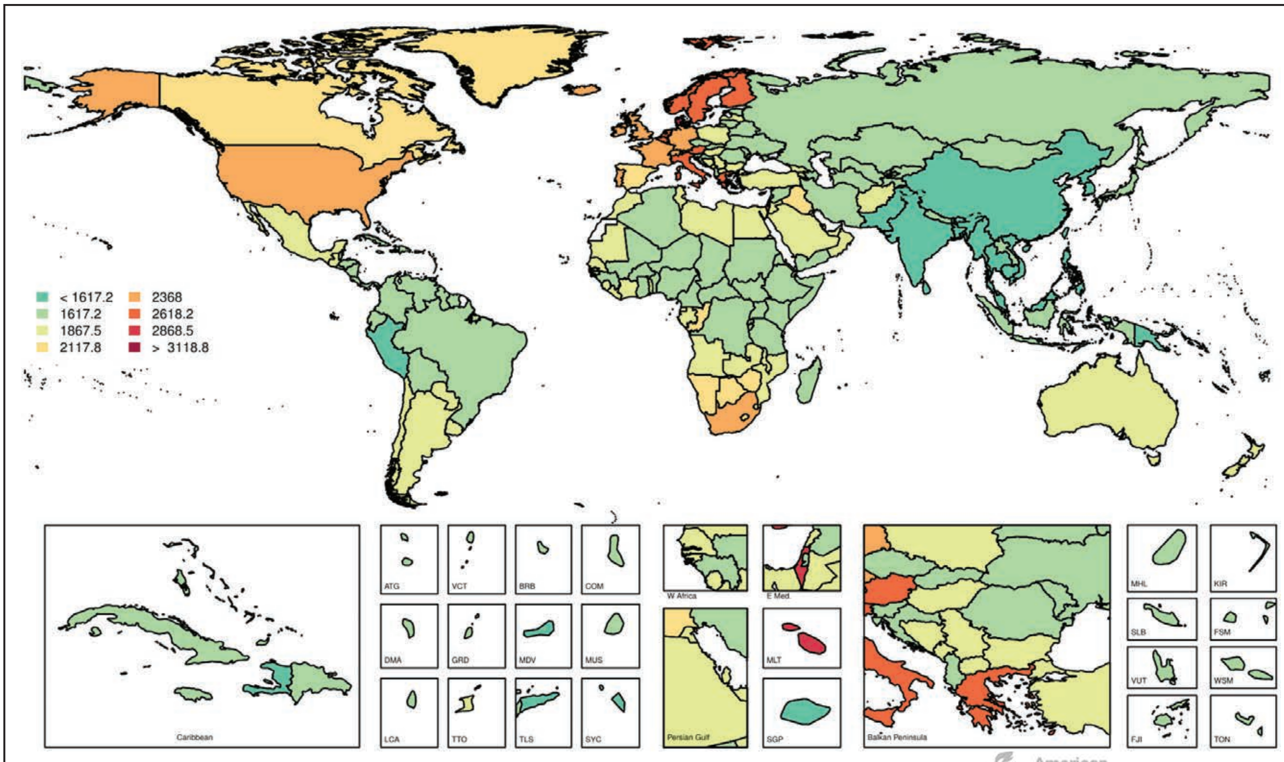

Chart 23-6. Age-standardized prevalence of peripheral artery disease per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Data derived from Global Burden of Disease Study 2016, Institute for Health Metrics and Evaluation, University of Washington.[57] Printed with permission. Copyright © 2017, University of Washington.

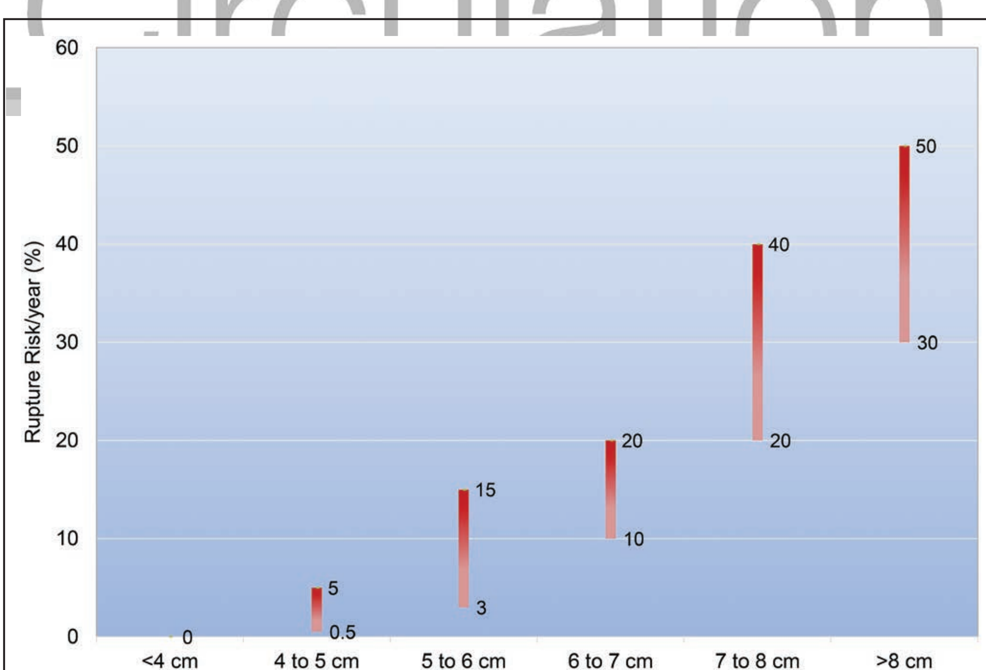

Chart 23-7. Association between diameter and minimum and maximum risk of abdominal aortic aneurysm rupture per year.
Data derived from Brewster et al.[61]

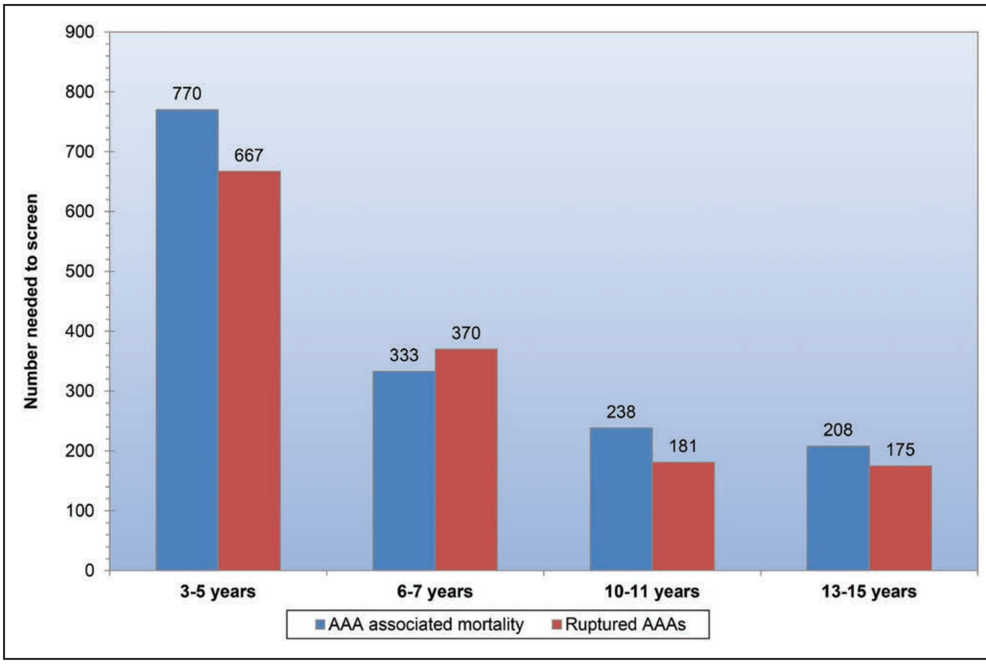

Chart 23-8. Numbers needed to screen to avoid an AAA-associated death and a ruptured AAA.
AAA indicates abdominal aortic aneurysm.
Data derived from Eckstein et al.[62]

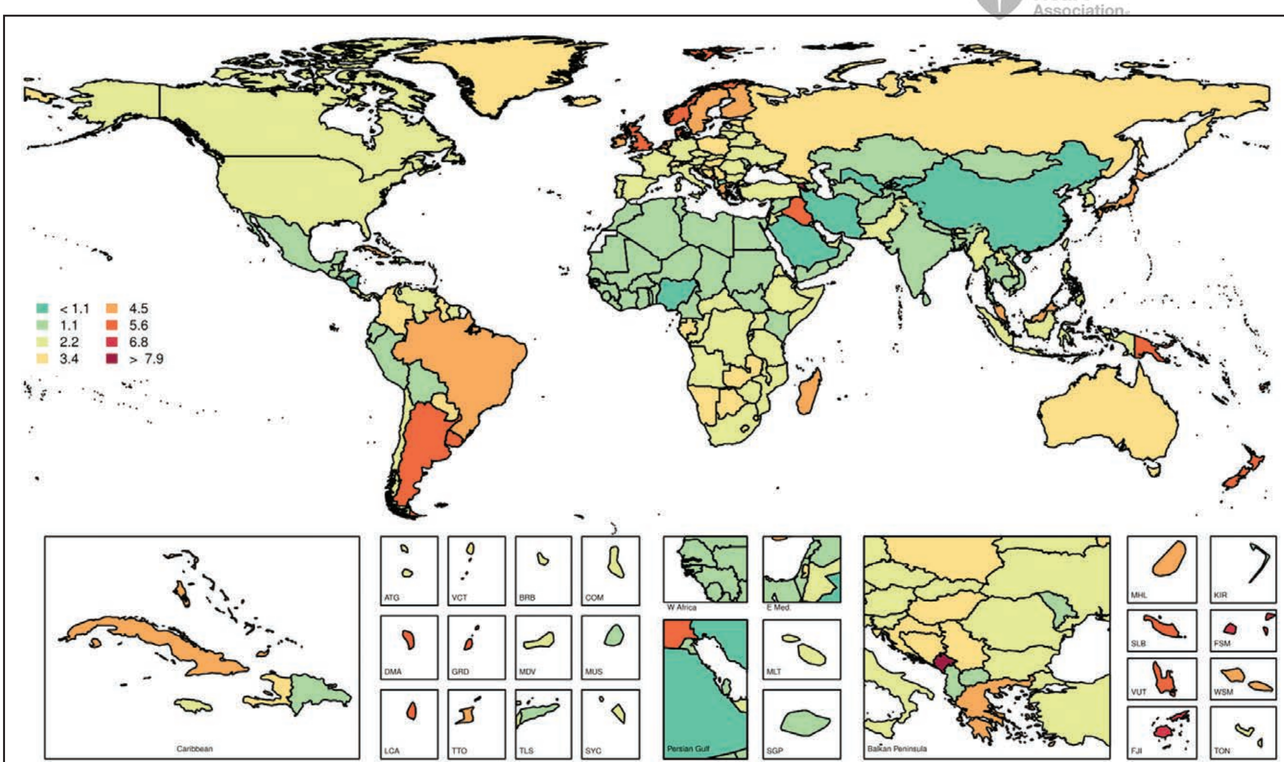

Chart 23-9. Age-standardized mortality rates of aortic aneurysm per 100 000, both sexes, 2016.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
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REFERENCES

1. Centers for Disease Control and Prevention (CDC). Lower extremity disease among persons aged ≥40 years with and without diabetes: United States, 1999–2002. *MMWR Morb Mortal Wkly Rep*. 2005;54:1158–1160.
2. Allison MA, Ho E, Denenberg JO, Langer RD, Newman AB, Fabsitz RR, Criqui MH. Ethnic-specific prevalence of peripheral arterial disease in the United States. *Am J Prev Med*. 2007;32:328–333. doi: 10.1016/j.amepre.2006.12.010
3. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA*. 2001;286:1317–1324.
4. McDermott MM, Greenland P, Liu K, Guralnik JM, Criqui MH, Dolan NC, Chan C, Celic L, Pearce WH, Schneider JR, Sharma L, Clark E, Gibson D, Martin GJ. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA*. 2001;286:1599–1606.
5. Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, Zakharyan A, Hirsch AT. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. *J Vasc Surg*. 2014;60:686–695.e2. doi: 10.1016/j.jvs.2014.03.290
6. Agarwal S, Sud K, Shishehbor MH. Nationwide trends of hospital admission and outcomes among critical limb ischemia patients: from 2003-2011. *J Am Coll Cardiol*. 2016;67:1901–1913. doi: 10.1016/j.jacc.2016.02.040
7. National Center for Health Statistics. Centers for Disease Control and Prevention website. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2016. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed May 21, 2018.
8. Ankle Brachial Index Collaboration. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA*. 2008;300:197–208. doi: 10.1001/jama.300.2.197
9. Lo RC, Bensley RP, Dahlberg SE, Matyal R, Hamdan AD, Wyers M, Chaikof EL, Schermerhorn ML. Presentation, treatment, and outcome differences between men and women undergoing revascularization or amputation for lower extremity peripheral arterial disease. *J Vasc Surg*. 2014;59:409–418.e3. doi: 10.1016/j.jvs.2013.07.114
10. Criqui MH, Ninomiya JK, Wingard DL, Ji M, Fronek A. Progression of peripheral arterial disease predicts cardiovascular disease morbidity and mortality. *J Am Coll Cardiol*. 2008;52:1736–1742. doi: 10.1016/j.jacc.2008.07.060
11. Aboyans V, Desormais I, Lacroix P, Salazar J, Criqui MH, Laskar M. The general prognosis of patients with peripheral arterial disease differs according to the disease localization. *J Am Coll Cardiol*. 2010;55:898–903. doi: 10.1016/j.jacc.2009.09.055
12. Barba A, Estallo L, Rodríguez L, Baquer M, Vega de Céniga M. Detection of abdominal aortic aneurysm in patients with peripheral artery disease. *Eur J Vasc Endovasc Surg*. 2005;30:504–508. doi: 10.1016/j.ejvs.2005.05.011
13. Kurvers HA, van der Graaf Y, Blankensteijn JD, Visseren FL, Eikelboom B; SMART Study Group. Screening for asymptomatic internal carotid artery stenosis and aneurysm of the abdominal aorta: comparing the yield between patients with manifest atherosclerosis and patients with risk factors for atherosclerosis only. *J Vasc Surg*. 2003;37:1226–1233.
14. Lee JY, Lee SW, Lee WS, Han S, Park YK, Kwon CH, Jang JY, Cho YR, Park GM, Ahn JM, Kim WJ, Park DW, Kang SJ, Kim YH, Lee CW, Park SW, Park SJ. Prevalence and clinical implications of newly revealed, asymptomatic abnormal ankle-brachial index in patients with significant coronary artery disease. *JACC Cardiovasc Interv*. 2013;6:1303–1313. doi: 10.1016/j.jcin.2013.08.008
15. Leertouwer TC, Pattynama PM, van den Berg-Huysmans A. Incidental renal artery stenosis in peripheral vascular disease: a case for treatment? *Kidney Int*. 2001;59:1480–1483. doi: 10.1046/j.1523-1755.2001.0590041480.x
16. Heald CL, Fowkes FG, Murray GD, Price JF; Ankle Brachial Index Collaboration. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: systematic review. *Atherosclerosis*. 2006;189:61–69. doi: 10.1016/j.atherosclerosis.2006.03.011
17. Jones WS, Patel MR, Dai D, Subherwal S, Stafford J, Calhoun S, Peterson ED. Temporal trends and geographic variation of lower-extremity amputation in patients with peripheral artery disease: results from U.S. Medicare 2000-2008. *J Am Coll Cardiol*. 2012;60:2230–2236. doi: 10.1016/j.jacc.2012.08.983
18. Jones WS, Patel MR, Dai D, Vemulapalli S, Subherwal S, Stafford J, Peterson ED. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. *Am Heart J*. 2013;165:809–815, 815.e1. doi: 10.1016/j.ahj.2012.12.002
19. Jones WS, Mi X, Qualls LG, Vemulapalli S, Peterson ED, Patel MR, Curtis LH. Trends in settings for peripheral vascular intervention and the effect of changes in the outpatient prospective payment system. *J Am Coll Cardiol*. 2015;65:920–927. doi: 10.1016/j.jacc.2014.12.048
20. McDermott MM, Greenland P, Liu K, Guralnik JM, Celic L, Criqui MH, Chan C, Martin GJ, Schneider J, Pearce WH, Taylor LM, Clark E. The ankle brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study. *Ann Intern Med*. 2002;136:873–883.
21. McDermott MM, Liu K, Greenland P, Guralnik JM, Criqui MH, Chan C, Pearce WH, Schneider JR, Ferrucci L, Celic L, Taylor LM, Vonesh E, Martin GJ, Clark E. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA*. 2004;292:453–461. doi: 10.1001/jama.292.4.453
22. McDermott MM, Guralnik JM, Tian L, Liu K, Ferrucci L, Liao Y, Sharma L, Criqui MH. Associations of borderline and low normal ankle-brachial index values with functional decline at 5-year follow-up: the WALCS (Walking and Leg Circulation Study). *J Am Coll Cardiol*. 2009;53:1056–1062. doi: 10.1016/j.jacc.2008.09.063
23. McDermott MM, Applegate WB, Bonds DE, Buford TW, Church T, Espeland MA, Gill TM, Guralnik JM, Haskell W, Lovato LC, Pahor M, Pepine CJ, Reid KF, Newman A. Ankle brachial index values, leg symptoms, and functional performance among community-dwelling older men and women in the lifestyle interventions and independence for elders study. *J Am Heart Assoc*. 2013;2:e000257. doi: 10.1161/JAHA.113.000257
24. Garg PK, Liu K, Tian L, Guralnik JM, Ferrucci L, Criqui MH, Tan J, McDermott MM. Physical activity during daily life and functional decline in peripheral arterial disease. *Circulation*. 2009;119:251–260. doi: 10.1161/CIRCULATIONAHA.108.791491
25. Garg PK, Tian L, Criqui MH, Liu K, Ferrucci L, Guralnik JM, Tan J, McDermott MM. Physical activity during daily life and mortality in patients with peripheral arterial disease. *Circulation*. 2006;114:242–248. doi: 10.1161/CIRCULATIONAHA.105.605246
26. McDermott MM, Guralnik JM, Tian L, Ferrucci L, Liu K, Liao Y, Criqui MH. Baseline functional performance predicts the rate of mobility loss in persons with peripheral arterial disease. *J Am Coll Cardiol*. 2007;50:974–982. doi: 10.1016/j.jacc.2007.05.030
27. McDermott MM, Tian L, Liu K, Guralnik JM, Ferrucci L, Tan J, Pearce WH, Schneider JR, Criqui MH. Prognostic value of functional performance for mortality in patients with peripheral artery disease. *J Am Coll Cardiol*. 2008;51:1482–1489. doi: 10.1016/j.jacc.2007.12.034
28. Parmenter BJ, Raymond J, Dinnen P, Singh MA. A systematic review of randomized controlled trials: walking versus alternative exercise prescription as treatment for intermittent claudication. *Atherosclerosis*. 2011;218:1–12. doi: 10.1016/j.atherosclerosis.2011.04.024
29. Armstrong EJ, Wu J, Singh GD, Dawson DL, Pevec WC, Amsterdam EA, Laird JR. Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease. *J Vasc Surg*. 2014;60:1565–1571. doi: 10.1016/j.jvs.2014.08.064
30. Jonason T, Bergström R. Cessation of smoking in patients with intermittent claudication: effects on the risk of peripheral vascular complications, myocardial infarction and mortality. *Acta Med Scand*. 1987;221:253–260.
31. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FG, Hamburg NM, Kinlay S, Lookstein R, Misra S, Mureebe L, Olin JW, Patel RA, Regensteiner JG, Schanzer A, Shishehbor MH, Stewart KJ, Treat-Jacobson D, Walsh ME. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135:e726–e779. doi: 10.1161/CIR.0000000000000471
32. Ramos R, García-Gil M, Comas-Cufí M, Quesada M, Marrugat J, Elosua R, Sala J, Grau M, Martí R, Ponjoan A, Alves-Cabratosa L, Blanch J, Bolíbar B. Statins for prevention of cardiovascular events in a low-risk population with low ankle brachial index. *J Am Coll Cardiol*. 2016;67:630–640. doi: 10.1016/j.jacc.2015.11.052
33. Westin GG, Armstrong EJ, Bang H, Yeo KK, Anderson D, Dawson DL, Pevec WC, Amsterdam EA, Laird JR. Association between statin medications and mortality, major adverse cardiovascular event, and amputation-free survival in patients with critical limb ischemia. *J Am Coll Cardiol*. 2014;63:682–690. doi: 10.1016/j.jacc.2013.09.073
34. Lindholt JS, Søgaard R. Population screening and intervention for vascular disease in Danish men (VIVA): a randomised controlled trial. *Lancet*. 2017;390:2256–2265. doi: 10.1016/S0140-6736(17)32250-X

35. Hira RS, Cowart JB, Akeroyd JM, Ramsey DJ, Pokharel Y, Nambi V, Jneid H, Deswal A, Denktas A, Taylor A, Nasir K, Ballantyne CM, Petersen LA, Virani SS. Risk factor optimization and guideline-directed medical therapy in US veterans with peripheral arterial and ischemic cerebrovascular disease compared to veterans with coronary heart disease. *Am J Cardiol*. 2016;118:1144–1149. doi: 10.1016/j.amjcard.2016.07.027
36. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, Massaro JM, Lewis BA, Cerezo J, Oldenburg NC, Thum CC, Goldberg S, Jaff MR, Steffes MW, Comerota AJ, Ehrman J, Treat-Jacobson D, Walsh ME, Collins T, Badenhop DT, Bronas U, Hirsch AT; for the CLEVER Study Investigators. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) study. *Circulation*. 2012;125:130–139. doi: 10.1161/CIRCULATIONAHA.111.075770
37. Decision memo for supervised exercise therapy (SET) for symptomatic peripheral artery disease. May 25, 2017. Centers for Disease Control and Prevention website. https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=287. Accessed September 10, 2018
38. Centers for Disease Control and Prevention website. National Ambulatory Medical Care Survey: 2015 State and National Summary Tables. https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2015_namcs_web_tables.pdf. Accessed June 14, 2018.
39. Centers for Disease Control and Prevention website. National Hospital Ambulatory Medical Care Survey: 2015 Emergency Department Summary Tables. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2015_ed_web_tables.pdf. Accessed June 14, 2018.
40. Price JF, Mowbray PI, Lee AJ, Rumley A, Lowe GD, Fowkes FG. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh Artery Study. *Eur Heart J*. 1999;20:344–353.
41. Joosten MM, Pai JK, Bertoia ML, Rimm EB, Spiegelman D, Mittleman MA, Mukamal KJ. Associations between conventional cardiovascular risk factors and risk of peripheral artery disease in men. *JAMA*. 2012;308:1660–1667. doi: 10.1001/jama.2012.13415
42. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, Criqui MH. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382:1329–1340. doi: 10.1016/S0140-6736(13)61249-0
43. Berger JS, Hochman J, Lobach I, Adelman MA, Riles TS, Rockman CB. Modifiable risk factor burden and the prevalence of peripheral artery disease in different vascular territories. *J Vasc Surg*. 2013;58:673–81.e1. doi: 10.1016/j.jvs.2013.01.053
44. Garg PK, Biggs ML, Carnethon M, Ix JH, Criqui MH, Britton KA, Djoussé L, Sutton-Tyrrell K, Newman AB, Cushman M, Mukamal KJ. Metabolic syndrome and risk of incident peripheral artery disease: the Cardiovascular Health Study. *Hypertension*. 2014;63:413–419. doi: 10.1161/HYPERTENSIONAHA.113.01925
45. Wattanakit K, Folsom AR, Selvin E, Coresh J, Hirsch AT, Weatherley BD. Kidney function and risk of peripheral arterial disease: results from the Atherosclerosis Risk in Communities (ARIC) Study. *J Am Soc Nephrol*. 2007;18:629–636. doi: 10.1681/ASN.2005111204
46. Weissgerber TL, Turner ST, Bailey KR, Mosley TH Jr, Kardia SL, Wiste HJ, Miller VM, Kullo IJ, Garovic VD. Hypertension in pregnancy is a risk factor for peripheral arterial disease decades after pregnancy. *Atherosclerosis*. 2013;229:212–216. doi: 10.1016/j.atherosclerosis.2013.04.012
47. Arya S, Binney Z, Khakharia A, Brewster LP, Goodney P, Patzer R, Hockenberry J, Wilson PWF. Race and socioeconomic status independently affect risk of major amputation in peripheral artery disease. *J Am Heart Assoc*. 2018;7:e007425. doi: 10.1161/JAHA.117.007425
48. Ruiz-Canela M, Estruch R, Corella D, Salas-Salvadó J, Martínez-González MA. Association of Mediterranean diet with peripheral artery disease: the PREDIMED randomized trial. *JAMA*. 2014;311:415–417. doi: 10.1001/jama.2013.280618
49. Collins TC, Slovut DP, Newton R Jr, Johnson WD, Larrivee S, Patterson J, Johnston JA, Correa A. Ideal cardiovascular health and peripheral artery disease in African Americans: results from the Jackson Heart Study. *Prev Med Rep*. 2017;7:20–25. doi: 10.1016/j.pmedr.2017.05.005
50. Wassel CL, Loomba R, Ix JH, Allison MA, Denenberg JO, Criqui MH. Family history of peripheral artery disease is associated with prevalence and severity of peripheral artery disease: the San Diego Population Study. *J Am Coll Cardiol*. 2011;58:1386–1392. doi: 10.1016/j.jacc.2011.06.023
51. Wahlgren CM, Magnusson PK. Genetic influences on peripheral arterial disease in a twin population. *Arterioscler Thromb Vasc Biol*. 2011;31:678–682. doi: 10.1161/ATVBAHA.110.210385
52. Carmelli D, Fabsitz RR, Swan GE, Reed T, Miller B, Wolf PA. Contribution of genetic and environmental influences to ankle-brachial blood pressure index in the NHLBI Twin Study. National Heart, Lung, and Blood Institute. *Am J Epidemiol*. 2000;151:452–458.
53. Kullo IJ, Leeper NJ. The genetic basis of peripheral arterial disease: current knowledge, challenges, and future directions. *Circ Res*. 2015;116:1551–1560. doi: 10.1161/CIRCRESAHA.116.303518
54. Helgadottir A, Thorleifsson G, Magnusson KP, Grétarsdottir S, Steinthorsdottir V, Manolescu A, Jones GT, Rinkel GJ, Blankensteijn JD, Ronkainen A, Jääskeläinen JE, Kyo Y, Lenk GM, Sakalihasan N, Kostulas K, Gottsäter A, Flex A, Stefansson H, Hansen T, Andersen G, Weinsheimer S, Borch-Johnsen K, Jorgensen T, Shah SH, Quyyumi AA, Granger CB, Reilly MP, Austin H, Levey AI, Vaccarino V, Palsdottir E, Walters GB, Jonsdottir T, Snorradottir S, Magnusdottir D, Gudmundsson G, Ferrell RE, Sveinbjornsdottir S, Hernesniemi J, Niemelä M, Limet R, Andersen K, Sigurdsson G, Benediktsson R, Verhoeven EL, Teijink JA, Grobbee DE, Rader DJ, Collier DA, Pedersen O, Pola R, Hillert J, Lindblad B, Valdimarsson EM, Magnadottir HB, Wijmenga C, Tromp G, Baas AF, Ruigrok YM, van Rij AM, Kuivaniemi H, Powell JT, Matthiasson SE, Gulcher JR, Thorgeirsson G, Kong A, Thorsteinsdottir U, Stefansson K. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. *Nat Genet*. 2008;40:217–224. doi: 10.1038/ng.72
55. Murabito JM, White CC, Kavousi M, Sun YV, Feitosa MF, Nambi V, Lamina C, Schillert A, Coassin S, Bis JC, Broer L, Crawford DC, Franceschini N, Frikke-Schmidt R, Haun M, Holewijn S, Huffman JE, Hwang SJ, Kiechl S, Kollerits B, Montasser ME, Nolte IM, Rudock ME, Senft A, Teumer A, van der Harst P, Vitart V, Waite LL, Wood AR, Wassel CL, Absher DM, Allison MA, Amin N, Arnold A, Asselbergs FW, Aulchenko Y, Bandinelli S, Barbalic M, Boban M, Brown-Gentry K, Couper DJ, Criqui MH, Dehghan A, den Heijer M, Dieplinger B, Ding J, Dörr M, Espinola-Klein C, Felix SB, Ferrucci L, Folsom AR, Fraedrich G, Gibson Q, Goodloe R, Gunjaca G, Haltmayer M, Heiss G, Hofman A, Kieback A, Kiemeney LA, Kolcic I, Kullo IJ, Kritchevsky SB, Lackner KJ, Li X, Lieb W, Lohman K, Meisinger C, Melzer D, Mohler ER 3rd, Mudnic I, Mueller T, Navis G, Oberhollenzer F, Olin JW, O'Connell J, O'Donnell CJ, Palmas W, Penninx BW, Petersmann A, Polasek O, Psaty BM, Rantner B, Rice K, Rivadeneira F, Rotter JI, Seldenrijk A, Stadler M, Summerer M, Tanaka T, Tybjaerg-Hansen A, Uitterlinden AG, van Gilst WH, Vermeulen SH, Wild SH, Wild PS, Willeit J, Zeller T, Zemunik T, Zgaga L, Assimes TL, Blankenberg S, Boerwinkle E, Campbell H, Cooke JP, de Graaf J, Herrington D, Kardia SL, Mitchell BD, Murray A, Münzel T, Newman AB, Oostra BA, Rudan I, Shuldiner AR, Snieder H, van Duijn CM, Völker U, Wright AF, Wichmann HE, Wilson JF, Witteman JC, Liu Y, Hayward C, Borecki IB, Ziegler A, North KE, Cupples LA, Kronenberg F. Association between chromosome 9p21 variants and the ankle-brachial index identified by a meta-analysis of 21 genome-wide association studies. *Circ Cardiovasc Genet*. 2012;5:100–112. doi: 10.1161/CIRCGENETICS.111.961292
56. Khor CC, Davila S, Breunis WB, Lee YC, Shimizu C, Wright VJ, Yeung RS, Tan DE, Sim KS, Wang JJ, Wong TY, Pang J, Mitchell P, Cimaz R, Dahdah N, Cheung YF, Huang GY, Yang W, Park IS, Lee JK, Wu JY, Levin M, Burns JC, Burgner D, Kuijpers TW, Hibberd ML; Hong Kong–Shanghai Kawasaki Disease Genetics Consortium; Korean Kawasaki Disease Genetics Consortium; Taiwan Kawasaki Disease Genetics Consortium; International Kawasaki Disease Genetics Consortium; US Kawasaki Disease Genetics Consortium; Blue Mountains Eye Study. Genome-wide association study identifies FCGR2A as a susceptibility locus for Kawasaki disease. *Nat Genet*. 2011;43:1241–1246. doi: 10.1038/ng.981
57. Global Burden of Disease Study 2016. Global Burden of Disease Study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed May 1, 2018.
58. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WR, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor LM Jr, White CJ, White J, White RA. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force

on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). *Circulation*. 2006;113:e463–e654. doi: 10.1161/CIRCULATIONAHA.106.174526
59. Sweeting MJ, Thompson SG, Brown LC, Powell JT; RESCAN Collaborators. Meta-analysis of individual patient data to examine factors affecting growth and rupture of small abdominal aortic aneurysms. *Br J Surg*. 2012;99:655–665. doi: 10.1002/bjs.8707
60. Clouse WD, Hallett JW Jr, Schaff HV, Spittell PC, Rowland CM, Ilstrup DM, Melton LJ 3rd. Acute aortic dissection: population-based incidence compared with degenerative aortic aneurysm rupture. *Mayo Clin Proc*. 2004;79:176–180.
61. Brewster DC, Cronenwett JL, Hallett JW Jr, Johnston KW, Krupski WC, Matsumura JS; Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. Guidelines for the treatment of abdominal aortic aneurysms: report of a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. *J Vasc Surg*. 2003;37:1106–1117. doi: 10.1067/mva.2003.363
62. Eckstein H-H, Reeps C, Zimmermann A, Söllner H. Ultrasound screening for abdominal aortic aneurysms. *Gefässchirurgie*. 2015;20(suppl 1):1–12. doi: 10.1007/s00772-014-1398-7
63. Guirguis-Blake JM, Beil TL, Sun X, Senger CA, Whitlock EP. *Primary Care Screening for Abdominal Aortic Aneurysm: A Systematic Evidence Review for the U.S. Preventive Services Task Force*. Rockville, MD: Agency for Healthcare Research and Quality; 2014. Evidence Synthesis No. 109. AHRQ publication No. 14-05202-EF-1.
64. Wanhainen A, Hultgren R, Linné A, Holst J, Gottsäter A, Langenskiöld M, Smidfelt K, Björck M, Svensjö S; on behalf of the Swedish Aneurysm Screening Study Group (SASS). Outcome of the Swedish Nationwide Abdominal Aortic Aneurysm Screening Program. *Circulation*. 2016;134:1141–1148. doi: 10.1161/CIRCULATIONAHA.116.022305
65. Di Eusanio M, Trimarchi S, Patel HJ, Hutchison S, Suzuki T, Peterson MD, Di Bartolomeo R, Folesani G, Pyeritz RE, Braverman AC, Montgomery DG, Isselbacher EM, Nienaber CA, Eagle KA, Fattori R. Clinical presentation, management, and short-term outcome of patients with type A acute dissection complicated by mesenteric malperfusion: observations from the International Registry of Acute Aortic Dissection. *J Thorac Cardiovasc Surg*. 2013;145:385–390.e1. doi: 10.1016/j.jtcvs.2012.01.042
66. Trimarchi S, Tolenaar JL, Tsai TT, Froehlich J, Pegorer M, Upchurch GR, Fattori R, Sundt TM 3rd, Isselbacher EM, Nienaber CA, Rampoldi V, Eagle KA. Influence of clinical presentation on the outcome of acute B aortic dissection: evidences from IRAD. *J Cardiovasc Surg (Torino)*. 2012;53:161–168.
67. Filardo G, Powell JT, Martinez MAM, Ballard DJ. Surgery for small asymptomatic abdominal aortic aneurysms. *Cochrane Database Syst Rev*. 2015;(2):CD001835. doi: 10.1002/14651858.CD001835.pub4
68. Karthikesalingam A, Holt PJ, Vidal-Diez A, Ozdemir BA, Poloniecki JD, Hinchliffe RJ, Thompson MM. Mortality from ruptured abdominal aortic aneurysms: clinical lessons from a comparison of outcomes in England and the USA. *Lancet*. 2014;383:963–969. doi: 10.1016/S0140-6736(14)60109-4
69. Dua A, Kuy S, Lee CJ, Upchurch GR Jr, Desai SS. Epidemiology of aortic aneurysm repair in the United States from 2000 to 2010. *J Vasc Surg*. 2014;59:1512–1517. doi: 10.1016/j.jvs.2014.01.007
70. Jackson RS, Chang DC, Freischlag JA. Comparison of long-term survival after open vs endovascular repair of intact abdominal aortic aneurysm among Medicare beneficiaries. *JAMA*. 2012;307:1621–1628. doi: 10.1001/jama.2012.453
71. Schermerhorn ML, Buck DB, O'Malley AJ, Curran T, McCallum JC, Darling J, Landon BE. Long-term outcomes of abdominal aortic aneurysm in the Medicare population. *N Engl J Med*. 2015;373:328–338. doi: 10.1056/NEJMoa1405778
72. Lederle FA, Freischlag JA, Kyriakides TC, Matsumura JS, Padberg FT Jr, Kohler TR, Kougias P, Jean-Claude JM, Cikrit DF, Swanson KM; OVER Veterans Affairs Cooperative Study Group. Long-term comparison of endovascular and open repair of abdominal aortic aneurysm. *N Engl J Med*. 2012;367:1988–1997. doi: 10.1056/NEJMoa1207481
73. Karthikesalingam A, Vidal-Diez A, Holt PJ, Loftus IM, Schermerhorn ML, Soden PA, Landon BE, Thompson MM. Thresholds for abdominal aortic aneurysm repair in England and the United States. *N Engl J Med*. 2016;375:2051–2059. doi: 10.1056/NEJMoa1600931
74. Ullery BW, Tran K, Chandra V, Mell MW, Harris EJ, Dalman RL, Lee JT. Association of an endovascular-first protocol for ruptured abdominal aortic aneurysms with survival and discharge disposition. *JAMA Surg*. 2015;150:1058–1065. doi: 10.1001/jamasurg.2015.1861
75. Zettervall SL, Schermerhorn ML, Soden PA, McCallum JC, Shean KE, Deery SE, O'Malley AJ, Landon B. The effect of surgeon and hospital volume on mortality after open and endovascular repair of abdominal aortic aneurysms. *J Vasc Surg*. 2017;65:626–634. doi: 10.1016/j.jvs.2016.09.036
76. Goodney PP, Brooke BS, Wallaert J, Travis L, Lucas FL, Goodman DC, Cronenwett JL, Stone DH. Thoracic endovascular aneurysm repair, race, and volume in thoracic aneurysm repair. *J Vasc Surg*. 2013;57:56–63, 63.e1. doi: 10.1016/j.jvs.2012.07.036
77. Groves EM, Khoshchehreh M, Le C, Malik S. Effects of weekend admission on the outcomes and management of ruptured aortic aneurysms. *J Vasc Surg*. 2014;60:318–324. doi: 10.1016/j.jvs.2014.02.052
78. Pape LA, Awais M, Woznicki EM, Suzuki T, Trimarchi S, Evangelista A, Myrmel T, Larsen M, Harris KM, Greason K, Di Eusanio M, Bossone E, Montgomery DG, Eagle KA, Nienaber CA, Isselbacher EM, O'Gara P. Presentation, diagnosis, and outcomes of acute aortic dissection: 17-year trends from the International Registry of Acute Aortic Dissection. *J Am Coll Cardiol*. 2015;66:350–358. doi: 10.1016/j.jacc.2015.05.029
79. Singh K, Bønaa KH, Jacobsen BK, Bjørk L, Solberg S. Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study: the Tromsø Study. *Am J Epidemiol*. 2001;154:236–244.
80. Lederle FA. In the clinic: abdominal aortic aneurysm. *Ann Intern Med*. 2009;150:ITC5-1–ITC5-15. doi: 10.7326/0003-4819-150-9-200905050-01005
81. De Rango P, Farchioni L, Fiorucci B, Lenti M. Diabetes and abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg*. 2014;47:243–261. doi: 10.1016/j.ejvs.2013.12.007
82. Robson JC, Kiran A, Maskell J, Hutchings A, Arden N, Dasgupta B, Hamilton W, Emin A, Culliford D, Luqmani RA. The relative risk of aortic aneurysm in patients with giant cell arteritis compared with the general population of the UK. *Ann Rheum Dis*. 2015;74:129–135. doi: 10.1136/annrheumdis-2013-204113
83. Guo DC, Grove ML, Prakash SK, Eriksson P, Hostetler EM, LeMaire SA, Body SC, Shalhub S, Estrera AL, Safi HJ, Regalado ES, Zhou W, Mathis MR, Eagle KA, Yang B, Willer CJ, Boerwinkle E, Milewicz DM; GenTAC Investigators; BAVCon Investigators. Genetic variants in LRP1 and ULK4 are associated with acute aortic dissections. *Am J Hum Genet*. 2016;99:762–769. doi: 10.1016/j.ajhg.2016.06.034
84. LeMaire SA, McDonald ML, Guo DC, Russell L, Miller CC 3rd, Johnson RJ, Bekheirnia MR, Franco LM, Nguyen M, Pyeritz RE, Bavaria JE, Devereux R, Maslen C, Holmes KW, Eagle K, Body SC, Seidman C, Seidman JG, Isselbacher EM, Bray M, Coselli JS, Estrera AL, Safi HJ, Belmont JW, Leal SM, Milewicz DM. Genome-wide association study identifies a susceptibility locus for thoracic aortic aneurysms and aortic dissections spanning FBN1 at 15q21.1. *Nat Genet*. 2011;43:996–1000. doi: 10.1038/ng.934
85. van 't Hof FN, Ruigrok YM, Lee CH, Ripke S, Anderson G, de Andrade M, Baas AF, Blankensteijn JD, Böttinger EP, Bown MJ, Broderick J, Bijlenga P, Carrell DS, Crawford DC, Crosslin DR, Ebeling C, Eriksson JG, Fornage M, Foroud T, von Und Zu Fraunberg M, Friedrich CM, Gaál EI, Gottesman O, Guo DC, Harrison SC, Hernesniemi J, Hofman A, Inoue I, Jääskeläinen JE, Jones GT, Kiemeney LA, Kivisaari R, Ko N, Koskinen S, Kubo M, Kullo IJ, Kuivaniemi H, Kurki MI, Laakso A, Lai D, Leal SM, Lehto H, LeMaire SA, Low SK, Malinowski J, McCarty CA, Milewicz DM, Mosley TH, Nakamura Y, Nakaoka H, Niemelä M, Pacheco J, Peissig PL, Pera J, Rasmussen-Torvik L, Ritchie MD, Rivadeneira F, van Rij AM, Santos-Cortez RL, Saratzis A, Slowik A, Takahashi A, Tromp G, Uitterlinden AG, Verma SS, Vermeulen SH, Wang GT; Aneurysm Consortium; Vascular Research Consortium of New Zealand; Han B, Rinkel GJ, de Bakker PI. Shared genetic risk factors of intracranial, abdominal, and thoracic aneurysms. *J Am Heart Assoc*. 2016;5:e002603. doi: 10.1161/JAHA.115.002603
86. Verloes A, Sakalihasan N, Koulischer L, Limet R. Aneurysms of the abdominal aorta: familial and genetic aspects in three hundred thirteen pedigrees. *J Vasc Surg*. 1995;21:646–655.
87. Davis FM, Rateri DL, Daugherty A. Abdominal aortic aneurysm: novel mechanisms and therapies. *Curr Opin Cardiol*. 2015;30:566–573. doi: 10.1097/HCO.0000000000000216
88. Gretarsdottir S, Baas AF, Thorleifsson G, Holm H, den Heijer M, de Vries JP, Kranendonk SE, Zeebregts CJ, van Sterkenburg SM, Geelkerken RH, van Rij AM, Williams MJ, Boll AP, Kostic JP, Jonasdottir A, Jonasdottir A, Walters GB, Masson G, Sulem P, Saemundsdottir J, Mouy M, Magnusson KP, Tromp G, Elmore JR, Sakalihasan N, Limet R, Defraigne JO, Ferrell RE, Ronkainen A, Ruigrok YM, Wijmenga C, Grobbee DE, Shah SH, Granger CB, Quyyumi AA, Vaccarino V, Patel RS, Zafari AM, Levey AI, Austin H, Girelli D, Pignatti PF, Olivieri O, Martinelli N, Malerba G, Trabetti E, Becker LC, Becker DM, Reilly MP, Rader DJ, Mueller T, Dieplinger B, Haltmayer

M, Urbonavicius S, Lindblad B, Gottsäter A, Gaetani E, Pola R, Wells P, Rodger M, Forgie M, Langlois N, Corral J, Vicente V, Fontcuberta J, España F, Grarup N, Jørgensen T, Witte DR, Hansen T, Pedersen O, Aben KK, de Graaf J, Holewijn S, Folkersen L, Franco-Cereceda A, Eriksson P, Collier DA, Stefansson H, Steinthorsdottir V, Rafnar T, Valdimarsson EM, Magnadottir HB, Sveinbjornsdottir S, Olafsson I, Magnusson MK, Palmason R, Haraldsdottir V, Andersen K, Onundarson PT, Thorgeirsson G, Kiemeney LA, Powell JT, Carey DJ, Kuivaniemi H, Lindholt JS, Jones GT, Kong A, Blankensteijn JD, Matthiasson SE, Thorsteinsdottir U, Stefansson K. Genome-wide association study identifies a sequence variant within the DAB2IP gene conferring susceptibility to abdominal aortic aneurysm. *Nat Genet*. 2010;42:692–697. doi: 10.1038/ng.622

89. Yasuno K, Bilguvar K, Bijlenga P, Low SK, Krischek B, Auburger G, Simon M, Krex D, Arlier Z, Nayak N, Ruigrok YM, Niemelä M, Tajima A, von und zu Fraunberg M, Dóczi T, Wirjatijasa F, Hata A, Blasco J, Oszvald A, Kasuya H, Zilani G, Schoch B, Singh P, Stüer C, Risselada R, Beck J, Sola T, Ricciardi F, Aromaa A, Illig T, Schreiber S, van Duijn CM, van den Berg LH, Perret C, Proust C, Roder C, Ozturk AK, Gaál E, Berg D, Geisen C, Friedrich CM, Summers P, Frangi AF, State MW, Wichmann HE, Breteler MM, Wijmenga C, Mane S, Peltonen L, Elio V, Sturkenboom MC, Lawford P, Byrne J, Macho J, Sandalcioglu EI, Meyer B, Raabe A, Steinmetz H, Rüfenacht D, Jääskeläinen JE, Hernesniemi J, Rinkel GJ, Zembutsu H, Inoue I, Palotie A, Cambien F, Nakamura Y, Lifton RP, Günel M. Genome-wide association study of intracranial aneurysm identifies three new risk loci. *Nat Genet*. 2010;42:420–425. doi: 10.1038/ng.563
90. Bourcier R, Le Scouarnec S, Bonnaud S, Karakachoff M, Bourcereau E, Heurtebise-Chrétien S, Menguy C, Dina C, Simonet F, Moles A, Lenoble C, Lindenbaum P, Chatel S, Isidor B, Génin E, Deleuze JF, Schott JJ, Le Marec H, ICAN Study Group; Loirand G, Desal H, Redon R. Rare coding variants in ANGPTL6 are associated with familial forms of intracranial aneurysm. *Am J Hum Genet*. 2018;102:133–141. doi: 10.1016/j.ajhg.2017.12.006
91. Kiando SR, Tucker NR, Castro-Vega LJ, Katz A, D'Escamard V, Tréard C, Fraher D, Albuisson J, Kadian-Dodov D, Ye Z, Austin E, Yang ML, Hunker K, Barlassina C, Cusi D, Galan P, Empana JP, Jouven X, Gimenez-Roqueplo AP, Bruneval P, Hyun Kim ES, Olin JW, Gornik HL, Azizi M, Plouin PF, Ellinor PT, Kullo IJ, Milan DJ, Ganesh SK, Boutouyrie P, Kovacic JC, Jeunemaitre X, Bouatia-Naji N. PHACTR1 is a genetic susceptibility locus for fibromuscular dysplasia supporting its complex genetic pattern of inheritance. *PLoS Genet*. 2016;12:e1006367. doi: 10.1371/journal.pgen.1006367
92. Hansen KJ, Edwards MS, Craven TE, Cherr GS, Jackson SA, Appel RG, Burke GL, Dean RH. Prevalence of renovascular disease in the elderly: a population-based study. *J Vasc Surg*. 2002;36:443–451.
93. Kalra PA, Guo H, Gilbertson DT, Liu J, Chen SC, Ishani A, Collins AJ, Foley RN. Atherosclerotic renovascular disease in the United States. *Kidney Int*. 2010;77:37–43. doi: 10.1038/ki.2009.406
94. Shafique S, Peixoto AJ. Renal artery stenosis and cardiovascular risk. *J Clin Hypertens (Greenwich)*. 2007;9:201–208.
95. Conlon PJ, Little MA, Pieper K, Mark DB. Severity of renal vascular disease predicts mortality in patients undergoing coronary angiography. *Kidney Int*. 2001;60:1490–1497. doi: 10.1046/j.1523-1755.2001.00953.x
96. Cooper CJ, Murphy TP, Cutlip DE, Jamerson K, Henrich W, Reid DM, Cohen DJ, Matsumoto AH, Steffes M, Jaff MR, Prince MR, Lewis EF, Tuttle KR, Shapiro JI, Rundback JH, Massaro JM, D'Agostino RB Sr, Dworkin LD; CORAL Investigators. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med*. 2014;370:13–22. doi: 10.1056/NEJMoa1310753

24. QUALITY OF CARE

See Tables 24-1 through 24-11 and Chart 24-1

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The Institute of Medicine has defined quality of care as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge,"[1] and further defined 6 specific domains for improving health care: safety, effectiveness, patient or people-centeredness, timeliness, efficiency, and equity.

Abbreviations Used in Chapter 24

ACC	American College of Cardiology
ACEI	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
ACTION	Acute Coronary Treatment and Intervention Outcomes Network
AED	automated external defibrillator
AF	atrial fibrillation
AHA	American Heart Association
AMI	acute myocardial infarction
ARB	angiotensin receptor blocker
ASCVD	atherosclerotic cardiovascular disease
AVAIL	Adherence Evaluation After Ischemic Stroke Longitudinal
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CHA_2DS_2-VASc	Clinical prediction rule for estimating the risk of stroke based on congestive heart failure, hypertension, diabetes mellitus, and sex (1 point each); age ≥75 y and stroke/transient ischemic attack/thromboembolism (2 points each); plus history of vascular disease, age 65–74 y, and (female) sex category
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CPR	cardiopulmonary resuscitation
CVD	cardiovascular disease
DM	diabetes mellitus
DNR	do not resuscitate
DVT	deep vein thrombosis
ECG	electrocardiogram
ED	emergency department
EF	ejection fraction
EMS	emergency medical services
ERR	excess readmission ratio
$ETco_2$	end-tidal CO_2
GLORIA-AF	Global Registry on Long-term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation
GWTG	Get With The Guidelines
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HF	heart failure
HF-ACTION	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
HMO	health maintenance organization
HR	hazard ratio
IHCA	in-hospital cardiac arrest

(*Continued*)

Abbreviations Used in Chapter 24 Continued

IQR	interquartile range
IV	intravenous
LDL-C	low-density lipoprotein cholesterol
LV	left ventricular
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MD	medical doctor
MEPS	Medical Expenditure Panel Survey
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
N/A	not available or not applicable
NCDR	National Cardiovascular Data Registry
NSTEMI	non–ST-segment–elevation myocardial infarction
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
PCI	percutaneous coronary intervention
PINNACLE	Practice Innovation and Clinical Excellence
PPO	preferred provider organization
QALY	quality-adjusted life-year
ROC	Resuscitation Outcomes Consortium
RR	relative risk
RSMR	risk-standardized mortality rate
rtPA	recombinant tissue-type plasminogen activator
SD	standard deviation
STEMI	ST-segment–elevation myocardial infarction
TIA	transient ischemic stroke
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist
tPA	tissue-type plasminogen activator
UFH	unfractionated heparin
VF	ventricular fibrillation
VT	ventricular tachycardia

Assessing care quality requires the development and implementation of performance measures, explicit standards or metrics of care against which actual clinical care delivered can be judged.[2] Performance measures are standards that, if not followed, represent clinician error. This differs from guidelines, which are clinical recommendations applicable to most clinical scenarios but ultimately left to reasonable clinician discretion. Measuring performance requires a robust process for data collection across care facilities and clinicians, data transfer, analysis, and dissemination. Over the past 15 years, there has been a proliferation of clinical registries in the United States and worldwide designed to help us better understand and improve quality, performance, and outcomes. Early registries have focused primarily on the inpatient setting (MI, HF, stroke) or discrete procedures (PCI, defibrillator implantation, peripheral vascular interventions, cardiothoracic surgery). In the United States, these have been principally run by the ACC's NCDR[3] and the AHA's GWTG Program.[4] More recently, a variety of elective procedural registries have also been developed by the AHA and ACC, such as for AF ablation and left atrial appendage occlusion. New outpatient registries such as the ACC's PINNACLE Registry use electronic health record data transfer rather than case report form data

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entry to examine performance measures across a wide range of cardiovascular conditions. Increasingly, outpatient postmarketing registries have been sponsored by pharmaceutical or device companies and managed by contract research organizations, such as for anticoagulation in AF. Finally, medical claims data from payers (Medicare, commercial claims) or integrated healthcare systems (Veterans Affairs) have also examined quality.

In the following sections, data on quality of care will be presented across these 6 domains to highlight current care and to stimulate efforts to improve the quality of cardiovascular care nationally. Rather than group findings by domains as we have in prior years, we now group findings by disease or therapeutic area. Where possible, data are reported from recently published literature or as standardized quality indicators drawn from quality-improvement registries whose methods are consistent with performance measures endorsed by the ACC and the AHA.[2,5,6]

Additional data on adherence to ACC/AHA clinical practice guidelines are also included to supplement performance measures data where appropriate. The select data presented are meant to provide illustrative examples of quality of care and are not meant to be comprehensive given the sheer volume of quality data published each year.

Acute Myocardial Infarction (See Tables 24-1 through 24-5)

- The ACTION Registry–GWTG is currently the largest US-based hospital registry of inpatient AMI care and is the current best source for national-level quality data (Tables 24-1 through 24-5).
- Wadhera and colleagues[5] examined a large cohort of Medicare beneficiaries with 642 105 index hospitalizations for AMI and showed that higher 30-day payments were associated with lower 30-day mortality after adjustment for patient characteristics and comorbidities (adjusted OR for additional $1000 payments, 0.986 [95% CI, 0.979–0.992]; *P*<0.001). This could have implications for payment programs that incent reduction in payments without considering value.
- Chatterjee and Joynt-Maddox[6] examined patterns in 30-day mortality from AMI as they relate to public reporting of these outcomes. In data from 2009 to 2015 from 2751 hospitals with publicly reported mortality data for AMI, they showed 30-day mortality among baseline poor performers (worst quartile in 2009 and 2010 in public reporting, before value-based payment) was higher at baseline but improved more over time compared with other hospitals (18.6% in 2009 to 14.6% in 2015 [−0.74% per year; *P*<0.001] versus 15.7% in 2009 to 14.0% in 2015 [−0.26% per year; *P*<0.001]; $P_{interaction}$<0.001).
- In a study examining the association between higher-than-expected risk-adjusted 30-day readmission rates (ERR>1) after AMI and MI care processes and outcomes, Pandey and colleagues[7] showed participating hospitals' risk-adjusted 30-day readmission rates after MI were not associated with in-hospital quality of MI care (adjusted OR, 0.94 [95% CI, 0.81–1.08] per 0.1-unit increase in MI ERR for overall defect-free care). Among the 51 453 patients with 1-year outcomes data available, higher MI ERR was associated with higher all-cause readmission within 1 year of discharge; however, this association was largely driven by readmissions early after discharge and was not significant in landmark analyses beginning 30 days after discharge. The MI ERR was not associated with risk for mortality within 1 year of discharge.
- Bucholz and colleagues[8] showed that patients admitted to high-performing hospitals after AMI had longer life expectancies than patients treated at low-performing hospitals. This survival benefit appeared in the first 30 days and persisted over 17 years of follow-up. The study sample included 119 735 patients with AMI who were admitted to 1824 hospitals. On average, patients treated at high-performing hospitals lived between 0.74 and 1.14 years longer than patients treated at low-performing hospitals.
- Makam and Nguyen[9] showed cardiac biomarker testing in the ED is common even among those without symptoms suggestive of ACS. Biomarker testing occurred in 8.2% of visits in the absence of symptoms related to ACS, representing 8.5 million visits. Among individuals who were subsequently hospitalized, cardiac biomarkers were tested in 47% of all visits. Biomarkers were tested in 35.4% of visits in this group despite the absence of ACS-related symptoms.
- Using data from the ACTION Registry–GWTG, among 202 213 patients discharged after AMI from 526 US participating sites between January 2007 and March 2011, Rao and colleagues[10] showed that only 14.5% of the eligible patients without a documented contraindication received aldosterone antagonists. Fewer than 2% of the participating sites used aldosterone antagonists in ≥50% of eligible patients.
- According to national Medicare data from July 2015 through June 2016, the median (IQR) hospital RSMR for MI was 13.1% (12.6%, 13.5%), and the median (IQR) risk-standardized 30-day readmission rate was 15.8% (15.5%, 16.2%).[11]

- Mathews and colleagues[12] examined post-MI medication adherence as a hospital-level variable using data from 347 US hospitals participating in the ACTION Registry–GWTG. They observed that postdischarge use of secondary prevention medications varied significantly across US hospitals and was inversely associated with 2-year outcomes at the hospital level.

Heart Failure (See Tables 24-6 and 24-7)

- Current US HF quality data are best captured by the widespread but voluntary GWTG–HF Program (Tables 24-6 and 24-7).
- Elucidating the validity of use of hospital volume as a structural metric for assessing quality of HF care, Kumbhani and colleagues[13] examined the relationship between admission volume, process-of-care metrics, and short- and long-term outcomes in patients admitted with acute HF in the GWTG–HF registry with linked Medicare inpatient data. In their cohort of 125 595 patients at 342 hospitals, they found that hospital volume as a structural metric correlated with process measures but not with 30-day outcomes and only marginally with outcomes up to 6 months of follow-up. Lower-volume hospitals were significantly less likely to be adherent to HF process measures than higher-volume hospitals. On multivariable modeling, higher hospital volume was not associated with a difference in the in-hospital mortality (OR, 0.99 [95% CI, 0.94–1.05]; P=0.78), 30-day mortality (HR, 0.99 [95% CI, 0.97–1.01]; P=0.26), or 30-day readmissions (HR, 0.99 [95% CI, 0.97–1.00]; P=0.10). Gupta and colleagues[14] examined the association of the Hospital Readmissions Reduction Program with readmission and mortality outcomes among patients hospitalized with HF. Among a cohort of 115 245 fee-for-service Medicare beneficiaries discharged after HF hospitalizations, the 1-year risk-adjusted readmission rate declined from 57.2% to 56.3% (HR, 0.92 [95% CI, 0.89–0.96]), and the 1-year risk-adjusted mortality rate increased from 31.3% to 36.3% (HR, 1.10 [95% CI, 1.06–1.14]) after the Hospital Readmissions Reduction Program implementation.
- Chatterjee and Joynt-Maddox[6] examined patterns in 30-day mortality from HF as they relate to public reporting of these outcomes. In data from 2009 to 2015 from 3796 hospitals with publicly reported mortality data for HF, they showed baseline poor performers (worst quartile in 2009 and 2010 in public reporting, before value-based payment) improved over time (from 13.5% to 13.0%; −0.12% per year; P<0.001), but mean mortality among all other HF hospitals increased during the study period. (from 10.9% to 12.0%; 0.17% per year; P<0.001, $P_{interaction}$<0.001). In a secondary analysis of the TOPCAT and HF-ACTION trials focused on patient-reported outcomes, Pokharel and colleagues[15] observed that the most recent of a series of Kansas City Cardiomyopathy Questionnaire scores was most strongly associated with subsequent death and cardiovascular hospitalization.
- Using pooled participant-level data from the CHS and MESA, Pandey and colleagues[16] studied sex differences in the lifetime risk of HF. At an index age of 45 years, the lifetime risk for any HF through age 90 years was higher in males than females (27.4% versus 23.8%). Among participants with antecedent MI before HF diagnosis, the remaining lifetime risks for HF with preserved EF and HF with reduced EF were 2.5-fold and 4-fold higher, respectively, than for participants without antecedent MI.
- Using NIS data, Ziaeian and colleagues[17] showed HF hospitalization rates decreased 30.8% between 2002 and 2013. The ratio of males to females increased from 20% greater to 39% greater (P_{trend}=0.002) over that time. Black males and black females had rates that were 229% (P_{trend}=0.141) and 240% (P_{trend}=0.725) those of whites in 2013. Hispanic males had a rate that was 32% greater in 2002, and the difference narrowed to 4% greater (P_{trend}=0.047) in 2013 relative to whites. For Hispanic females, the rate was 55% greater in 2002 and narrowed to 8% greater (P_{trend}=0.004) in 2013 relative to whites. Asian/Pacific Islander males had a 27% lower rate in 2002, which improved to 43% lower (P_{trend}=0.040) in 2013 relative to whites. For Asian/Pacific Islander females, the hospitalization rate was 24% lower in 2002 and improved to 43% lower (P_{trend}=0.021) in 2013 relative to whites.
- Among 106 304 patients hospitalized with HF at 317 centers in the AHA GWTG–HF registry, there was a graded inverse association between 30-day RSMR and long-term mortality (quartile 1 versus quartile 4: 5-year mortality, 73.7% versus 76.8%). Lower hospital-level 30-day RSMR was associated with greater 1-, 3-, and 5-year survival for patients with HF. These differences in 30-day survival continued to accrue beyond 30 days and persisted long term, which suggests that 30-day RSMR could be a useful HF performance metric.[18]
- Pandey et al[19] reported results from the GWTG–HF registry evaluating the association between HF ERR and performance measures, as

well as in-hospital and 1-year clinical outcomes. They stratified participating centers into groups with low (HF ERR ≤1) versus high (HF ERR >1) risk-adjusted readmission rates. There were no differences between the low and high risk-adjusted 30-day readmission groups in median adherence rate to all performance measures (95.7% versus 96.5%, *P*=0.37) or median percentage of defect-free care (90.0% versus 91.1%, *P*=0.47). The composite 1-year outcome of death or all-cause readmission rates was also not different between the 2 groups (median 62.9% versus 65.3%; *P*=0.10). The high HF ERR group had higher 1-year all-cause readmission rates (median 59.1% versus 54.7%; *P*=0.01); however, 1-year mortality rates were lower among the high versus low group, with a trend toward statistical significance (median 28.2% versus 31.7%; *P*=0.07). The authors concluded that the quality of care and clinical outcomes were comparable among hospitals with high versus low risk-adjusted 30-day HF readmission rates.

- In a longitudinal cohort study of 48 million hospitalizations among 20 million Medicare fee-for-service patients across 3497 hospitals, Desai and colleagues[20] showed that patients at hospitals subject to penalties under the Hospital Readmissions Reduction Program had greater reductions in readmission rates than those at nonpenalized hospitals. Reductions in readmission rates were greater for target versus nontarget conditions for patients at the penalized hospitals but not at nonpenalized hospitals.
- According to national Medicare data from July 2015 through June 2016, the median (IQR) hospital RSMR for HF was 11.6% (10.8%, 12.4%), and the median (IQR) risk-standardized 30-day readmission rate was 21.4% (20.8%, 22.1%).[11]
- Krumholz and colleagues[21] examined readmission outcomes among patients who had multiple admissions at >1 hospital within a given year to attempt to separate hospital from patient effects. They found the observed readmission rate to be consistently higher among patients admitted to hospitals in a worse-performing quartile than among those admitted to hospitals in a better-performing quartile, but the only statistically significant difference was observed when one was in the best-performing quartile and the other was in the worst (absolute difference in readmission rate 2.0 percentage points [95% CI, 0.4–3.5]).
- In a Medicare cohort comprising almost 3 million admissions for HF and 1.2 million for MI, Dharmarajan and colleagues[22] studied the association between changes in hospital readmission rates and changes in mortality rates. They observed that among Medicare fee-for-service beneficiaries hospitalized for HF and AMI, reductions in hospital 30-day readmission rates were weakly but significantly correlated with reductions in hospital 30-day mortality rates after discharge.

Prevention and Risk Factor Modification (See Table 24-8)

- The National Committee for Quality Assurance Health Plan Employer Data and Information Set consists of established measures of quality of care related to CVD prevention in the United States (Table 24-8).
- Pokharel and colleagues[23] examined practice-level variation in statin therapy among 40- to 75-year-old patients with DM and no CVD between May 2008 and October 2013 from the ACC's PINNACLE Registry. Among 215 193 patients (582 048 encounters) from 204 cardiology practices, statins were prescribed in 61.6% of patients with DM. Among 182 practices with ≥30 patients with DM, the median practice statin prescription rate was 62.3%, with no noticeable change over time. There was a 57% practice-level variation in statin use for 2 similar patients that was not affected by adjustment for patient-related variables, which suggests that practice- or provider-related factors primarily determined variation in statin use.
- Using data from the PINNACLE Registry, Hira and colleagues[24] showed that among 27 533 patients receiving prasugrel, 13.9% (N=3824) had a contraindication to prasugrel use (ie, history of TIA or stroke). This was considered inappropriate prasugrel use. A further 4.4% of patients (N=1210) were receiving it for a nonrecommended indication (age >75 years without history of DM or MI or weight <60 kg). Both inappropriate and nonrecommended prasugrel use showed wide practice-level variation (median rate ratio of 2.89 [95% CI, 2.75–3.03] and 2.29 [95% CI, 2.05–2.51], respectively).
- In an analysis from the PINNACLE Registry, Hira and colleagues[25] showed that among 68 808 patients receiving aspirin therapy for primary prevention, roughly 11.6% (7972 of 68 808) were receiving inappropriate aspirin therapy (10-year risk of CVD <6%). There was significant practice-level variation in inappropriate aspirin use (range, 0%–71.8%; median, 10.1%; IQR, 6.4%) for practices with an adjusted median rate ratio of 1.63 (95% CI, 1.47–1.77).
- Using aspirin dosing data from 221 199 patients with MI enrolled in the ACTION Registry–GWTG,

Hall and colleagues[26] showed a 25-fold variation in the use of high-dose aspirin (325 mg/d) across participating centers. Overall, 60.9% of patients were discharged on high-dose aspirin. High-dose aspirin was prescribed to 73% of patients treated with PCI and 44.6% of patients managed medically; 56.7% of patients with an in-hospital bleeding event were also discharged on high-dose aspirin. Among 9075 patients discharged on aspirin, thienopyridine, and warfarin, 44.0% were prescribed high-dose aspirin therapy.

- Data from the PINNACLE Registry showed that among 156 145 patients with CAD in 58 practices, just over two-thirds (N=103 830, or 66.5%) of patients were prescribed the optimal combination of medications (β-blockers, ACEIs or angiotensin receptor blockers, statins) for which they were eligible. After adjustment for patient factors, the practice median rate ratio for prescription was 1.25 (95% CI, 1.20–1.32), which indicates a 25% likelihood that any 2 practices would differ in treating identical CAD patients.[10]
- A study of 35 191 CHD patients from the US Department of Veterans Affairs healthcare system showed that among 27 947 patients with LDL-C levels <100 mg/dL, 9200 (32.9%) received additional lipid assessments without any treatment intensification during the 11 months from the index lipid panel. Even among 13 114 patients with LDL-C <70 mg/dL, repeat lipid testing was performed in 8177 patients (62.4%) during 11 months of follow-up. These results show that redundant lipid testing is common in patients with CHD.[27]
- Heller and colleagues[28] determined the cost-effectiveness of statins after the expanded recommendations in the "2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults."[28a] They determined the ACC/AHA guideline would potentially result in up to 12.3 million more statin users than the Adult Treatment Panel III guideline, with a marginal number needed to treat for 10 years per QALY gained of 68. Moderate-intensity statin use in all males 45 to 74 years of age and females 55 to 74 years of age would result in 28.9 million more statin users than the ACC/AHA guideline, with a marginal number needed to treat for 10 years per QALY gained of 108. In all cases, they estimated benefits would be greater in males than females.[28]
- Using data from MEPS, Salami and colleagues[29] described trends in statin use and related out-of-pocket expense from 2002 to 2013. They found that statin use increased overall and among those with established ASCVD, but use in higher-risk groups was suboptimal. Statin use was significantly lower in females (OR, 0.81 [95% CI, 0.79–0.85]) and racial/ethnic minorities (OR, 0.65 [95% CI, 0.61–0.70]). Gross domestic product–adjusted total cost for statins decreased from $17.2 billion (out-of-pocket cost, $7.6 billion) in 2002 to 2003 to $16.9 billion (out-of-pocket cost, $3.9 billion) in 2012 to 2013, and the mean annual out-of-pocket costs for patients decreased from $348 to $94.

Atrial Fibrillation

- Of all CVD, AF may have the largest quantity of registries, with at least 10 non–industry-funded and 6 industry-funded registries.[30] Almost all of these emerged after the introduction of direct oral anticoagulants to the market, and performance measures and utilization of anticoagulation has remained a major focus.
- In 2016, the ACC and AHA revised the clinical performance and quality measures for AF and atrial flutter.[31] The 3 pairs of inpatient and outpatient performance measures include documentation of CHA_2DS_2-VASc score, oral anticoagulant prescription, and planned or monthly international normalized ratio testing for warfarin. The 18 quality measures reflect metrics for appropriate medications for comorbidities (HF), inappropriate prescription of specific anticoagulant drugs and antiarrhythmic drugs in specific clinical scenarios, and documentation of shared decision making. Overuse of oral anticoagulants in AF patients with very low stroke risk has been observed but has not yet been formalized into quality or performance measures.
- There is considerable variation across registries in estimated use of anticoagulation. In general, administrative claims data and electronic health record data from healthcare systems tend to show lower oral anticoagulant prescription than site-based informed-consent studies.
- Over the past decade, the proportion of AF patients with AF receiving oral anticoagulants has increased from ≈67% to >80%.[30]
- The highest uptake is reported in European registries (90%) and the lowest in Asia (58%).[30] However, methodological factors are likely a major source of difference in estimates, including selection bias of both numerator and denominator (patient, clinician, site, and in some registries, requirement of informed consent), patient characteristics, and oral anticoagulant ascertainment methodology. For example, in the outpatient, electronic health record–based PINNACLE-AF US

registry, oral anticoagulant prescription for those with CHA_2DS_2-VASc score ≥2 in 2014 was 48%. In the industry-funded, informed-consent, postmarketing GLORIA-AF international registry, oral anticoagulant prescription between 2011 and 2014 was 80%.[32]

- Healthcare insurance coverage may influence oral anticoagulant and novel oral anticoagulant use. An analysis of 363 309 prevalent AF patients from the PINNACLE-AF outpatient registry found considerable variation in oral anticoagulant use across insurance plans.[33] Relative to Medicare, Medicaid insurance was associated with a lower odds of oral anticoagulant prescription and of novel oral anticoagulant use.
- Potential overuse in low-risk patients remains a concern, with oral anticoagulants administered to AF patients with no stroke risk factors.[30] Methodological limitations of comorbidity ascertainment could lead to overestimation of overuse.
- Inappropriate use of aspirin for patients at moderate to high risk of stroke remains a concern. In PINNACLE-AF, which examined the use of aspirin rather than guideline-recommended oral anticoagulants for patients with CHA_2DS_2-VASc score ≥2, 40% of patients were treated with aspirin alone, and this was influenced by CHD comorbidities.[34]
- Treating specialty can influence likelihood of therapy and resultant outcomes. In the Veterans Health Administration, the largest integrated healthcare system in the United States, cardiology outpatient care within 90 days of newly diagnosed AF was associated with a reduced adjusted risk of stroke (HR, 0.91 [95% CI, 0.86–0.96]) and death (HR, 0.89 [95% CI, 0.88–0.91]), although with an increased risk of arrhythmia-related hospitalization (HR, 1.48 [95% CI, 1.35–1.42]).[35] This finding was statistically mediated by an increase in 90-day oral anticoagulant prescription.

Other Treatments

The AHA GWTG–AF program has been designed to track the 2016 performance measures, but there are no published data yet.[36] Data on use of rate versus rhythm control, appropriate and inappropriate use of antiarrhythmic drugs, and procedural factors related to catheter ablation are expected to be forthcoming. The NCDR AF ablation and left atrial appendage occlusion registries have also not yet published data.

Stroke (See Tables 24-4 and 24-9)

- The AHA GWTG–Stroke program (Tables 24-4 and 24-9) remains the largest stroke quality improvement program. The US-based program is an ongoing, voluntary hospital registry and performance improvement initiative for acute stroke and supplies most quality data for acute stroke care.
- Care processes that would lead to best functional outcomes after acute stroke are poorly understood. A study of 2083 ischemic stroke patients from 82 hospitals with data in both the AVAIL registry and GWTG–Stroke found that one-third of acute stroke patients were functionally dependent or dead at 3 months after stroke. Functional rates varied considerably across hospitals, which indicates the need to understand which process measures could be targeted to minimize hospital variation and improve poststroke functional outcomes.[37]
- Door-to-needle time for tPA administration decreased on average by 10 minutes, from 77 minutes (IQR 60–98 minutes) to 67 minutes (IQR 51–87 minutes), after implementation of Target: Stroke Phase I, the first stage of AHA's GWTG–Stroke quality improvement program. During this period, in-hospital all-cause mortality declined (from 9.93% to 8.25%), and discharge to home became more frequent (37.6% versus 42.7%).[38]
- Target: Stroke Phase II was launched in April 2014 to promote further reduction in door-to-needle time. There was significant site variation in door-to-needle time; 16 strategies were identified that were significantly associated with reduced door-to-needle time. It was estimated that door-to-needle time could be reduced on average by an additional 20 minutes if all strategies were implemented.[39]
- A study of 204 591 patients with ischemic and hemorrhagic strokes admitted to 1563 GWTG–Stroke participating hospitals between April 1, 2003, and June 30, 2010, showed that 63.7% of the patients arrived at the hospital by EMS. Older patients, those with Medicaid and Medicare, and those with severe strokes were more likely to activate EMS. Conversely, minority race/ethnicity (black, Hispanic, Asian) and living in rural communities were associated with a lower likelihood of EMS use. EMS transport was independently associated with an onset-to-door time ≤3 hours, a higher proportion of patients meeting door-to-imaging time of ≤25 minutes, more patients meeting a door-to-needle time of ≤60 minutes, and more eligible patients being treated with tPA if onset of symptoms was ≤2 hours. The authors concluded that although EMS use was associated with rapid evaluation and treatment of stroke, more than one-third of stroke patients fail to use EMS.[40]

Implantable Defibrillators

- In a comparative effectiveness study of single-versus dual-chamber implantable cardioverter-defibrillators using data from the Implantable Cardioverter Defibrillator Registry, Peterson and colleagues[41] found that among patients receiving an implantable cardioverter-defibrillator for primary prevention without indications for pacing, the use of a dual-chamber device compared with a single-chamber device was associated with a higher risk of device-related complications and similar 1-year mortality and hospitalization outcomes. In a propensity-matched cohort, rates of complications were lower for single-chamber devices (3.51% versus 4.72%; *P*<0.001; risk difference, −1.20 [95% CI, −1.72 to −0.69]), but device type was not significantly associated with 1-year mortality (unadjusted rate, 9.85% versus 9.77%; HR, 0.99 [95% CI, 0.91–1.07]; *P*=0.79), 1-year all-cause hospitalization (unadjusted rate, 43.86% versus 44.83%; HR, 1.00 [95% CI, 0.97–1.04]; *P*=0.82), or hospitalization for HF (unadjusted rate, 14.73% versus 15.38%; HR, 1.05 [95% CI, 0.99–1.12]; *P*=0.19).

Resuscitation (See Tables 24-10 and 24-11 and Chart 24-1)

- Quality measures in resuscitation have targeted inpatient care settings. Started in 1999, the AHA GWTG–Resuscitation Registry remains the dominant source of US quality improvement data (Tables 24-10 and 24-11; Chart 24-1). GWTG–Resuscitation is a voluntary hospital registry and performance improvement initiative for in-hospital cardiac arrest.
- Process measures for in-hospital resuscitation are generally based on time to correct administration of specific resuscitation and postresuscitation procedures, drugs, or therapies. Recent findings are discussed here.
- Among Medicare beneficiaries participating in GWTG–Resuscitation, 1-year survival after in-hospital cardiac arrest has increased modestly over the past decade for both shockable and nonshockable presenting arrest rhythms (Chart 24-1).[42] However, despite an overall improvement in survival, there remains lower survival in IHCA during off-hours (nights and weekends) compared with on-hours events.[43]
- In 103 932 in-hospital cardiac arrests between 2000 and 2014, 12.7% had delays to epinephrine administration, with marked variation across hospitals. The delay was inversely correlated to risk-standardized survival. Whether reduction in this process measure could improve outcomes has not yet been demonstrated.[44]
- A composite performance score for in-hospital arrest varied significantly across hospitals (89.7% [IQR 85.4%–93.1%]). Hospital process composite quality performance was associated with risk-standardized discharge rates and favorable neurological status at discharge.[45]
- Chan et al[46] demonstrated that rates of survival to discharge were lower for black patients (25.2%) than for white patients (37.4%) after IHCA. Lower rates of survival to discharge for blacks reflected lower rates of both successful resuscitation (55.8% versus 67.4%) and postresuscitation survival (45.2% versus 55.5%). Adjustment for the hospital site at which patients received care explained a substantial portion of the racial differences in successful resuscitation (adjusted RR, 0.92 [95% CI, 0.88–0.96]; *P*<0.001) and eliminated the racial differences in postresuscitation survival (adjusted RR, 0.99 [95% CI, 0.92–1.06]; *P*=0.68). The authors concluded that much of the racial difference was associated with the hospital center in which black patients received care.
- Stub et al[47] reported a post hoc secondary analysis of a large, partial factorial trial of interventions for patients with OHCA. The quality of hospital-based postresuscitation care given to each patient was assigned an evidence-based quality score that considered (1) initiation of temperature management; (2) achievement of target temperature 32°C to 34°C; (3) continuation of temperature management for >12 hours; (4) performance of coronary angiography within 24 hours; and (5) no withdrawal of life-sustaining treatment before day 3. These were aggregated as hospital-level composite performance scores, which varied widely (median [IQR] scores from lowest to highest hospital quartiles, 21% [20%–25%] versus 59% [55%–64%]). Adjusted survival to discharge increased with each quartile of composite performance score (from lowest to highest: 16.2%, 20.8%, 28.5%, and 34.8%; *P*<0.01). Adjusted rates of favorable neurological outcome also increased (from lowest quartile to highest: 8.3%, 13.8%, 22.2%, and 25.9%; *P*<0.01). Hospital score was significantly associated with outcome after risk adjustment for established baseline factors (highest versus lowest adherence quartile: adjusted OR of survival, 1.64 [95% CI, 1.13–2.38]).[47]

Table 24-1. AMI Quality-of-Care Measures, 2016

Quality-of-Care Measure	ACTION Registry–GWTG STEMI*	ACTION Registry–GWTG NSTEMI*
Aspirin within 24 h of admission†	98.4	97.8
Aspirin at discharge‡	99.2	98.4
β-Blockers at discharge	98.2	97.0
Lipid-lowering medication at discharge§	99.6	99.2
ARB/ACEI at discharge for patients with LVEF <40%	92.5	89.8
ACEI at discharge for AMI patients	64.8	52.0
ARB at discharge for AMI patients	12.9	17.0
Adult smoking cessation advice/counseling	98.1	98.1
Cardiac rehabilitation referral for AMI patients	83.4	75.2

Values are percentages. ACEI indicates angiotensin-converting enzyme inhibitor; ACTION Registry–GWTG, Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With The Guidelines; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; NSTEMI, non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

*ACTION Registry–GWTG: STEMI and NSTEMI patients are reported separately. Patients must be admitted with acute ischemic symptoms within the previous 24 hours, typically reflected by a primary diagnosis of STEMI or NSTEMI. Patients who are admitted for any other clinical condition are not eligible. Data reported include data from the first quarter of 2016 to the fourth quarter of 2016.

†Effective January 1, 2015, this measure was updated in the ACTION Registry–GWTG to exclude patients who are taking dabigatran, rivaroxaban, or apixaban (novel oral anticoagulant medications) at home.

‡Effective January 1, 2015, this measure was updated in the ACTION Registry–GWTG to exclude patients who were prescribed dabigatran, rivaroxaban, or apixaban (novel oral anticoagulant medications) at discharge.

§Denotes statin use at discharge. Use of nonstatin lipid-lowering agent was 3.9% for STEMI patients and 6.2% for NSTEMI patients in the ACTION Registry–GWTG.

Table 24-2. Time Trends in ACTION Registry–GWTG CAD Quality-of-Care Measures, 2010 to 2016

Quality-of-Care Measure	2010	2011	2012	2013	2014	2015	2016
Aspirin within 24 h of admission*	97	97.6	97.8	95.4	98.1	98.6	98.5
Aspirin at discharge†	98	98.3	98.4	98.4	98.7	98.7	98.7
β-Blockers at discharge	96	96.7	97.1	97.1	97.6	97.5	97.5
Statin use at discharge	92	98.4	98.8	98.8	99.1	99.2	99.4
ARB/ACEI at discharge for patients with LVEF <40%	86	87.8	89.7	90.0	91.2	90.2	91.0
Adult smoking cessation advice/counseling	98	98.4	98.4	98.4	98.6	98.0	98.1
Cardiac rehabilitation referral for AMI patients	75	76.5	77.3	77.2	79.4	77.8	78.6

Values are percentages. ACEI indicates angiotensin-converting enzyme inhibitor; ACTION Registry–GWTG, Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With The Guidelines; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CAD, coronary artery disease; and LVEF, left ventricular ejection fraction.

*Effective January 1, 2015, this measure was updated in the ACTION Registry–GWTG to exclude patients taking dabigatran, rivaroxaban, or apixaban (novel oral anticoagulant medications) at home.

†Effective January 1, 2015, this measure was updated in the ACTION Registry–GWTG to exclude patients who were prescribed dabigatran, rivaroxaban, or apixaban (novel oral anticoagulant medications) at discharge.

Table 24-3. Additional ACTION Registry–GWTG Quality-of-Care Metrics for AMI Care, 2016

Quality Metrics	Overall	STEMI	NSTEMI
ECG within 10 min of arrival	68.1	77.0	64.2
Aspirin within 24 h of arrival	98.5	98.4	97.8
Any anticoagulant use*	95.0	96.7	93.8
Dosing errors			
UFH dose	49.4	46.9	49.6
Enoxaparin dose	9.0	6.3	9.1
Glycoprotein IIb/IIIa inhibitor dose	5.0	5.2	4.5
Aspirin at discharge	98.7	99.2	98.4
Prescribed statins on discharge	99.4	99.6	99.2
Adult smoking cessation advice/counseling	98.1	98.1	98.1
Cardiac rehabilitation referral	78.6	83.4	75.2
In-hospital mortality† (95% CI)	4.17 (4.01–4.41)	6.17 (5.90–6.64)	2.92 (2.79–3.17)

Values are percentages. Data reported include data from the first quarter of 2015 to the fourth quarter of 2015. ACTION Registry–GWTG indicates Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With The Guidelines; AMI, acute myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; STEMI, ST-segment–elevation myocardial infarction; and UFH, unfractionated heparin.

*Includes UFH, low-molecular-weight heparin, or direct thrombin inhibitor use.

†Includes all patients.

Table 24-4. Timely Reperfusion for AMI and Stroke

Quality-of-Care Measure	GWTG–Stroke (for Stroke)	ACTION Registry–GWTG STEMI
STEMI		
Thrombolytic agents within 30 min	N/A	52.0
PCI within 90 min*	N/A	95.9
Stroke		
IV tPA in patients who arrived <2 h after symptom onset, treated ≤3 h	87.74†	N/A
IV tPA in patients who arrived <3.5 h after symptom onset, treated ≤4.5 h	81.03†‡	N/A
IV tPA door-to-needle time ≤60 min	83.54†	N/A

Values are percentages. AMI data from the ACTION registry, 2016. Stroke data from the GWTG–Stroke registry June 2017 to May 2018. ACTION Registry–GWTG indicates Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With The Guidelines; AMI, acute myocardial infarction; IV, intravenous; N/A, not applicable; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and tPA, tissue plasminogen activator.

*Excludes transfers.

†Reflects analysis performed for 2018 update.

‡IV tPA in patients who arrived <3.5 hours after symptom onset, treated ≤4.5 hours measure was changed in 2016 to include in-hospital strokes in the denominator.

Table 24-5. Quality of Care by Race/Ethnicity and Sex in the ACTION Registry, 2014

Quality-of-Care Measure	Race/Ethnicity			Sex	
	White	Black	Other	Males	Females
Aspirin at admission	98.1	98.2	98.3	98.4	97.7
Aspirin at discharge	98.8	98.0	98.8	98.9	98.2
β-Blockers at discharge	97.6	97.2	97.5	97.9	97.0
Time to PCI ≤90 min for STEMI patients	96.1	94.3	96.0	96.2	95.2
ARB/ACEI at discharge for patients with LVEF <40%	91.2	91.7	88.5	91.5	90.5
Statins at discharge	99.1	98.9	99.4	99.3	98.8

Values are percentages. Data reported include data from first quarter of 2015 to fourth quarter of 2015. ACEI indicates angiotensin-converting enzyme inhibitor; ACTION, Acute Coronary Treatment and Intervention Outcomes Network; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

Table 24-6. HF Quality-of-Care Measures, 2016

Quality-of-Care Measure	AHA GWTG–HF
LVEF assessment	98.94
ARB/ACEI at discharge for patients with LVSD	93.66
Complete discharge instructions	94.06
β-Blockers at discharge for patients with LVSD, no contraindications	97.81
Anticoagulation for AF or atrial flutter, no contraindications	85.48

Values are percentages. ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AHA, American Heart Association; ARB, angiotensin receptor blocker; GWTG–HF, Get With The Guidelines–Heart Failure; HF, heart failure; LVEF, left ventricular ejection fraction; and LVSD, left ventricular systolic dysfunction.

Table 24-7. Quality of Care by Race/Ethnicity and Sex in the GWTG–HF Program, 2016

Quality-of-Care Measure	Race/Ethnicity			Sex	
	White	Black	Hispanic	Males	Females
Postdischarge appointment*	78.35	79.18	70.65	77.64	77.62
Complete set of discharge instructions	93.60	95.21	95.17	94.63	93.37
Measure of LV function*	99.07	99.29	97.01	99.06	98.81
ACEI or ARB at discharge for patients with LVSD, no contraindications*	93.45	94.83	92.14	93.68	93.83
Smoking cessation counseling, current smokers	92.10	93.96	93.79	93.15	92.49
Evidence-based specific β-blockers*	91.88	94.69	91.52	92.88	92.25
β-Blockers at discharge for patients with LVSD, no contraindications	97.82	98.16	96.93	97.95	97.59
Hydralazine/nitrates at discharge for patients with LVSD, no contraindications†	…	31.53	20.00	33.30	28.07
Anticoagulation for AF or atrial flutter, no contraindications	86.11	84.23	83.14	86.10	84.73
Composite quality-of-care measure (using discharge instructions and β-blocker at discharge)	96.46	96.99	95.79	96.65	96.35

Values are percentages. ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ellipses, data not available; GWTG–HF, Get With The Guidelines–Heart Failure; LV, left ventricular; and LVSD, left ventricular systolic dysfunction.

*Indicates the 4 key achievement measures targeted in GWTG–HF.

†For black patients only.

Table 24-8. National Committee for Quality Assurance Health Plan Employer Data and Information Set Measures of Care, 2016

	Commercial		Medicare		Medicaid
	HMO	PPO	HMO	PPO	HMO
Cardiovascular disease					
β-Blocker persistence after MI*	84.4	83.8	90.1	89.9	79.9
BP control†	62.4	54.5	69.6	69.7	56.5
Statin therapy for patients with CVD	79.2	79.9	77.3	76.8	74.7
DM					
HbA_{1c} testing	90.6	89.3	93.5	93.6	86.7
HbA_{1c} >9.0%	33.0	42.5	26.3	23.3	43.3
Eye examination performed	53.6	47.5	70.4	69.6	54.9
Monitoring nephropathy	90.2	88.1	95.6	95.3	89.9
BP <140/90 mm Hg	61.6	50.5	63.9	60.6	59.7
Statin therapy for patients with DM	60.2	58.9	70.7	67.8	60.2
Tobacco, nutrition, and lifestyle					
Advising smokers and tobacco users to quit	75.1	72.3	85.6	83.8	76.2
BMI percentile assessment in children and adolescents (3–17 y of age)	65.2	52.0	N/A	N/A	69.1
Nutrition counseling (children and adolescents [3–17 y of age])	60.8	50.0	N/A	N/A	65.3
Counseling for physical activity (children and adolescents [3–17 y of age])	55.5	44.9	N/A	N/A	57.6
BMI assessment for adults 18–74 y of age	76.6	62.9	94.2	91.8	80.7
Physical activity discussion in older adults (≥65 y of age) (2015 data)	N/A		53.5	55.3	N/A
Physical activity advice in older adults (≥65 y of age) (2015 data)	N/A		50.5	49.9	N/A

Values are percentages. BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; HbA_{1c}, hemoglobin A_{1c}; HMO, health maintenance organization; MI, myocardial infarction; N/A, not available or not applicable; and PPO, preferred provider organization.

*β-Blocker persistence: received persistent β-blocker treatment for 6 months after acute myocardial infarction hospital discharge.

†Adults 18 to 59 years of age with BP <140/90 mm Hg, adults aged 60 to 85 years with a diagnosis of DM and BP <140/90 mm Hg, and adults aged 60 to 85 years without a diagnosis of DM and BP <150/90 mm Hg.

Table 24-9. Quality of Care by Race/Ethnicity and Sex in the GWTG–Stroke Program, 2016

	Race/Ethnicity			Sex	
Quality-of-Care Measure	White	Black	Hispanic	Males	Females
IV tPA in patients who arrived ≤2 h after symptom onset, treated ≤3 h*	86.37	87.38	87.03	87.25	86.23
IV tPA in patients who arrived <3.5 h after symptom onset, treated ≤4.5 h†	45.83	49.24	50.97	47.54	46.58
IV tPA door-to-needle time ≤60 min	79.51	80.11	80.79	81.31	78.37
Thrombolytic complications: IV tPA and life-threatening, serious systemic hemorrhage	10.62	10.77	7.46	10.70	11.00
Antithrombotic agents <48 h after admission*	97.40	97.08	96.53	97.41	97.10
DVT prophylaxis by second hospital day*	99.24	99.19	99.04	99.21	99.23
Antithrombotic agents at discharge*	98.82	98.40	97.95	98.72	98.46
Anticoagulation for atrial fibrillation at discharge*	96.16	95.63	96.09	96.33	95.94
Therapy at discharge if LDL-C >100 mg/dL or LDL-C not measured or on therapy at admission*	98.01	98.33	97.51	98.43	97.68
Counseling for smoking cessation*	97.48	97.40	97.11	97.49	97.39
Lifestyle changes recommended for BMI >25 kg/m^2	52.86	54.45	54.37	53.20	53.29
Composite quality-of-care measure	97.89	97.76	97.37	97.95	97.61

Values are percentages. BMI indicates body mass index; DVT, deep vein thrombosis; GWTG, Get With The Guidelines; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; and tPA, tissue-type plasminogen activator.

*Indicates the 7 key achievement measures targeted in GWTG–Stroke.

†This measure was changed in 2016 to include in-hospital strokes in the denominator.

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Table 24-10. Quality of Care for Patients With Out-of-Hospital Cardiac Arrest at US ROC Sites (January 1, 2014 to December 31, 2014)

	Overall	Adults	Children
Bystander and EMS care*			
Bystander CPR, %	46.1 (45.0–47.3)	45.7 (44.6–46.9)	61.4 (54.9–67.9)
Shocked by AED before EMS, %	2.0 (1.7–2.4)	2.1 (1.7–2.4)	1.4 (0.0–3.0)
Chest compression fraction during first 5 min of CPR, %	0.85 (0.12)	0.85 (0.12)	0.83 (0.13)
Compression depth, mm	48.1 (10.7)	48.1 (10.7)	47.2 (9.5)
Preshock pause duration, s	10.8 (11.0)	10.8 (10.9)	16.2 (16.4)
Time to first EMS defibrillator applied, min	8.8 (4.5)	8.8 (4.5)	8.7 (4.2)
Hospital-based metrics†			
Hypothermia induced after initial VT/VF, %‡	66.3 (62.3–70.3)	66.2 (62.1–70.2)	100 (100–100)
No order for withdrawal/DNR during first 72 h, %§	45.0 (42.1–48.0)	44.8 (41.9–47.8)	100 (100–100)
Implantable cardioverter-defibrillator assessment, initial VT/VF, no AMI per MD notes or final ECG interpretation, %‖	30.3 (24.8–35.8)	30.0 (24.5–35.6)	100 (100–100)

Values are mean (95% confidence interval) or mean (SD). Because age is missing for some cases, these cases are not included in either adults or children, thus explaining why overall rates equal the adult rates when rates for children are not available. AED indicates automated external defibrillator; AMI, acute myocardial infarction; CPR, cardiopulmonary resuscitation; DNR, do not resuscitate; EMS, emergency medical services; MD, medical doctor; ROC, Resuscitation Outcomes Consortium; VF; ventricular fibrillation; and VT, ventricular tachycardia.

*Data are from EMS-treated cases.

†During 2014, there was 1 pediatric case with initial rhythm VT/VF admitted to the hospital.

‡Denominator is all cases with initial rhythm VT/VF and admitted to the hospital.

§Denominator is all cases admitted to the hospital.

‖Denominator is all cases with initial rhythm VT/VF, no indication of AMI, no percutaneous coronary intervention, no bypass, and admitted to the hospital.

Table 24-11. Quality of Care of Patients With In-Hospital Cardiac Arrest Among GWTG–Resuscitation Hospitals, 2016

	Adults	Children
Event outside critical care setting	46.3	12.5
All objective CPR data collected	98.7	99.1
ET_{CO_2} used during arrest	6.9	33.2
Induced hypothermia after resuscitation from shockable rhythm	7.6	10.7

Values are mean percentages. CPR indicates cardiopulmonary resuscitation; ET_{CO_2}, end-tidal CO_2; and GWTG, Get With The Guidelines.

Source: GWTG–Resuscitation Investigators, June 2017.

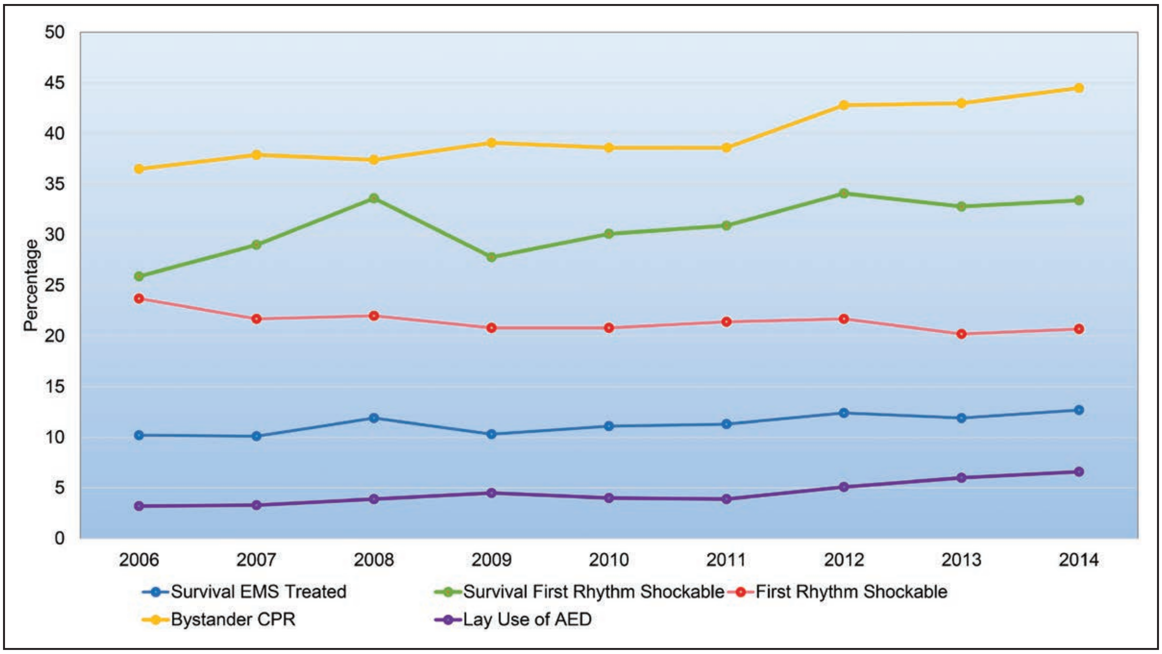

Chart 24-1. Survival rates after out-of-hospital cardiac arrest in US sites of the Resuscitation Outcomes Consortium, 2006 to 2014.
AED indicates automated external defibrillator; CPR, cardiopulmonary resuscitation; and EMS, emergency medical services.

REFERENCES

1. Committee on Quality of Health Care in America, Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academy Press; 2001.
2. Quality of Care and Outcomes Research in CVD and Stroke Working Groups. Measuring and improving quality of care: a report from the American Heart Association/American College of Cardiology First Scientific Forum on Assessment of Healthcare Quality in Cardiovascular Disease and Stroke. *Circulation*. 2000;101:1483–1493.
3. American College of Cardiology Quality Improvement for Institutions Registries. https://cvquality.acc.org/NCDR-Home/Registries. Accessed March 6, 2018.
4. American Heart Association Focus on Quality. American Heart Association website. http://www.heart.org/en/professional/quality-improvement. Accessed August 31, 2018.
5. Wadhera RK, Joynt Maddox KE, Wang Y, Shen C, Bhatt DL, Yeh RW. Association between 30-day episode payments and acute myocardial infarction outcomes among Medicare beneficiaries. *Circ Cardiovasc Qual Outcomes*.2018;11:e004397.doi:10.1161/CIRCOUTCOMES.117.004397
6. Chatterjee P, Joynt Maddox KE. US national trends in mortality from acute myocardial infarction and heart failure: policy success or failure? *JAMA Cardiol*. 2018;3:336–340. doi: 10.1001/jamacardio.2018.0218
7. Pandey A, Golwala H, Hall HM, Wang TY, Lu D, Xian Y, Chiswell K, Joynt KE, Goyal A, Das SR, Kumbhani D, Julien H, Fonarow GC, de Lemos JA. Association of US Centers for Medicare and Medicaid Services hospital 30-day risk-standardized readmission metric with care quality and outcomes after acute myocardial infarction: findings from the National Cardiovascular Data Registry/Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines. *JAMA Cardiol*. 2017;2:723–731. doi: 10.1001/jamacardio.2017.1143
8. Bucholz EM, Butala NM, Ma S, Normand ST, Krumholz HM. Life expectancy after myocardial infarction, according to hospital performance. *N Engl J Med*. 2016;375:1332–1342. doi: 10.1056/NEJMoa1513223
9. Makam AN, Nguyen OK. Use of cardiac biomarker testing in the emergency department. *JAMA Intern Med*. 2015;175:67–75. doi: 10.1001/jamainternmed.2014.5830
10. Rao KK, Enriquez JR, de Lemos JA, Alexander KP, Chen AY, McGuire DK, Fonarow GC, Das SR. Use of aldosterone antagonists at discharge after myocardial infarction: results from the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry-Get With The Guidelines (GWTG). *Am Heart J*. 2013;166:709–715. doi: 10.1016/j.ahj.2013.06.020
11. Medicare Hospital Quality 2017 Chartbook: Performance Report on Outcome Measures. Centers for Medicare & Medicaid Services website. https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/OutcomeMeasures.html. Accessed April 20, 2017.
12. Mathews R, Wang W, Kaltenbach LA, Thomas L, Shah RU, Ali M, Peterson ED, Wang TY. Hospital variation in adherence rates to secondary prevention medications and the implications on quality. *Circulation*. 2018;137:2128–2138. doi: 10.1161/CIRCULATIONAHA.117.029160
13. Kumbhani DJ, Fonarow GC, Heidenreich PA, Schulte PJ, Lu D, Hernandez A, Yancy C, Bhatt DL. Association between hospital volume, processes of care, and outcomes in patients admitted with heart failure: insights from Get With The Guidelines-Heart Failure. *Circulation*. 2018;137:1661–1670. doi: 10.1161/CIRCULATIONAHA.117.028077
14. Gupta A, Allen LA, Bhatt DL, Cox M, DeVore AD, Heidenreich PA, Hernandez AF, Peterson ED, Matsouaka RA, Yancy CW, Fonarow GC. Association of the Hospital Readmissions Reduction Program implementation with readmission and mortality outcomes in heart failure. *JAMA Cardiol*. 2018;3:44–53. doi: 10.1001/jamacardio.2017.4265
15. Pokharel Y, Khariton Y, Tang Y, Nassif ME, Chan PS, Arnold SV, Jones PG, Spertus JA. Association of serial Kansas City Cardiomyopathy Questionnaire assessments with death and hospitalization in patients with heart failure with preserved and reduced ejection fraction: a secondary analysis of 2 randomized clinical trials. *JAMA Cardiol*. 2017;2:1315–1321. doi: 10.1001/jamacardio.2017.3983
16. Pandey A, Omar W, Ayers C, LaMonte M, Klein L, Allen NB, Kuller LH, Greenland P, Eaton CB, Gottdiener JS, Lloyd-Jones DM, Berry JD. Sex and race differences in lifetime risk of heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. *Circulation*. 2018;137:1814–1823. doi: 10.1161/CIRCULATIONAHA.117.031622
17. Ziaeian B, Kominski GF, Ong MK, Mays VM, Brook RH, Fonarow GC. National differences in trends for heart failure hospitalizations by sex and race/ethnicity. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003552. doi: 10.1161/CIRCOUTCOMES.116.003552
18. Pandey A, Patel KV, Liang L, DeVore AD, Matsouaka R, Bhatt DL, Yancy CW, Hernandez AF, Heidenreich PA, de Lemos JA, Fonarow GC. Association of hospital performance based on 30-day risk-standardized mortality rate with long-term survival after heart failure hospitalization: an analysis of the Get With The Guidelines-Heart Failure Registry. *JAMA Cardiol*. 2018;3:489–497. doi: 10.1001/jamacardio.2018.0579
19. Pandey A, Golwala H, Xu H, DeVore AD, Matsouaka R, Pencina M, Kumbhani DJ, Hernandez AF, Bhatt DL, Heidenreich PA, Yancy CW, de Lemos JA, Fonarow GC. Association of 30-day readmission metric for

heart failure under the Hospital Readmissions Reduction Program with quality of care and outcomes. *JACC Heart Fail*. 2016;4:935–946. doi: 10.1016/j.jchf.2016.07.003
20. Desai NR, Ross JS, Kwon JY, Herrin J, Dharmarajan K, Bernheim SM, Krumholz HM, Horwitz LI. Association between hospital penalty status under the Hospital Readmission Reduction Program and readmission rates for target and nontarget conditions. *JAMA*. 2016;316:2647–2656. doi: 10.1001/jama.2016.18533
21. Krumholz HM, Wang K, Lin Z, Dharmarajan K, Horwitz LI, Ross JS, Drye EE, Bernheim SM, Normand ST. Hospital-readmission risk: isolating hospital effects from patient effects. *N Engl J Med*. 2017;377:1055–1064. doi: 10.1056/NEJMsa1702321
22. Dharmarajan K, Wang Y, Lin Z, Normand ST, Ross JS, Horwitz LI, Desai NR, Suter LG, Drye EE, Bernheim SM, Krumholz HM. Association of changing hospital readmission rates with mortality rates after hospital discharge. *JAMA*. 2017;318:270–278. doi: 10.1001/jama.2017.8444
23. Pokharel Y, Gosch K, Nambi V, Chan PS, Kosiborod M, Oetgen WJ, Spertus JA, Ballantyne CM, Petersen LA, Virani SS. Practice-level variation in statin use among patients with diabetes: insights from the PINNACLE registry. *J Am Coll Cardiol*. 2016;68:1368–1369. doi: 10.1016/j.jacc.2016.06.048
24. Hira RS, Kennedy K, Jneid H, Alam M, Basra SS, Petersen LA, Ballantyne CM, Nambi V, Chan PS, Virani SS. Frequency and practice-level variation in inappropriate and nonrecommended prasugrel prescribing: insights from the NCDR PINNACLE registry. *J Am Coll Cardiol*. 2014;63(pt A):2876–2877. doi: 10.1016/j.jacc.2014.04.011
25. Hira RS, Kennedy K, Nambi V, Jneid H, Alam M, Basra SS, Ho PM, Deswal A, Ballantyne CM, Petersen LA, Virani SS. Frequency and practice-level variation in inappropriate aspirin use for the primary prevention of cardiovascular disease: insights from the National Cardiovascular Disease Registry's Practice Innovation and Clinical Excellence registry. *J Am Coll Cardiol*. 2015;65:111–121. doi: 10.1016/j.jacc.2014.10.035
26. Hall HM, de Lemos JA, Enriquez JR, McGuire DK, Peng SA, Alexander KP, Roe MT, Desai N, Wiviott SD, Das SR. Contemporary patterns of discharge aspirin dosing after acute myocardial infarction in the United States: results from the National Cardiovascular Data Registry (NCDR). *Circ Cardiovasc Qual Outcomes*. 2014;7:701–707. doi: 10.1161/CIRCOUTCOMES.113.000822
27. Virani SS, Woodard LD, Wang D, Chitwood SS, Landrum CR, Urech TH, Pietz K, Chen GJ, Hertz B, Murawsky J, Ballantyne CM, Petersen LA. Correlates of repeat lipid testing in patients with coronary heart disease. *JAMA Intern Med*. 2013;173:1439–1444. doi: 10.1001/jamainternmed.2013.8198
28. Heller DJ, Coxson PG, Penko J, Pletcher MJ, Goldman L, Odden MC, Kazi DS, Bibbins-Domingo K. Evaluating the impact and cost-effectiveness of statin use guidelines for primary prevention of coronary heart disease and stroke. *Circulation*. 2017;136:1087–1098. doi: 10.1161/CIRCULATIONAHA.117.027067
28a. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published corrections appear in *Circulation*. 2015;132:e396 and *Circulation*. 2014;129(Suppl 2):S46-S48]. *Circulation*. 2014;129(Suppl 2):S1–S45.
29. Salami JA, Warraich HJ, Valero-Elizondo J, Spatz ES, Desai NR, Rana JS, Virani SS, Blankstein R, Khera A, Blaha MJ, Blumenthal RS, Katzen BT, Lloyd-Jones D, Krumholz HM, Nasir K. National trends in nonstatin use and expenditures among the US adult population from 2002 to 2013: insights from Medical Expenditure Panel Survey. *J Am Heart Assoc*. 2018;7:e007132. doi: 10.1161/JAHA.117.007132
30. Mazurek M, Huisman MV, Lip GYH. Registries in atrial fibrillation: from trials to real-life clinical practice. *Am J Med*. 2017;130:135–145. doi: 10.1016/j.amjmed.2016.09.012
31. Heidenreich PA, Solis P, Mark Estes NA 3rd, Fonarow GC, Jurgens CY, Marine JE, McManus DD, McNamara RL. 2016 ACC/AHA clinical performance and quality measures for adults with atrial fibrillation or atrial flutter: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Circ Cardiovasc Qual Outcomes*. 2016;9:443–488. doi: 10.1161/HCQ.0000000000000018
32. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, Halperin JL, Ma CS, Zint K, Elsaesser A, Bartels DB, Lip GY; GLORIA-AF Investigators. The changing landscape for stroke prevention in AF: findings from the GLORIA-AF Registry phase 2. *J Am Coll Cardiol*. 2017;69:777–785. doi: 10.1016/j.jacc.2016.11.061
33. Yong CM, Liu Y, Apruzzese P, Doros G, Cannon CP, Maddox TM, Gehi A, Hsu JC, Lubitz SA, Virani S, Turakhia MP; ACC PINNACLE Investigators. Association of insurance type with receipt of oral anticoagulation in insured patients with atrial fibrillation: a report from the American College of Cardiology NCDR PINNACLE registry. *Am Heart J*. 2018;195:50–59. doi: 10.1016/j.ahj.2017.08.010
34. Hsu JC, Maddox TM, Kennedy K, Katz DF, Marzec LN, Lubitz SA, Gehi AK, Turakhia MP, Marcus GM. Aspirin instead of oral anticoagulant prescription in atrial fibrillation patients at risk for stroke. *J Am Coll Cardiol*. 2016;67:2913–2923. doi: 10.1016/j.jacc.2016.03.581
35. Perino AC, Fan J, Schmitt SK, Askari M, Kaiser DW, Deshmukh A, Heidenreich PA, Swan C, Narayan SM, Wang PJ, Turakhia MP. Treating specialty and outcomes in newly diagnosed atrial fibrillation: from the TREAT-AF Study. *J Am Coll Cardiol*. 2017;70:78–86. doi: 10.1016/j.jacc.2017.04.054
36. Lewis WR, Piccini JP, Turakhia MP, Curtis AB, Fang M, Suter RE, Page RL 2nd, Fonarow GC. Get With The Guidelines AFIB: novel quality improvement registry for hospitalized patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2014;7:770–777. doi: 10.1161/CIRCOUTCOMES.114.001263
37. Bettger JP, Thomas L, Liang L, Xian Y, Bushnell CD, Saver JL, Fonarow GC, Peterson ED. Hospital variation in functional recovery after stroke. *Circ Cardiovasc Qual Outcomes*. 2017;10:e002391. doi: 10.1161/CIRCOUTCOMES.115.002391
38. Fonarow GC, Zhao X, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Xian Y, Hernandez AF, Peterson ED, Schwamm LH. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. *JAMA*. 2014;311:1632–1640. doi: 10.1001/jama.2014.3203
39. Xian Y, Xu H, Lytle B, Blevins J, Peterson ED, Hernandez AF, Smith EE, Saver JL, Messé SR, Paulsen M, Suter RE, Reeves MJ, Jauch EC, Schwamm LH, Fonarow GC. Use of strategies to improve door-to-needle times with tissue-type plasminogen activator in acute ischemic stroke in clinical practice: findings from Target: Stroke. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003227. doi: 10.1161/CIRCOUTCOMES.116.003227
40. Ekundayo OJ, Saver JL, Fonarow GC, Schwamm LH, Xian Y, Zhao X, Hernandez AF, Peterson ED, Cheng EM. Patterns of emergency medical services use and its association with timely stroke treatment: findings from Get With the Guidelines-Stroke. *Circ Cardiovasc Qual Outcomes*. 2013;6:262–269. doi: 10.1161/CIRCOUTCOMES.113.000089
41. Peterson PN, Varosy PD, Heidenreich PA, Wang Y, Dewland TA, Curtis JP, Go AS, Greenlee RT, Magid DJ, Normand SL, Masoudi FA. Association of single- vs dual-chamber ICDs with mortality, readmissions, and complications among patients receiving an ICD for primary prevention. *JAMA*. 2013;309:2025–2034. doi: 10.1001/jama.2013.4982
42. Thompson LE, Chan PS, Tang F, Nallamothu BK, Girotra S, Perman SM, Bose S, Daugherty SL, Bradley SM; American Heart Association's Get With the Guidelines-Resuscitation Investigators. Long-term survival trends of Medicare patients after in-hospital cardiac arrest: insights from Get With The Guidelines-Resuscitation. *Resuscitation*. 2018;123:58–64. doi: 10.1016/j.resuscitation.2017.10.023
43. Ofoma UR, Basnet S, Berger A, Kirchner HL, Girotra S; American Heart Association Get With The Guidelines–Resuscitation Investigators. Trends in survival after in-hospital cardiac arrest during nights and weekends. *J Am Coll Cardiol*. 2018;71:402–411. doi: 10.1016/j.jacc.2017.11.043
44. Khera R, Chan PS, Donnino M, Girotra S; for the American Heart Association's Get With The Guidelines-Resuscitation Investigators. Hospital variation in time to epinephrine for nonshockable in-hospital cardiac arrest. *Circulation*. 2016;134:2105–2114. doi: 10.1161/CIRCULATIONAHA.116.025459
45. Anderson ML, Nichol G, Dai D, Chan PS, Thomas L, Al-Khatib SM, Berg RA, Bradley SM, Peterson ED; American Heart Association's Get With The Guidelines–Resuscitation Investigators. Association between hospital process composite performance and patient outcomes after in-hospital cardiac arrest care. *JAMA Cardiol*. 2016;1:37–45. doi: 10.1001/jamacardio.2015.0275
46. Chan PS, Nichol G, Krumholz HM, Spertus JA, Jones PG, Peterson ED, Rathore SS, Nallamothu BK; American Heart Association National Registry of Cardiopulmonary Resuscitation (NRCPR) Investigators. Racial differences in survival after in-hospital cardiac arrest. *JAMA*. 2009;302:1195–1201. doi: 10.1001/jama.2009.1340
47. Stub D, Schmicker RH, Anderson ML, Callaway CW, Daya MR, Sayre MR, Elmer J, Grunau BE, Aufderheide TP, Lin S, Buick JE, Zive D, Peterson ED, Nichol G; ROC Investigators. Association between hospital post-resuscitative performance and clinical outcomes after out-of-hospital cardiac arrest. *Resuscitation*. 2015;92:45–52. doi: 10.1016/j.resuscitation.2015.04.015

25. MEDICAL PROCEDURES

See Tables 25-1 and 25-2 and Charts 25-1 through 25-4

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Trends in Operations and Procedures (See Tables 25-1 and 25-2 and Charts 25-1 and 25-2)

- The mean hospital charges for cardiovascular procedures in 2014 ranged from $43 484 for carotid endarterectomy to $808 770 for heart transplantations (Table 25-1).
- The trends in the numbers of 5 common cardiovascular procedures in the United States from 1993 to 2014 are presented in Chart 25-1. Of the 5 procedures, cardiac catheterization was the most common procedure for all years presented (Chart 25-1).
- Of the 10 leading diagnostic groups in the United States, the greatest number of surgical procedures were cardiovascular and obstetrical procedures (Chart 25-2).
- The total number of inpatient cardiovascular operations and procedures decreased 6%, from 8 461 000 in 2004 to 7 971 000 in 2014 (NHLBI tabulation of HCUP data; Table 25-2).
- Data from the HCUP were examined for trends from 1997 to 2014 for use of PCI and CABG.[1]

Coronary Artery Bypass Grafting

- The number of inpatient discharges for CABG decreased from 683 000 in 1997 to 371 000 in 2014 (Chart 25-1).
- In 1997, the number of inpatient discharges for CABG was 484 000 for males and 199 000 for females; these declined to 277 000 and 94 000, respectively, in 2014.

Abbreviations Used in Chapter 25

ASD	atrial septal defect
AV	atrioventricular
CABG	coronary artery bypass graft
HCUP	Healthcare Cost and Utilization Project
HLHS	hypoplastic left heart syndrome
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
NHLBI	National Heart, Lung, and Blood Institute
PCI	percutaneous coronary intervention
PTCA	percutaneous transluminal coronary angioplasty
STS	Society of Thoracic Surgeons
VSD	ventricular septal defect

Inpatient Cardiac Catheterization and PCI (See Tables 25-1 and 25-2)

- Inpatient PCI discharges decreased from 359 000 for males and 190 000 for females in 1997 to 325 000 and 155 000, respectively, by 2014 (Chart 25-1).
- Data on Medicare beneficiaries undergoing a coronary revascularization procedure between 2008 and 2012 indicate that the rapid growth in nonadmission PCIs (from 60 405 to 106 495) has been more than offset by the decrease in PCI admissions (from 363 384 to 295 434).[2]
- In 2014, the mean inpatient hospital charge for PCI was $84 813 (Table 25-1).
- From 2004 to 2014, the number of inpatient cardiac catheterizations decreased from 1 486 000 to 1 016 000 annually (HCUP, NHLBI tabulation; Chart 25-1).
- In 2014, an estimated 480 000 inpatient PCI (previously referred to as percutaneous transluminal coronary angioplasty, or PTCA) procedures were performed in the United States (HCUP, NHLBI tabulation; Chart 25-1).
- In 2014, ≈68% of PCI procedures were performed on males, and ≈50% were performed on people ≥65 years of age (HCUP, NHLBI tabulation; Table 25-2).
- Inpatient hospital deaths for PCI increased from 0.8% in 2004 to 2.1% in 2014 (HCUP, NHLBI tabulation). In 2014, ≈82% of stents implanted during PCI were drug-eluting stents compared with 18% that were bare-metal stents (HCUP, NHLBI tabulation).
- The rate of any cardiac stent procedure per 10 000 population rose by 61% from 1999 to 2006, then declined by 27% between 2006 and 2009.[3]

Cardiac Open Heart Surgery

- Data from the STS Adult Cardiac Surgery Database, which voluntarily collects data from ≈80% of all hospitals that perform CABG in the United States, indicate that a total of 159 869 procedures involved isolated CABG in 2016.[4]
- Among other major procedures, there were 28 493 isolated aortic valve replacements and 7706 isolated mitral valve replacements; 17 507 procedures involved both aortic valve replacement and CABG, whereas 2935 procedures involved both mitral valve replacement and CABG.[4]

Congenital Heart Surgery, 2013 to 2016

According to data from the STS Congenital Heart Surgery Database[5]:

- There were 122 193 procedures performed from January 2013 to December 2016. The in-hospital mortality rate was 3.0% during that time period. The 5 most common diagnoses were type 2 VSD (6.2%), HLHS (6.0%), patent ductus arteriosus (4.8%), open sternum with open skin (4.1%), and secundum ASD (4.0%).[5]
- The 5 most common primary procedures were delayed sternal closure (8.0%), patch VSD repair (6.3%), mediastinal exploration (3.6%), patch ASD repair (3.2%), and complete AV canal (AV septal defect) repair (2.8%).[5]

Heart Transplantations (See Charts 25-3 and 25-4)

According to data from the Organ Procurement and Transplantation Network (as of April 27, 2018)[6]

- In 2017, 3244 heart transplantations were performed in the United States (Chart 25-3). There are 254 transplantation hospitals in the United States, 139 of which performed heart transplantations in 2017.
- Of the recipients in 2017, 71.6% were male, and 61.6% were white; 23.3% were black, whereas 10.0% were Hispanic. Heart transplantations by recipient age are shown in Chart 25-4.
- For transplantations that occurred between 2012 and 2015, the 1-year survival rate was 90.5% for males and 91.1% for females; the 5-year survival rates based on 2008 to 2011 transplantations were 78.3% for males and 77.7% for females. The 1- and 5-year survival rates for white cardiac transplantation patients were 90.7% and 79.0%, respectively. For black patients, they were 90.7% and 74.1%, respectively. For Hispanic patients, they were 90.1% and 79.9%, respectively. For Asian patients, they were 91.3% and 80.0%, respectively.
- As of April 27, 2018, 3994 patients were on the transplant waiting list for a heart transplant, and 55 patients were on the list for a heart/lung transplant.

Table 25-1. 2014 National HCUP Statistics: Mean Hospital Charges, In-Hospital Death Rates, and Mean Length of Stay for Various Cardiovascular Procedures

Procedure	Mean Hospital Charges, $	In-Hospital Death Rate, %	Mean Length of Stay, d	*ICD-9-CM* Procedure Codes
Total vascular and cardiac surgery and procedures	90 215	3.34	6.3	35–39, 00.50–00.51, 00.53–00.55, 00.61–00.66
Cardiac revascularization (bypass)	168 541	1.78	9.3	36.1–36.3
PCI	84 813	2.07	3.5	00.66, 17.55, 36.01, 36.02, 36.05
Cardiac catheterization	57 494	1.42	4.2	37.21–37.23
Pacemakers	83 521	1.46	5.1	37.7–37.8, 00.50, 00.53
Implantable defibrillators	171 476	0.69	6.3	37.94–37.99, 00.51, 00.54
Carotid endarterectomy	43 484	0.27	2.6	38.12
Heart valves	201 557	3.36	9.7	35.00–35.14, 35.20–35.28, 35.96, 35.97, 35.99
Heart transplantations	808 770	7.84	45.4	37.51

Principal procedure only. HCUP indicates Healthcare Cost and Utilization Project; *ICD-9-CM*, *International Classification of Diseases, Clinical Modification, 9th Revision*; and PCI, percutaneous coronary intervention.

Data derived from the Agency for Healthcare Research and Quality.

Table 25-2. Estimated* Inpatient Cardiovascular Operations, Procedures, and Patient Data by Sex and Age: United States, 2014 (in Thousands)

Operation/Procedure/ Patients	*ICD-9-CM* Procedure Codes	All	Sex		Age, y			
			Male	Female	18–44	45–64	64–84	≥85
Heart valves	35.00–35.14, 35.20–35.28, 35.96, 35.97, 35.99	156	92	63	11	40	83	16
PCI	00.66, 17.55, 36.01, 36.02, 36.05	480	325	155	26	213	212	28
PCI with stents	36.06, 36.07	434	294	140	24	194	191	25
Coronary artery bypass graft	36.1–36.3	371	276	94	10	148	204	9
Cardiac catheterization	37.21–37.23	1016	625	391	68	432	455	54
Pacemakers	37.7, 37.8, 00.50, 00.53	351	185	166	9	57	197	85
Pacemaker devices	37.8, 00.53	141	72	69	3	19	80	38
Pacemaker leads	37.7, 00.50	210	114	97	7	38	117	47
Implantable defibrillators	37.94–37.99, 00.51, 00.54	60	43	17	4	21	30	3
Carotid endarterectomy	38.12	86	51	35	0	20	60	6
Total vascular and cardiac surgery and procedures†‡	35–39, 00.50–00.51, 00.53– 00.55, 00.61–00.66	7971	4602	3368	777	2860	3402	558

These data do not reflect any procedures performed on an outpatient basis. Many more procedures are being performed on an outpatient basis. Some of the lower numbers in this table compared with 2006 probably reflect this trend. Data include procedures performed on newborn infants. Some of the *ICD-9-CM* procedure codes may have changed over the years. *ICD-9-CM* indicates *International Classification of Diseases, Clinical Modification, 9th Revision*; and PCI, percutaneous coronary intervention.

*Breakdowns are not available for some procedures, so entries for some categories do not add to totals. These data include codes for which the estimated number of procedures is <5000. Categories with such small numbers are considered unreliable by the National Center for Health Statistics and in some cases may have been omitted.

†Totals include procedures not shown here.

‡This estimate includes angioplasty and stent insertions for noncoronary arteries.

Data derived from Healthcare Cost and Utilization Project National Inpatient Sample, 2014, Agency for Healthcare Research and Quality.

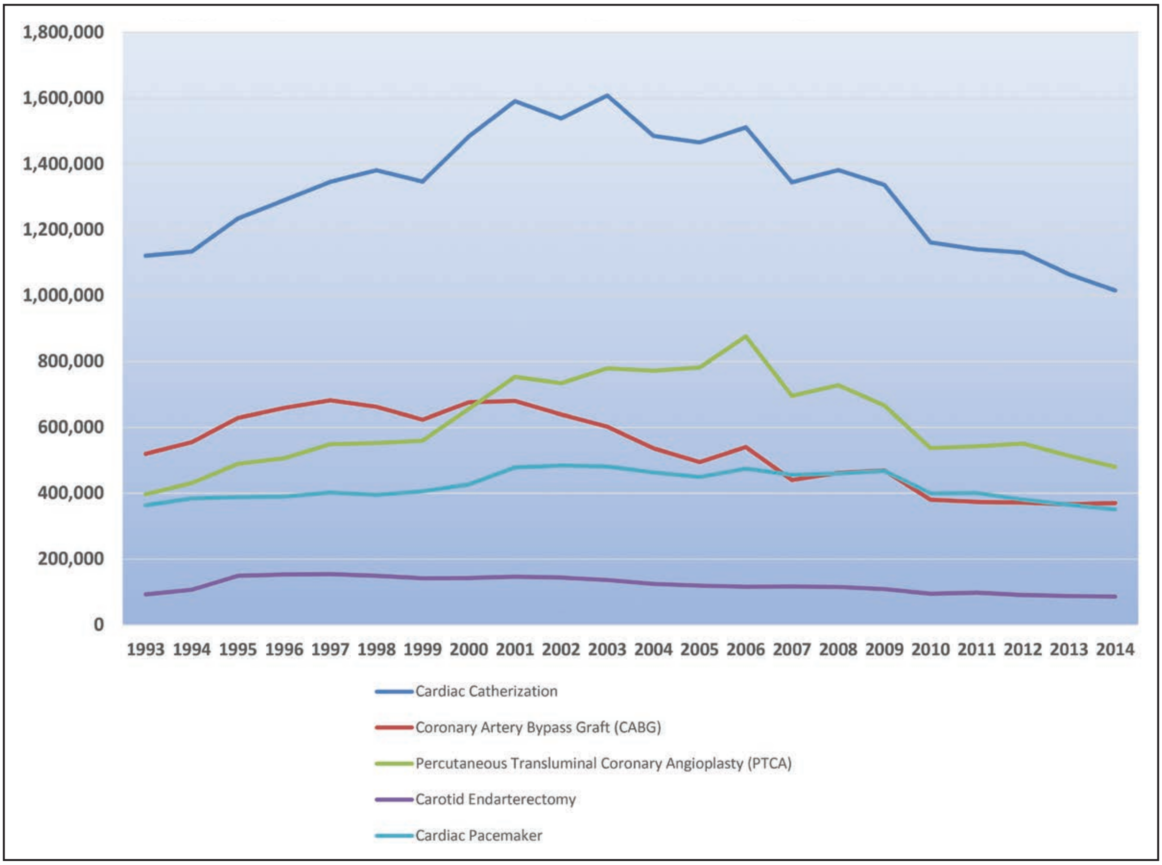

Chart 25-1. Trends in cardiovascular procedures, United States, 1993 to 2014; inpatient procedures only.
Data derived from Healthcare Cost and Utilization Project, National (Nationwide) Inpatient Sample, Agency for Healthcare Research.[1]

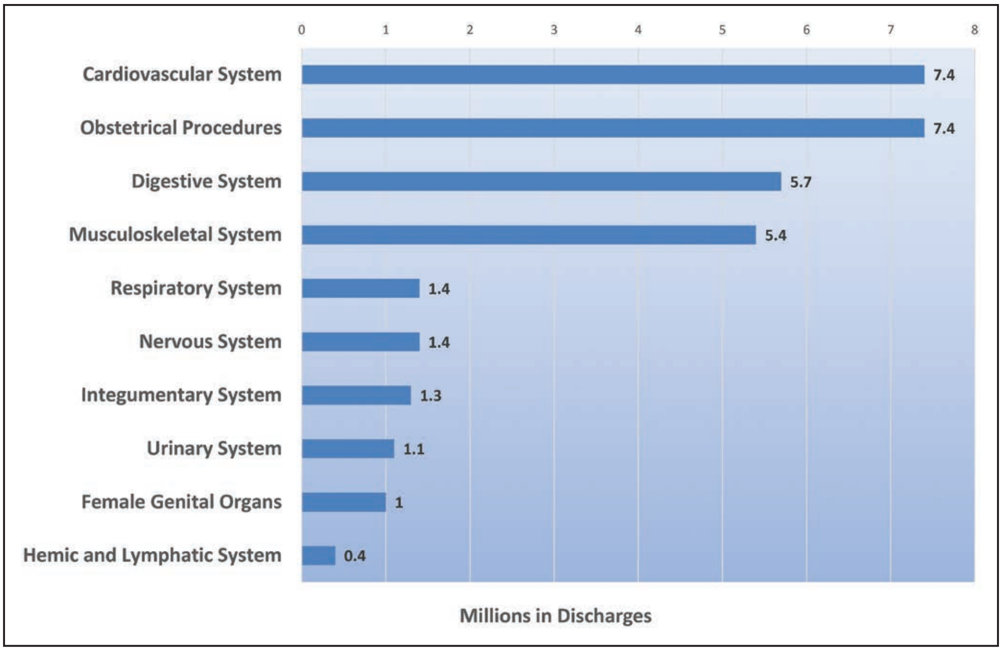

Chart 25-2. Number of surgical procedures in the 10 leading diagnostic groups, United States, 2014.
Data derived from Healthcare Cost and Utilization Project, National (Nationwide) Inpatient Sample, Agency for Healthcare Research.[1]

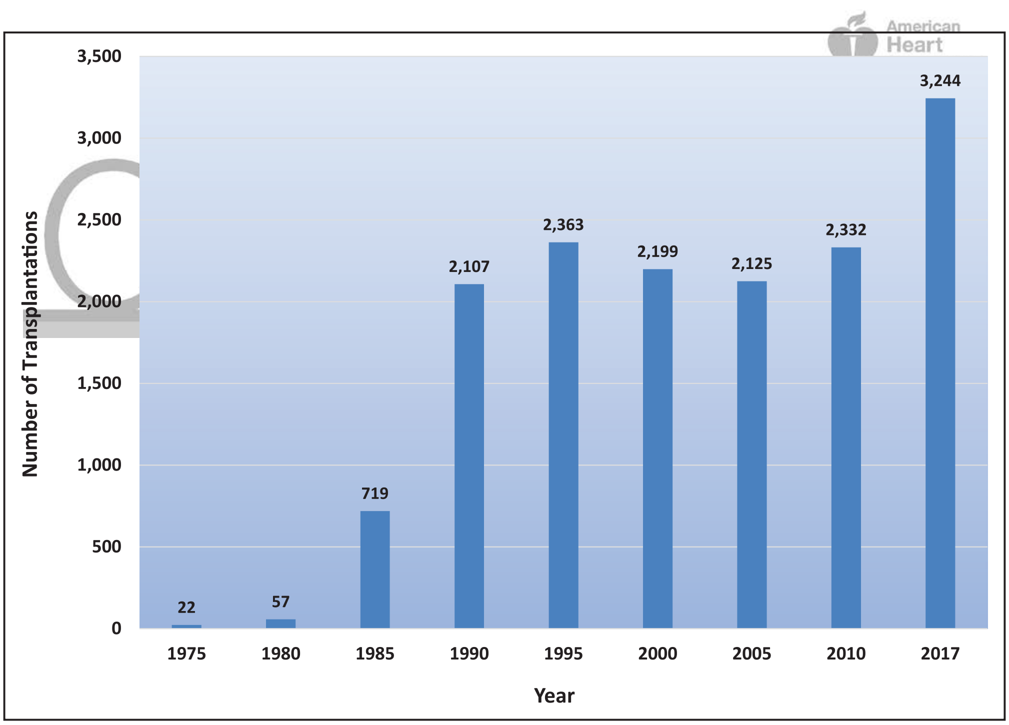

Chart 25-3. Trends in heart transplantations, 1975 to 2017.
Data derived from Organ Procurement and Transplantation Network as of April 27, 2018.[6]

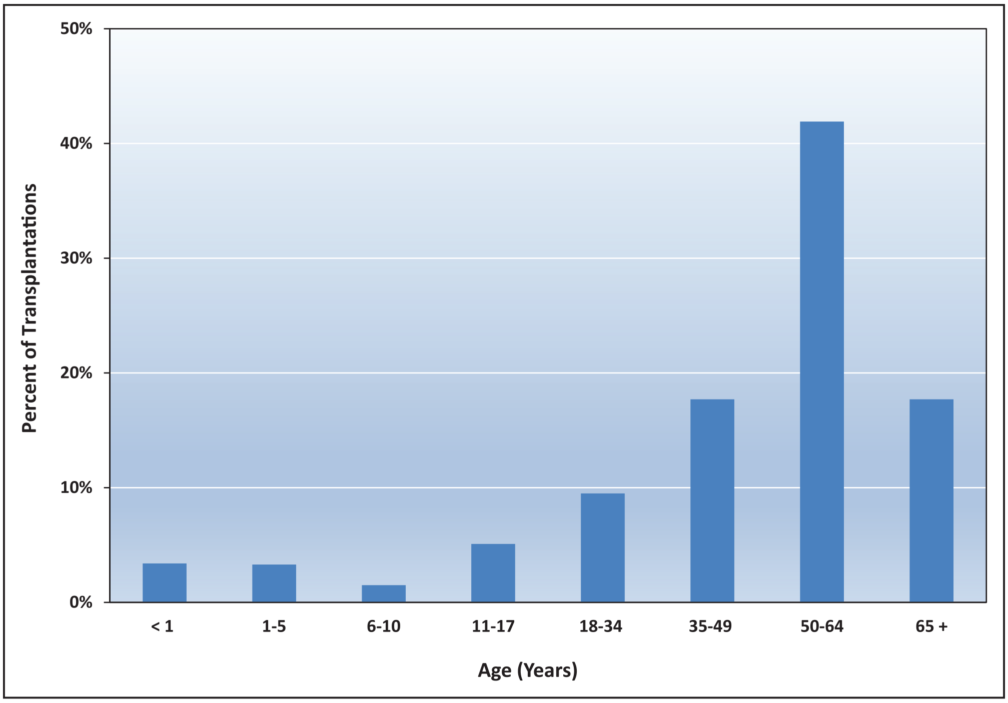

Chart 25-4. Heart transplantations in the United States by recipient age, 2017.
Data derived from Organ Procurement and Transplantation Network as of April 27, 2018.[6]

REFERENCES

1. HCUPnet: Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality website. https://hcupnet-archive.ahrq.gov/. Accessed May 1, 2017.
2. Culler SD, Kugelmass AD, Brown PP, Reynolds MR, Simon AW. Trends in coronary revascularization procedures among Medicare beneficiaries between 2008 and 2012. *Circulation*. 2015;131:362–370. doi: 10.1161/CIRCULATIONAHA.114.012485
3. Auerbach DI, Maeda JL, Steiner C. Hospital stays with cardiac stents, 2009. HCUP Statistical Brief #128. Rockville, MD: Agency for Healthcare Research and Quality; April 2012.
4. Adult Cardiac Surgery Database: Executive Summary: 10 Years: STS Period Ending 06/30/2017. Society of Thoracic Surgeons website. https://www.sts.org/sites/default/files/documents/ACSD2017Harvest3_ExecutiveSummary.pdf. Accessed March 14, 2018.
5. STS Congenital Heart Surgery Database. All Patients. STS Period Ending 12/31/2016. Society of Thoracic Surgeons website. https://www.sts.org/sites/default/files/documents/CHSD_ExecutiveSummary_AllPatients_Spring2017.pdf. Accessed March 14, 2018.
6. Organ Procurement and Transplantation Network website. https://optn.transplant.hrsa.gov/data/. Accessed April 27, 2018.

26. ECONOMIC COST OF CARDIOVASCULAR DISEASE

See Tables 26-1 and 26-2 and Charts 26-1 through 26-6

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Using data from MEPS, the annual direct and indirect cost of CVD in the United States is an estimated $351.2 billion (Table 26-1 and Chart 26-1). This figure includes $213.8 billion in expenditures (direct costs, which include the cost of physicians and other professionals, hospital services, prescribed medication, and home health care, but not the cost of nursing home care) and $137.4 billion in lost future productivity attributed to premature CVD and stroke mortality in 2014 to 2015 (indirect costs).

The direct costs for CVD and stroke for 2014 to 2015 (average annual) are available on the website of the nationally representative MEPS of the Agency for Healthcare Research and Quality.[1] Details on the advantages or disadvantages of using MEPS data are provided in the "Heart Disease and Stroke Statistics–2011 Update."[2] Indirect mortality costs are estimated for 2014 to 2015 (average annual) by multiplying the number of deaths for those years attributable to CVD and strokes, in age and sex groups, by estimates of the present value of lifetime earnings for those age and sex groups as of 2014 to 2015. Mortality data are from the National Vital Statistics System of the NCHS.[3] The present values of lifetime earnings are unpublished estimates furnished by the Institute for Health and Aging, University of California, San Francisco, by Wendy Max, PhD, on April 4, 2018. Those estimates incorporate a 3% discount rate, which is the recommended percentage.[4] The discount rate removes the effect of inflation in income over the lifetime of earnings. The estimate is for 2014, inflated to 2015 to account for the 2014 to 2015 change in hourly worker compensation in the business sector reported by the US Bureau of Labor Statistics.[5] The indirect costs exclude lost productivity costs attributable to chronic, prevalent nonfatal CVD and stroke illness during 2014 to 2015 among workers, people keeping house, people in institutions, and people unable to work. Those morbidity costs were substantial in very old studies, but because of the lack of contemporary data, an adequate update could not be made.

Abbreviations Used in Chapter 26

AHA	American Heart Association
CHD	coronary heart disease
CHF	congestive heart failure
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
ED	emergency department
GI	gastrointestinal (tract)
HBP	high blood pressure
HD	heart disease
HF	heart failure
MEPS	Medical Expenditure Panel Survey
NCHS	National Center for Health Statistics

Most Costly Diseases (See Tables 26-1 and 26-2 and Chart 26-2)

CVD and stroke accounted for 14% of total US health expenditures in 2014 to 2015, more than any major diagnostic group.[1] By way of comparison, CVD total direct costs shown in Table 26-1 are higher than the 2014 to 2015 Agency for Healthcare Research and Quality estimates for cancer, which were $84.0 billion (55% for outpatient or doctor office visits, 32% for inpatient care, and 9% for prescription drugs).[1]

Table 26-2 shows direct and indirect costs for CVD by sex and by 2 broad age groups. Chart 26-2 shows total direct costs for the 21 leading chronic diseases on the MEPS list. HD is the most costly condition.[1]

The estimated direct costs of CVD and stroke in the United States increased from $103.5 billion in 1996 to 1997 to $213.8 billion in 2014 to 2015 (Chart 26-3).

Projections (See Charts 26-3 through 26-6)

- The AHA developed methodology to project future costs of care for HBP, CHD, HF, stroke, and all other CVD.[6]
- By 2035, 45.1% of the US population is projected to have some form of CVD.[6]
- Between 2015 and 2035, total direct medical costs of CVD are projected to increase from $318 billion to $749 billion (2015$ in billions). Of this total in 2035, 55.5% will be attributable to hospital costs, 15.3% to medications, 15.0% to physicians, 7.2% to nursing home care, 5.5% to home health care, and 1.5% to other costs.[6]
- Indirect costs (attributable to lost productivity) for all fatal and nonfatal CVDs are estimated to increase from $237 billion in 2015 to $368 billion in 2035 (2015$ in billions), an increase of 55%.[6]
- Between 2015 and 2035, the total costs are expected to increase for total CVD, HBP and HBP as a risk factor, CHD, CHF, stroke, and other CVDs (Chart 26-4).
- Between 2015 and 2035, the projected total (direct and indirect) costs of total CVD are estimated to remain relatively stable for 18- to 44-year-olds, increase slightly for 45- to 64-year-olds, and

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increase sharply for 65- to 79-year-olds and adults aged ≥80 years (Chart 26-5).

- Whereas the direct costs of CVD for home health care, nursing homes, physicians, and medications are estimated to rise steadily between 2015 and 2035, projected hospital costs are estimated to more than double in this same time frame (Chart 26-6).
- These data indicate that CVD prevalence and costs are projected to increase substantially unless CVD incidence is reduced or short-term and long-term CVD care costs are better controlled.

Table 26-1. Estimated Direct and Indirect Costs (in Billions of Dollars) of CVD and Stroke: United States, Average Annual, 2014 to 2015

	Heart Disease*	Stroke	Hypertensive Disease†	Other Circulatory Conditions‡	Total CVD
Direct costs§					
Hospital inpatient stays	59.4	17.4	7.9	12.8	97.5
Hospital ED visits	6.3	0.8	1.3	1.0	9.4
Hospital outpatient or office-based provider visits	22.6	2.4	13.7	7.9	46.6
Home health care	11.1	6.6	8.2	1.6	27.5
Prescribed medicines	10.0	0.8	20.2	1.8	32.8
Total expenditures	109.4	28.0	51.3	25.1	213.8
Indirect costs‖					
Lost productivity/mortality	109.3	17.5	4.6	6.1	137.4
Grand totals	218.7	45.5	55.9	31.2	351.2

Numbers do not add to total because of rounding. CVD indicates cardiovascular disease; and ED, emergency department.

*This category includes coronary heart disease, heart failure, part of hypertensive disease, cardiac dysrhythmias, rheumatic heart disease, cardiomyopathy, pulmonary heart disease, and other or ill-defined heart diseases.

†Costs attributable to hypertensive disease are limited to hypertension without heart disease.

‡Other circulatory conditions include arteries, veins, and lymphatics.

§Medical Expenditure Panel Survey (MEPS) healthcare expenditures are estimates of direct payments for care of a patient with the given disease provided during the year, including out-of-pocket payments and payments by private insurance, Medicaid, Medicare, and other sources. Payments for over-the-counter drugs are not included. These estimates of direct costs do not include payments attributed to comorbidities. Total CVD costs are the sum of costs for the 4 diseases but with some duplication.

‖The Statistics Committee agreed to suspend presenting estimates of lost productivity attributable to morbidity until a better estimating method can be developed. Lost future earnings of people who died in 2014 to 2015, discounted at 3%.

Sources: Estimates from the Household Component of the MEPS of the Agency for Healthcare Research and Quality for direct costs (average annual 2014 to 2015).[1] Indirect mortality costs are based on 2014 to 2015 counts of deaths by the National Center for Health Statistics and an estimated present value of lifetime earnings furnished for 2014 by Wendy Max (Institute for Health and Aging, University of California, San Francisco, April 4,2018) and inflated to 2015 from change in worker compensation reported by the US Bureau of Labor Statistics. All estimates prepared by Michael Mussolino, National Heart, Lung, and Blood Institute.

Table 26-2. Costs of Total CVD and Stroke in Billions of Dollars by Age and Sex: United States, Average Annual, 2014 to 2015

	Total	Males	Females	Age <65 y	Age ≥65 y
Direct	213.8	122.4	91.4	85.5	128.3
Indirect mortality	137.4	102.3	35.1	115.5	21.9
Total	351.2	224.7	126.5	201.0	150.2

Numbers may not add to total because of rounding. CVD indicates cardiovascular disease.

Source: Medical Expenditure Panel Survey, average annual 2014 to 2015 (direct costs) and mortality data from the National Center for Health Statistics and present value of lifetime earnings from the Institute for Health and Aging, University of California, San Francisco (indirect costs).[1]

All estimates prepared by Michael Mussolino, National Heart, Lung, and Blood Institute.

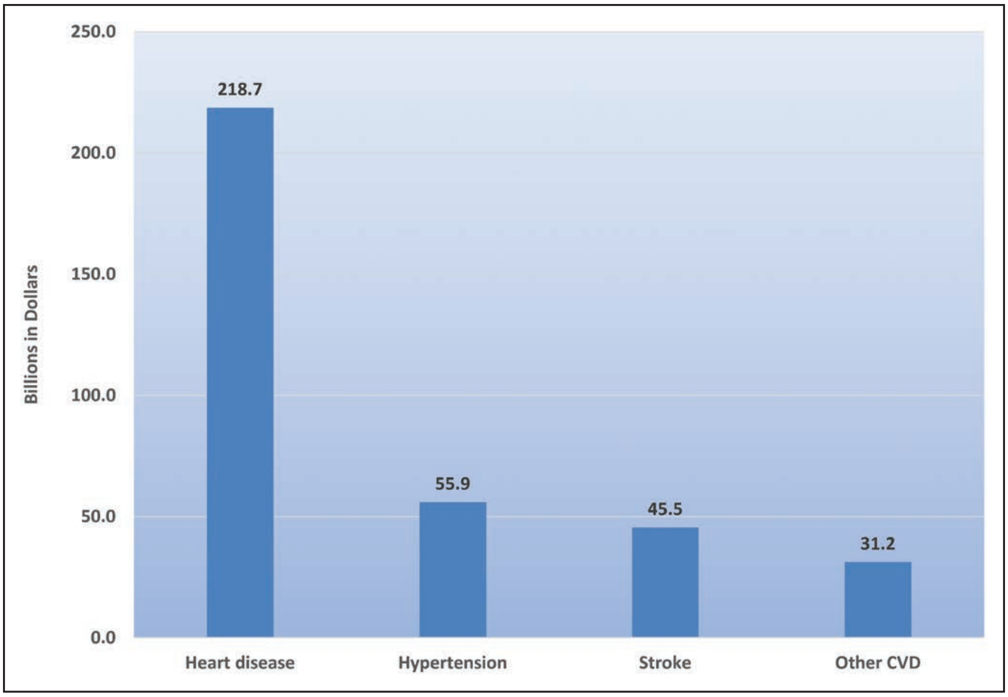

Chart 26-1. Direct and indirect costs of CVD and stroke (in billions of dollars), United States, average annual 2014 to 2015.
CVD indicates cardiovascular disease.
Source: Prepared by the National Heart, Lung, and Blood Institute.[1,3]

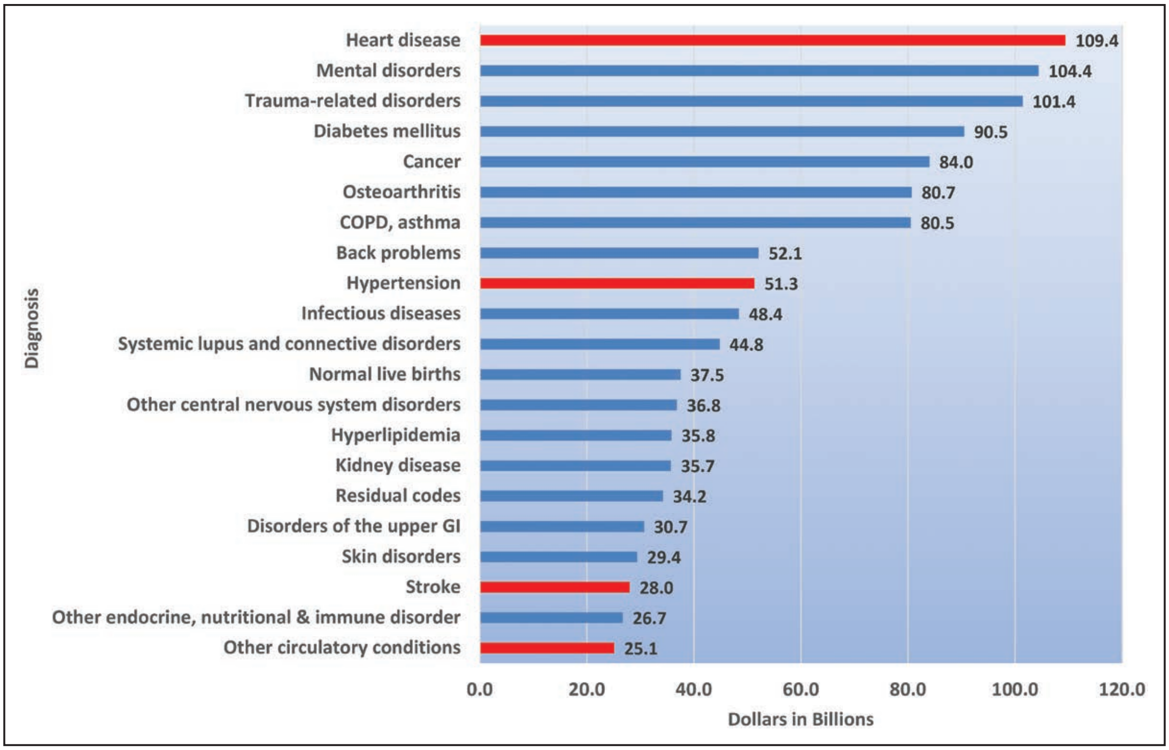

Chart 26-2. The 21 leading diagnoses for direct health expenditures, United States, average annual 2014 to 2015 (in billions of dollars).
COPD indicates chronic obstructive pulmonary disease; and GI, gastrointestinal (tract).
Source: National Heart, Lung, and Blood Institute; estimates are from the Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality, and exclude nursing home costs.[1]

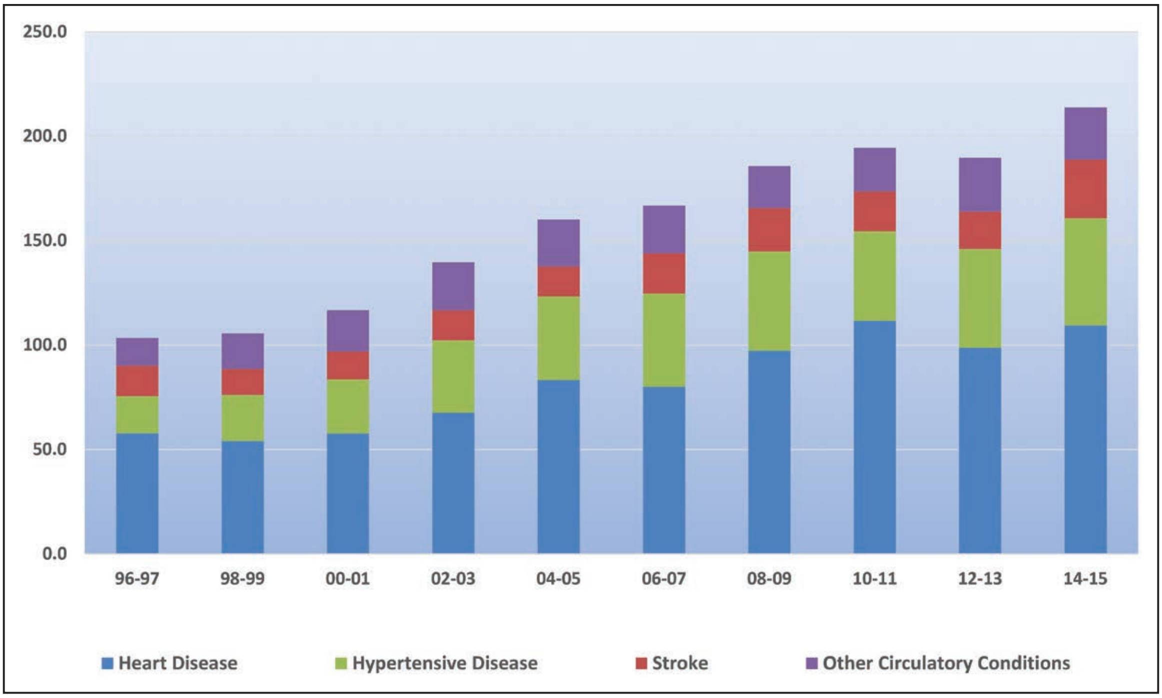

Chart 26-3. Estimated direct cost (in billions of dollars) of cardiovascular disease and stroke, United States, average annual (1996–1997 to 2014–2015).

Sources: Estimates from the Household Component of the Medical Expenditure Panel Survey of the Agency for Healthcare Research and Quality for direct costs (average annual 1996–1997 to 2014–2015).[1]

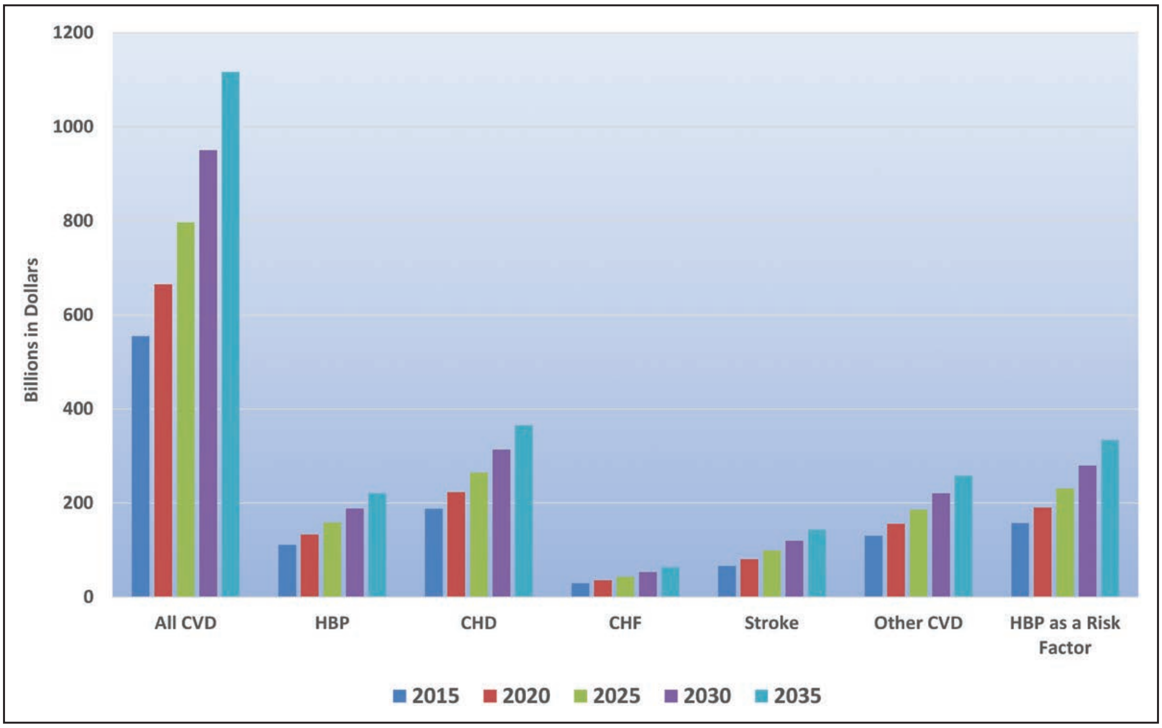

Chart 26-4. Projected total costs of CVD, United States, 2015 to 2035 (2015 dollars in billions).

CHD indicates coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; and HBP, high blood pressure.

Data from RTI International.[6] Copyright © 2016, American Heart Association, Inc.

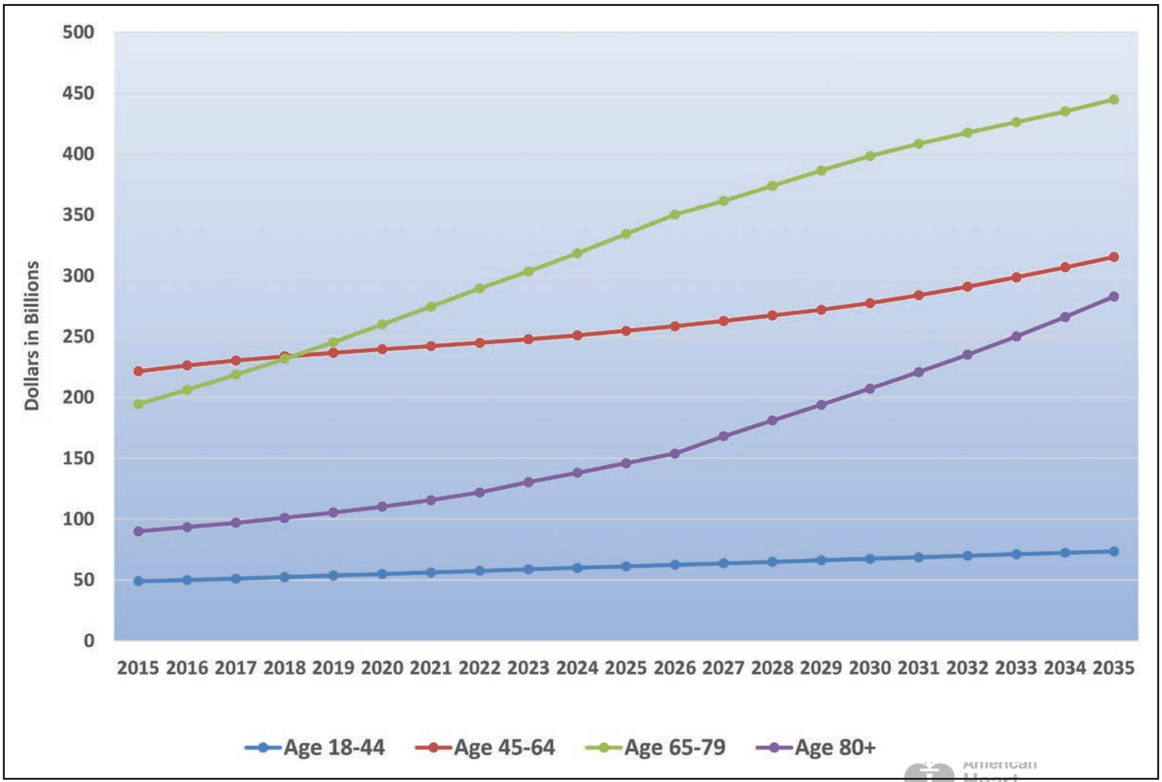

Chart 26-5. Projected total (direct and indirect) costs of total cardiovascular disease by age from 2015 to 2035 (2015 dollars in billions).
Data from RTI International.[6] Copyright © 2016, American Heart Association, Inc.

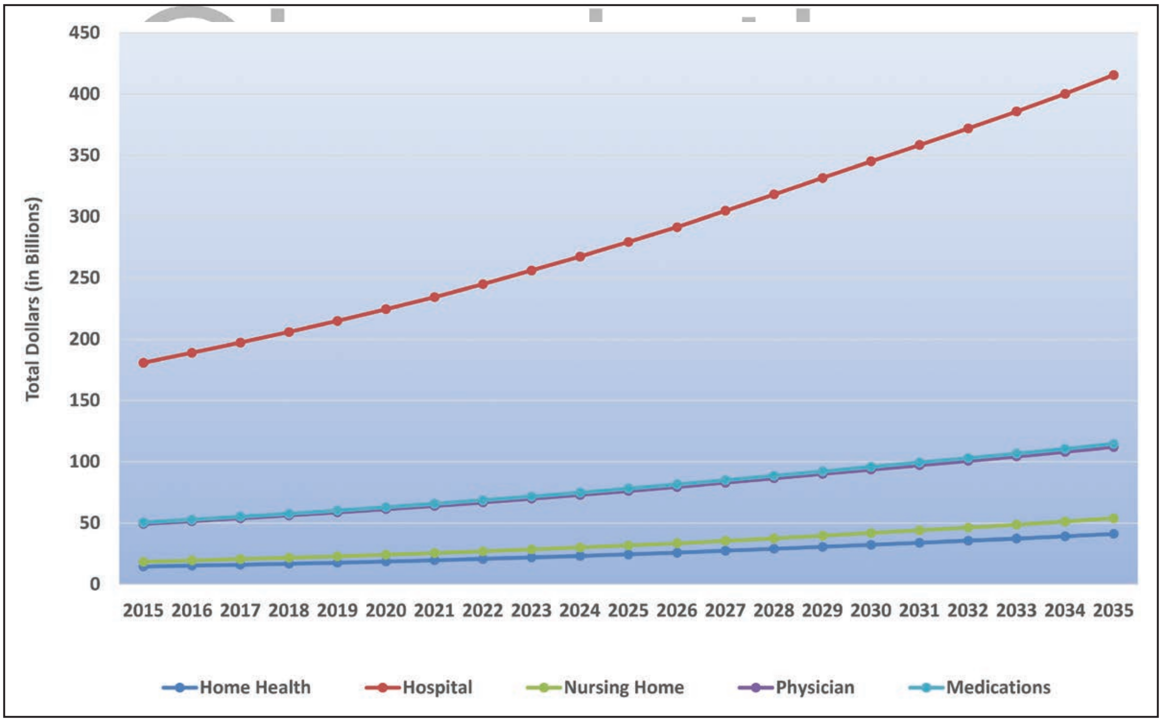

Chart 26-6. Projected direct costs of total cardiovascular disease by type of cost from 2015 to 2035 (2015 dollars in billions).
Data from RTI International.[6] Copyright © 2016, American Heart Association, Inc.

REFERENCES

1. Medical Expenditure Panel Survey: household component summary tables. Total expenditures in millions by condition, United States, 2014–2015. Agency for Healthcare Research and Quality website. https://meps.ahrq.gov/mepstrends/hc_cond/. Accessed March 15, 2018.
2. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2011 update: a report from the American Heart Association [published corrections appear in *Circulation*. 2011;124:e426 and *Circulation*. 2011;123:e240]. *Circulation*. 2011;123:e18–e209. doi: 10.1161/CIR.0b013e3182009701
3. National Center for Health Statistics. Centers for Disease Control and Prevention website. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2016. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed March 15, 2018.
4. Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.
5. US Bureau of Labor Statistics, Office of Compensation Levels and Trends. Employment Cost Index, Historical Listing – Volume V: Continuous Occupational and Industry Series: September 1975-December 2017. Table 4: employment cost index for total compensation, for civilian workers, by occupation and industry: continuous occupational and industry series. https://www.bls.gov/web/eci/ecicois.pdf. Accessed March 15, 2018.
6. RTI International. Projections of Cardiovascular Disease Prevalence and Costs: 2015–2035: Technical Report [report prepared for the American Heart Association]. Research Triangle Park, NC: RTI International; November 2016. RTI project number 021480.003.001.001. http://www.heart.org/idc/groups/heart-public/@wcm/@adv/documents/downloadable/ucm_491513.pdf. Accessed March 15, 2018.

27. AT-A-GLANCE SUMMARY TABLES

See Tables 27-1 through 27-3

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Sources: See the following summary tables for complete details:

- Overweight and Obesity—Table 6-1
- High TC and LDL-C and Low HDL-C—Table 7-1
- High Blood Pressure in the United States—Table 8-1
- Diabetes Mellitus—Table 9-1
- Cardiovascular Diseases—Table 13-1
- Stroke—Table 14-1
- Congenital Cardiovascular Defects—Table 15-1
- Coronary Heart Disease—Table 19-1; Angina Pectoris—Table 19-2
- Heart Failure—Table 20-2

Table 27-1. Males and CVD: At-a-Glance Table

Diseases and Risk Factors	Both Sexes	Total Males	NH White Males	NH Black Males	Hispanic Males	NH Asian Males	NH American Indian/ Alaska Native*
Overweight and obesity							
Prevalence, 2011–2014							
Overweight and obesity, BMI ≥25.0 kg/m^2†	157.2 M (69.4%)	78.8 M (72.5%)	73.0%	69.1%	79.6%	46.6%	…
Obesity, BMI ≥30.0 kg/m^2†	82.2 M (36.3%)	37.3 M (34.3%)	33.6%	37.5%	39.0%	11.2%	…
Blood cholesterol							
Prevalence, 2013–2016							
Total cholesterol ≥200 mg/dL‡	92.8 M (38.2%)	41.2 M (35.4%)	35.4%	29.8%	39.9%	38.7%	…
Total cholesterol ≥240 mg/dL‡	28.5 M (11.7%)	12.4 M (10.7%)	10.5%	8.9%	13.0%	11.7%	…
LDL-C ≥130 mg/dL, 2011–2014‡	71.3 M (30.3%)	34.0 M (30.0%)	29.3%	29.9%	36.6%	29.2%	…
HDL-C <40 mg/dL, 2013–2016‡	45.6 M (19.2%)	33.7 M (29.0%)	29.7%	19.8%	32.6%	25.9%	…
HBP							
Prevalence, 2013–2016†	116.4 M (46.0%)	58.7 M (49.0%)	48.2%	58.6%	47.4%	46.4%	…
Mortality, 2016§‖	82 735	39 577 (47.8%)¶	26 402	8429	3063	1153#	520
DM							
Prevalence, 2013–2016							
Diagnosed DM†	26.0 M (9.8%)	13.7 M (10.9%)	9.4%	14.7%	15.1%	12.8%	…
Undiagnosed DM†	9.4 M (3.7%)	5.5 M (4.6%)	4.7%	1.7%	6.3%	6.1%	…
Prediabetes†	91.8 M (37.6%)	51.7 M (44.0%)	43.7%	31.9%	48.1%	47.1%	…
Incidence, diagnosed DM, 2015**	1.5 M	…	…	…	…	…	…
Mortality, 2016§‖	80 058	43 763 (54.7%)¶	30 010	6976	4603	1414#	1078
Total CVD							
Prevalence, 2013–2016†	121.5 M (48.0%)	61.5 M (51.2%)	50.6%	60.1%	49.0%	47.4%	…
Mortality, 2016§‖	840 678	428 434 (51.0%)¶	332 556	52 874	27 801	11 023#	4313
Stroke							
Prevalence, 2013–2016†	7.0 M (2.5%)	3.2 M (2.5%)	2.4%	3.1%	2.0%	1.1%	…
New and recurrent strokes§	795.0 K	370.0 K (46.5%)¶	325.0 K††	45.0 K††	…	…	…
Mortality, 2016§	142 142	59 355 (41.8%)¶	43 713	8115	4798	2268#	632‡‡
CHD							
Prevalence, CHD, 2013–2016†	18.2 M (6.7%)	9.4 M (7.4%)	7.7%	7.2%	6.0%	4.8%	…
Prevalence, MI, 2013–2016†	8.4 M (3.0%)	5.1 M (4.0%)	4.0%	4.0%	3.4%	2.4%	…
Prevalence, AP, 2013–2016†	9.4 M (3.6%)	4.3 M (3.5%)	3.8%	3.6%	2.6%	2.0%	…
New and recurrent MI and fatal CHD§§	1.05 M	610.0 K	520.0 K††	90.0K††	…	…	…
New and recurrent MI§§	805.0 K	470.0 K	…	…	…	…	…
Incidence, stable AP‖‖	565.0 K	370.0 K	…	…	…	…	…

(Continued)

<zjs;AHA Statistical Update> • <zjss;10163> • <zdoi;10.1161/CIR.0000000000000659>

Table 27-1. Continued

Diseases and Risk Factors	Both Sexes	Total Males	NH White Males	NH Black Males	Hispanic Males	NH Asian Males	NH American Indian/ Alaska Native*
Mortality, 2016, CHD§‖	363 452	210 156 (57.8%)¶	167 036	21 900	13 696	5262	2069
Mortality, 2016, MI§‖	111 777	64 713 (57.9%)¶	51 594	6587	4331	1601#	606
HF							
Prevalence, 2013–2016†	6.2 M (2.2%)	3.0 M (2.4%)	2.2%	3.5%	2.5%	1.7%	…
Incidence, 2014¶¶	1.0 M	495.0 K	430.0 K††	65.0 K††	…	…	…
Mortality, 2016§‖	78 356	35 424 (45.2%)¶	29 155	3777	1721	561#	262

AP indicates angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes MI, AP, or both); CVD, cardiovascular disease; DM, diabetes mellitus; ellipses (…), data not available; HBP, high blood pressure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; K, thousands; LDL-C, low-density lipoprotein cholesterol; M, millions; MI, myocardial infarction (heart attack); and NH, non-Hispanic.

*Both sexes.

†Age ≥20 years.

‡Total data for total cholesterol are for Americans ≥20 years of age. Data for LDL-C, HDL-C, and all racial/ethnic groups are age adjusted for age ≥20 years.

§All ages.

‖Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

¶These percentages represent the portion of total incidence or mortality that is for males vs females.

#Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander.

**Age ≥18 years.

††Estimates include Hispanics and non-Hispanics. Estimates for whites include other nonblack races.

‡‡Estimate considered unreliable or does not meet standards of reliability or precision.

§§Age ≥35 years.

‖‖Age ≥45 years.

¶¶Age ≥55 years.

Table 27-2. Females and CVD: At-a-Glance Table

Diseases and Risk Factors	Both Sexes	Total Females	NH White Females	NH Black Females	Hispanic Females	NH Asian Females	NH American Indian/Alaska Native*
Overweight and obesity							
Prevalence, 2011–2014							
Overweight and obesity, BMI ≥25.0 kg/m²†	157.2 M (69.4%)	78.2 M (66.4%)	63.7%	82.2%	77.1%	34.6%	…
Obesity, BMI ≥30.0 kg/m²†	82.2 M (36.3%)	45.1 M (38.3%)	35.5%	56.9%	45.7%	11.9%	…
Blood cholesterol							
Prevalence, 2013–2016							
Total cholesterol ≥200 mg/dL‡	92.8 M (38.2%)	51.6 M (40.4%)	41.8%	33.1%	38.9%	39.6%	…
Total cholesterol ≥240 mg/dL‡	28.5 M (11.7%)	16.1 M (12.4%)	13.6%	9.0%	10.1%	10.8%	…
LDL-C ≥130 mg/dL, 2011–2014‡	71.3 M (30.3%)	37.3 M (30.4%)	32.1%	27.9%	28.7%	25.0%	…
HDL-C <40 mg/dL, 2013–2016‡	45.6 M (19.2%)	11.9 M (9.9%)	9.3%	8.1%	13.1%	7.9%	…
HBP							
Prevalence, 2013–2016†	116.4 M (46.0%)	57.7 M (42.8%)	41.3%	56.0%	40.8%	36.4%	…
Mortality, 2016§‖	82 735	43 158 (52.2%)¶	30 638	7897	2856	1362#	520
DM							
Prevalence, 2013–2016							
Diagnosed DM†	26.0 M (9.8%)	12.3 M (8.9%)	7.3%	13.4%	14.1%	9.9%	…
Undiagnosed DM†	9.4 M (3.7%)	3.9 M (2.8%)	2.6%	3.3%	4.0%	2.1%	…
Prediabetes†	91.8 M (37.6%)	40.1M (31.3%)	32.2%	24.0%	31.7%	29.4%	…
Incidence, diagnosed DM, 2015**	1.5 M	…	…	…	…	…	…
Mortality, 2016§‖	80 058	36 295 (45.3%)¶	23 389	7077	3943	1283#	1078

(*Continued*)

Table 27-2. Continued

Diseases and Risk Factors	Both Sexes	Total Females	NH White Females	NH Black Females	Hispanic Females	NH Asian Females	NH American Indian/Alaska Native*
Total CVD							
Prevalence, 2013–2016†	121.5 M (48.0%)	60.0 M (44.7%)	43.4%	57.1%	42.6%	37.2%	…
Mortality, 2016§‖	840 678	412 244 (49.0%)¶	322 328	51 767	24 428	10 672#	4313
Stroke							
Prevalence, 2013–2016†	7.0 M (2.5%)	3.8 M (2.6%)	2.5%	3.8%	2.2%	1.6%	…
New and recurrent strokes§	795.0 K	425.0 K (53.5%)¶	365.0 K**	60.0 K**	…	…	…
Mortality, 2016§	142 142	82 787 (58.2%)¶	63 778	10 074	5485	2949#	632††
CHD							
Prevalence, CHD, 2013–2016†	18.2 M (6.7%)	8.8 M (6.2%)	6.1%	6.5%	6.0%	3.2%	…
Prevalence, MI, 2013–2016†	8.4 M (3.0%)	3.3 M (2.3%)	2.2%	2.2%	2.0%	1.0%	…
Prevalence, AP, 2013–2016†	9.4 M (3.6%)	5.1 M (3.7%)	3.8%	3.8%	3.6%	1.6%	…
New and recurrent MI and fatal CHD‡‡	1.05 M	445.0 K	370.0 K**	75.0 K**	…	…	…
New and recurrent MI‡‡	805.0 K	335.0 K	…	…	…	…	…
Incidence, stable AP§§	565.0 K	195.0 K	…	…	…	…	…
Mortality, 2016, CHD§‖	363 452	153 296 (42.2%)¶	119 996	18 256	9878	3827	2069
Mortality, 2016, MI§‖	111 777	47 064 (42.1%)¶	36 664	5750	3086	1197#	606
HF							
Prevalence, 2013–2016†	6.2 M (2.2%)	3.2 M (2.1%)	1.9%	3.9%	2.1%	0.7%	…
Incidence, 2014‖‖	1.0 M	505.0K	425.0 K††	80.0 K††	…	…	…
Mortality, 2016§‖	78 356	42 932 (54.8%)¶	35 526	4584	1905	715#	262

AP indicates angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes MI, AP, or both); CVD, cardiovascular disease; DM, diabetes mellitus; ellipses (…), data not available; HBP, high blood pressure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; K, thousands; LDL-C, low-density lipoprotein cholesterol; M, millions; MI, myocardial infarction (heart attack); and NH, non-Hispanic.

*Both sexes.

†Age ≥20 years.

‡Total data for total cholesterol are for Americans ≥20 years of age. Data for LDL-C, HDL-C, and all racial/ethnic groups are age adjusted for age ≥20 years.

§All ages.

‖Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

¶These percentages represent the portion of total incidence or mortality that is for males vs females.

#Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander.

**Estimates include Hispanics and non-Hispanics. Estimates for whites include other nonblack races.

††Estimate considered unreliable or does not meet standards of reliability or precision.

‡‡Age ≥35 years.

§§ Age ≥45 years.

‖‖Age ≥55 years.

Table 27-3. Children, Youth, and CVD: At-a-Glance Table

Diseases and Risk Factors	Both Sexes	Total Males	Total Females	NH Whites		NH Blacks		Hispanic		NH Asian	
				Males	Females	Males	Females	Males	Females	Males	Females
Overweight and obesity											
Prevalence, 2011–2014											
Overweight and obesity, ages 2–19 y*	24.0 M (32.1%)	12.3 M (32.3%)	11.7 M (32.0%)	29.3%	28.0%	32.8%	37.6%	40.4%	39.8%	24.9%	15.0%
Obesity, ages 2–19 y*	12.3 M (16.5%)	6.2 M (16.3%)	6.1 M (16.7%)	14.0%	14.7%	17.5%	20.0%	21.7%	21.0%	11.4%	5.3%
Blood cholesterol, mg/dL, 2013–2016											
Mean total cholesterol, mg/dL											
Ages 6–11 y	157.8	157.9	157.7	157.1	159.1	158.8	158.2	158.7	153.9	160.1	161.5
Ages 12–19 y	154.4	151.6	157.5	150.6	157.2	150.8	156.0	152.7	156.0	155.4	170.2
Mean HDL-C, mg/dL											
Ages 6–11 y	56.0	57.4	54.5	56.6	54.7	62.5	58.1	55.9	52.2	58.1	54.4
Ages 12–19 y	51.8	49.9	53.8	49.2	53.5	54.4	56.9	49.6	52.2	52.8	56.6
Mean LDL-C, 2011–2014, mg/dL											
Ages 12–19 y	87.7	85.7	89.8	86.5	89.9	86.6	90.9	85.9	87.8	84.5	96.9
Congenital cardiovascular defects (all age groups: children and adults)											
Mortality, 2016†‡§‖	3063	1670 (54.5%)§	1393 (45.5%)§	973	821	284	248	322	245	66	54

CVD indicates cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; M, millions; and NH, non-Hispanic.
*In children, overweight and obesity are based on body mass index (BMI)-for-age values at or above the 85th percentile of the 2000 Centers for Disease Control and Prevention (CDC) growth charts. Obesity is based on BMI-for-age values at or above the 95th percentile of the CDC growth charts.
†All ages.
‡Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.
§These percentages represent the portion of total congenital cardiovascular mortality that is for males vs females.
‖NH American Indian/Alaska Native, Mortality: 38.

28. GLOSSARY

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- *Age-adjusted rates*—Used mainly to compare the rates of ≥2 communities or population groups or the nation as a whole over time. The American Heart Association (AHA) uses a standard population (2000), so these rates are not affected by changes or differences in the age composition of the population. Unless otherwise noted, all death rates in this publication are age adjusted per 100 000 population and are based on underlying cause of death.
- *Agency for Healthcare Research and Quality (AHRQ)*—A part of the US Department of Health and Human Services, this is the lead agency charged with supporting research designed to improve the quality of health care, reduce the cost of health care, improve patient safety, decrease the number of medical errors, and broaden access to essential services. The AHRQ sponsors and conducts research that provides evidence-based information on healthcare outcomes, quality, cost, use, and access. The information helps healthcare decision makers (patients, clinicians, health system leaders, and policy makers) make more informed decisions and improve the quality of healthcare services. The AHRQ conducts the Medical Expenditure Panel Survey (MEPS; ongoing).
- *Bacterial endocarditis*—An infection of the heart's inner lining (endocardium) or of the heart valves. The bacteria that most often cause endocarditis are streptococci, staphylococci, and enterococci.
- *Body mass index (BMI)*—A mathematical formula to assess body weight relative to height. The measure correlates highly with body fat. It is calculated as weight in kilograms divided by the square of the height in meters (kg/m^2).
- *Centers for Disease Control and Prevention/National Center for Health Statistics (CDC/NCHS)*—CDC is an agency within the US Department of Health and Human Services. The CDC conducts the Behavioral Risk Factor Surveillance System (BRFSS), an ongoing survey. The CDC/NCHS conducts or has conducted these surveys (among others):
  - — National Health Examination Survey (NHES I, 1960–1962; NHES II, 1963–1965; NHES III, 1966–1970)
  - — National Health and Nutrition Examination Survey I (NHANES I; 1971–1975)
  - — National Health and Nutrition Examination Survey II (NHANES II; 1976–1980)
  - — National Health and Nutrition Examination Survey III (NHANES III; 1988–1994)
  - — National Health and Nutrition Examination Survey (NHANES; 1999 to …) (ongoing)
  - — National Health Interview Survey (NHIS; ongoing)
  - — National Hospital Discharge Survey (NHDS; 1965–2010)
  - — National Ambulatory Medical Care Survey (NAMCS; ongoing)
  - — National Hospital Ambulatory Medical Care Survey (NHAMCS; ongoing)
  - — National Nursing Home Survey (periodic)
  - — National Home and Hospice Care Survey (periodic)
  - — National Vital Statistics System (ongoing)
- *Centers for Medicare & Medicaid Services*—The federal agency that administers the Medicare, Medicaid, and Child Health Insurance programs.
- *Comparability ratio*—Provided by the NCHS to allow time-trend analysis from one *International Classification of Diseases* (*ICD*) revision to another. It compensates for the "shifting" of deaths from one causal code number to another. Its application to mortality based on one *ICD* revision means that mortality is "comparability modified" to be more comparable to mortality coded to the other *ICD* revision.
- *Coronary heart disease (CHD) (ICD-10 codes I20–I25)*—This category includes acute myocardial infarction (I21–I22); other acute ischemic (coronary) heart disease (I24); angina pectoris (I20); atherosclerotic cardiovascular disease (I25.0); and all other forms of chronic ischemic (coronary) heart disease (I25.1–I25.9).
- *Death rate*—The relative frequency with which death occurs within some specified interval of time in a population. National death rates are computed per 100 000 population. Dividing the total number of deaths by the total population gives a crude death rate for the total population. Rates calculated within specific subgroups, such as age-specific or sex-specific rates, are often more meaningful and informative. They allow well-defined subgroups of the total population to be examined. Unless otherwise stated, all death rates in this publication are age adjusted and are per 100 000 population.
- *Diseases of the circulatory system (ICD-10 codes I00–I99)*—Included as part of what the AHA calls "cardiovascular disease" ("Total cardiovascular disease" in this Glossary).

<zjs;AHA Statistical Update> • <zjss;10163> • <zdoi;10.1161/CIR.0000000000000659>

- *Diseases of the heart (ICD-10 codes I00–I09, 111, 113, 120-151)*—Classification the NCHS uses in compiling the leading causes of death. Includes acute rheumatic fever/chronic rheumatic heart diseases (I00–I09); hypertensive heart disease (I11); hypertensive heart and renal disease (I13); CHD (I20–I25); pulmonary heart disease and diseases of pulmonary circulation (I26–I28); heart failure (I50); and other forms of heart disease (I29–I49, I50.1–I51). "Diseases of the heart" are not equivalent to "total cardiovascular disease," which the AHA prefers to use to describe the leading causes of death.
- *Hispanic origin*—In US government statistics, "Hispanic" includes people who trace their ancestry to Mexico, Puerto Rico, Cuba, Spain, the Spanish-speaking countries of Central or South America, the Dominican Republic, or other Spanish cultures, regardless of race. It does not include people from Brazil, Guyana, Suriname, Trinidad, Belize, or Portugal, because Spanish is not the first language in those countries. Most of the data in this update are for Mexican Americans or Mexicans, as reported by government agencies or specific studies. In many cases, data for all Hispanics are more difficult to obtain.
- *Hospital discharges*—The number of inpatients (including newborn infants) discharged from short-stay hospitals for whom some type of disease was the first-listed diagnosis. Discharges include those discharged alive, dead, or "status unknown."
- *International Classification of Diseases (ICD) codes*—A classification system in standard use in the United States. The *ICD* is published by the World Health Organization. This system is reviewed and revised approximately every 10 to 20 years to ensure its continued flexibility and feasibility. The 10th revision (*ICD-10*) began with the release of 1999 final mortality data. The *ICD* revisions can cause considerable change in the number of deaths reported for a given disease. The NCHS provides "comparability ratios" to compensate for the "shifting" of deaths from one *ICD* code to another. To compare the number or rate of deaths with that of an earlier year, the "comparability-modified" number or rate is used.
- *Incidence*—An estimate of the number of new cases of a disease that develop in a population, usually in a 1-year period. For some statistics, new and recurrent attacks, or cases, are combined. The incidence of a specific disease is estimated by multiplying the incidence rates reported in community- or hospital-based studies by the US population. The rates in this report change only when new data are available; they are not computed annually.
- *Major cardiovascular diseases*—Disease classification commonly reported by the NCHS; represents *ICD-10* codes I00 to I78. The AHA does not use "major cardiovascular diseases" for any calculations. See "Total cardiovascular disease" in this Glossary.
- *Metabolic syndrome*—Metabolic syndrome is defined* as the presence of any 3 of the following 5 diagnostic measures: Elevated waist circumference (≥102 cm in males or ≥88 cm in females), elevated triglycerides (≥150 mg/dL [1.7 mmol/L] or drug treatment for elevated triglycerides), reduced high-density lipoprotein cholesterol (<40 mg/dL [0.9 mmol/L] in males, <50 mg/dL [1.1 mmol/L] in females, or drug treatment for reduced high-density lipoprotein cholesterol), elevated blood pressure (≥130 mm Hg systolic blood pressure, ≥85 mm Hg diastolic blood pressure, or drug treatment for hypertension), and elevated fasting glucose (≥100 mg/dL or drug treatment for elevated glucose).
- *Morbidity*—Incidence and prevalence rates are both measures of morbidity (ie, measures of various effects of disease on a population).
- *Mortality*—Mortality data for states can be obtained from the NCHS website (http://cdc.gov/nchs/), by direct communication with the CDC/NCHS, or from the AHA on request. The total number of deaths attributable to a given disease in a population during a specific interval of time, usually 1 year, are reported. These data are compiled from death certificates and sent by state health agencies to the NCHS. The process of verifying and tabulating the data takes ≈2 years.
- *National Heart, Lung, and Blood Institute (NHLBI)*—An institute in the National Institutes of Health in the US Department of Health and Human Services. The NHLBI conducts such studies as the following:
  - — Framingham Heart Study (FHS; 1948 to …) (ongoing)
  - — Honolulu Heart Program (HHP; 1965–1997)
  - — Cardiovascular Health Study (CHS; 1988 to …) (ongoing)
  - — Atherosclerosis Risk in Communities (ARIC) Study (1985 to …) (ongoing)
  - — Strong Heart Study (SHS; 1989–1992, 1991–1998)
  - — Multi-Ethnic Study of Atherosclerosis (MESA; 2000–2012)

*According to criteria established by the AHA/NHLBI and published in *Circulation* (*Circulation*. 2005;112:2735–2752).

- — The NHLBI also published reports of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).
- *National Institute of Neurological Disorders and Stroke (NINDS)*—An institute in the National Institutes of Health of the US Department of Health and Human Services. The NINDS sponsors and conducts research studies such as these:
  - — Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS)
  - — Rochester (Minnesota) Stroke Epidemiology Project
  - — Northern Manhattan Study (NOMAS)
  - — Brain Attack Surveillance in Corpus Christi (BASIC) Project
- *Physical activity*—Any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level.
- *Physical fitness*—The ability to perform daily tasks with vigor and alertness, without undue fatigue, and with ample energy to enjoy leisure-time pursuits and respond to emergencies. Physical fitness includes a number of components consisting of cardiorespiratory endurance (aerobic power), skeletal muscle endurance, skeletal muscle strength, skeletal muscle power, flexibility, balance, speed of movement, reaction time, and body composition.
- *Prevalence*—An estimate of the total number of cases of a disease existing in a population during a specified period. Prevalence is sometimes expressed as a percentage of population. Rates for specific diseases are calculated from periodic health examination surveys that government agencies conduct. Annual changes in prevalence as reported in this Statistical Update reflect changes in the population size. Changes in rates can be evaluated only by comparing prevalence rates estimated from surveys conducted in different years. Note: In the data tables, which are located in the different disease and risk factor chapters, if the percentages shown are age adjusted, they will not add to the total.
- *Race and Hispanic origin*—Race and Hispanic origin are reported separately on death certificates. In this publication, unless otherwise specified, deaths of people of Hispanic origin are included in the totals for whites, blacks, American Indians or Alaska Natives, and Asian or Pacific Islanders according to the race listed on the decedent's death certificate. Data for Hispanic people include all people of Hispanic origin of any race. See "Hispanic origin" in this Glossary.
- *Stroke (ICD-10 codes I60–I69)*—This category includes subarachnoid hemorrhage (I60); intracerebral hemorrhage (I61); other nontraumatic intracranial hemorrhage (I62); cerebral infarction (I63); stroke, not specified as hemorrhage or infarction (I64); occlusion and stenosis of precerebral arteries not resulting in cerebral infarction (I65); occlusion and stenosis of cerebral arteries not resulting in cerebral infarction (I66); other cerebrovascular diseases (I67); cerebrovascular disorders in diseases classified elsewhere (I68); and sequelae of cerebrovascular disease (I69).
- *Total cardiovascular disease (ICD-10 codes I00–I99, Q20–Q28)*—This category includes rheumatic fever/rheumatic heart disease (I00–I09); hypertensive diseases (I10–I15); ischemic (coronary) heart disease (I20–I25); pulmonary heart disease and diseases of pulmonary circulation (I26–I28); other forms of heart disease (I30–I52); cerebrovascular disease (stroke) (I60–I69); atherosclerosis (I70); other diseases of arteries, arterioles, and capillaries (I71–I79); diseases of veins, lymphatics, and lymph nodes not classified elsewhere (I80–I89); and other and unspecified disorders of the circulatory system (I95–I99). When data are available, we include congenital cardiovascular defects (Q20–Q28).
- *Underlying cause of death or any-mention cause of death*—These terms are used by the NCHS when defining mortality. Underlying cause of death is defined by the World Health Organization as "the disease or injury which initiated the chain of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury." Any-mention cause of death includes the underlying cause of death and up to 20 additional multiple causes listed on the death certificate.