Circulation

AHA STATISTICAL UPDATE

Heart Disease and Stroke Statistics—2021 Update

A Report From the American Heart Association

WRITING GROUP MEMBERS

Salim S. Virani, MD, PhD, FAHA, Chair
Alvaro Alonso, MD, PhD, FAHA
Hugo J. Aparicio, MD, MPH
Emelia J. Benjamin, MD, ScM, FAHA
Marcio S. Bittencourt, MD, PhD, MPH, FAHA
Clifton W. Callaway, MD, PhD, FAHA
April P. Carson, PhD, MSPH, FAHA
Alanna M. Chamberlain, PhD, MPH, FAHA
Susan Cheng, MD, MMSc, MPH, FAHA
Francesca N. Delling, MD, MPH, FAHA
Mitchell S.V. Elkind, MD, MS, FAHA
Kelly R. Evenson, PhD, MS, FAHA
Jane F. Ferguson, PhD, FAHA
Deepak K. Gupta, MD, MSCI, FAHA
Sadiya S. Khan, MD, MSc, FAHA
Brett M. Kissela, MD, MS, FAHA
Kristen L. Knutson, PhD
Chong D. Lee, EdD, MEd, FAHA
Tené T. Lewis, PhD, FAHA
Junxiu Liu, PhD
Matthew Shane Loop, PhD, FAHA
Pamela L. Lutsey, PhD, MPH, FAHA
Jun Ma, MD, PhD, FAHA
Jason Mackey, MD, FAHA
Seth S. Martin, MD, MHS, FAHA
David B. Matchar, MD, FAHA
Michael E. Mussolino, PhD, FAHA
Sankar D. Navaneethan, MD, MS, MPH
Amanda Marma Perak, MD, MS, FAHA
Gregory A. Roth, MD, MPH, FAHA
Zainab Samad, MD
Gary M. Satou, MD, FAHA
Emily B. Schroeder, MD, PhD, FAHA
Svati H. Shah, MD, MHS, FAHA
Christina M. Shay, PhD, FAHA
Andrew Stokes, PhD
Lisa B. VanWagner, MD, MSc, FAST, FAHA
Nae-Yuh Wang, PhD, MS, FAHA
Connie W. Tsao, MD, MPH, Vice Chair
On behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee

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The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Key Words: AHA Scientific Statements ■ cardiovascular diseases ■ epidemiology ■ risk factors ■ statistics ■ stroke

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BACKGROUND: The American Heart Association, in conjunction with the National Institutes of Health, annually reports the most up-to-date statistics related to heart disease, stroke, and cardiovascular risk factors, including core health behaviors (smoking, physical activity, diet, and weight) and health factors (cholesterol, blood pressure, and glucose control) that contribute to cardiovascular health. The Statistical Update 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, heart failure, valvular disease, venous disease, and peripheral artery disease) and the associated outcomes (including quality of care, procedures, and economic costs).

METHODS: The American Heart Association, 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 annual Statistical Update. The 2021 Statistical Update is the product of a full year's worth of effort by dedicated volunteer clinicians and scientists, committed government professionals, and American Heart Association staff members. This year's edition includes data on the monitoring and benefits of cardiovascular health in the population, an enhanced focus on social determinants of health, adverse pregnancy outcomes, vascular contributions to brain health, the global burden of cardiovascular disease, and further evidence-based approaches to changing behaviors related to cardiovascular disease.

RESULTS: Each of the 27 chapters in the Statistical Update focuses on a different topic related to heart disease and stroke statistics.

CONCLUSIONS: The Statistical Update represents a critical resource for the lay public, policy makers, media professionals, clinicians, health care administrators, researchers, health advocates, and others seeking the best available data on these factors and conditions.

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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 (HD), 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

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, do not smoke or use smokeless tobacco, eat a heart-healthy diet, keep blood pressure healthy, and learn about blood sugar and diabetes.[1] AHA indicates American Heart Association; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

glucose control) that contribute to cardiovascular health. The Statistical Update represents a critical resource for the lay public, policy makers, media professionals, clinicians, health care 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 HD, rhythm disorders, subclinical atherosclerosis, coronary HD [CHD], heart failure [HF], valvular HD, venous disease, and peripheral artery 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 available 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. Below are a few highlights from this year's Statistical Update. Please see each chapter for references and additional information.

Cardiovascular Health (Chapter 2)

- The 5 US states with the highest health-adjusted life expectancy at birth include Hawaii, Minnesota, California, Connecticut, and Nebraska. The 5 US states with the lowest health-adjusted life expectancy at birth include West Virginia, Kentucky, Alabama, Oklahoma, and Louisiana.
- High body mass index, high fasting plasma glucose, and smoking are the first, second, and third leading years lived with disability and injury risk factors in the United States in both 1990 and 2019, whereas smoking dropped from first to third leading years lived with disability and injury risk factor during this time period.
- Smoking and high systolic BP remained the first and second leading years of life lost risk factors in the United States in both 1990 and 2019.
- High systolic BP and smoking are the first and second leading years of life lost risk factors globally in 2019.
- High fasting plasma glucose and high body mass index were the first and second leading years lived with disability and injury risk factors globally in 2019.

Smoking/Tobacco Use (Chapter 3)

- The prevalence of cigarette use in the past 30 days among middle and high school students in the United States was 2.3% and 5.8%, respectively, in 2019.
- Although there has been a consistent decline in adult and youth cigarette use in the United States, significant disparities persist. Substantially higher tobacco use prevalence rates are observed in American Indian/Alaska Native individuals and lesbian, gay, and bisexual populations.
- Over the past 8 years, there has been a sharp increase in electronic cigarette use among adolescents, increasing from 1.5% to 27.4% between 2011 and 2019; electronic cigarettes are now the most commonly used tobacco product in this demographic.
- Tobacco use was the second leading cause of disability-adjusted life-years in the United States in 2016. Globally, smoking accounted for 8.7 million deaths worldwide in 2019.
- Tobacco 21 legislation was signed into law in December 2019, increasing the federal minimum age for sale of tobacco products from 18 to 21 years. In January 2020, the US Food and Drug Administration issued a policy prioritizing enforcement against the development and distribution of certain unauthorized flavored electronic cigarette products such as fruit and mint flavors (ie, any flavors other than tobacco and menthol).

Physical Inactivity (Chapter 4)

- In a nationally representative sample of high school students in 2017, 26.1% reported achieving at least 60 minutes of daily physical activity.
- In a nationally representative sample of adults in 2018, 24.0% reported participating in adequate leisure-time aerobic and muscle-strengthening activity to meet US recommendations for physical activity.
- In a harmonization of 8 prospective studies using accelerometry to assess movement, over a median of 5.8 years of follow-up, the highest quartile of light and moderate to vigorous physical activity compared with the lowest quartile (least active) was associated with a lower risk of all-cause mortality. Time in sedentary behavior was associated with a higher risk of all-cause mortality compared with the lowest quartile (least sedentary).

Nutrition (Chapter 5)

- According to NHANES (National Health and Nutrition Examination Survey; 2015–2016), <10% adults met the guidelines for whole grains (≥3 servings per day), whole fruits (≥2 cups per day), and nonstarchy vegetables (≥2.5 cups per day).
- According to the AHA primary diet score, 47.8% of US adults had poor diet quality in 2015 to 2016. On the basis of the secondary score, 36.4% of US adults had poor diet quality in 2015 to 2016.
- In a large primary prevention trial among patients with CVD risk factors, patients randomized to unrestricted-calorie Mediterranean-style diets supplemented with extra-virgin olive oil or mixed nuts had a ≈30% reduction in the risk of stroke, myocardial infarction, and death attributable to cardiovascular causes, without changes in body weight.

Overweight and Obesity (Chapter 6)

- According to NHANES 2015 to 2018, among US adults ≥20 years of age, the age-adjusted prevalence of obesity was 39.9% in males and 41.1% in females; the prevalence of extreme obesity was 6.2% in males and 10.5% in females; the overall prevalence of obesity among youth 2 to 19 years of age was 19.0%.
- In a study of 2625 participants with new-onset diabetes 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 hazard ratios (HRs) of 2.08, 1.52, and 2.32, respectively.
- In the Systolic Blood Pressure Intervention Trial (SPRINT), there was a J-shaped associated between body mass index and all-cause mortality and risk of stroke. An increased risk of stroke was also seen when participants with obesity were compared with normal-weight participants in the Copenhagen City Heart Study (HR, 1.4) and the Copenhagen General Population Study (HR, 1.1).
- In a retrospective cohort study of individuals with a median follow-up of 3.9 years, patients in the bariatric surgery group had a cumulative incidence of major adverse cardiac events of 30.8% compared with 47.7% among matched patients who did not undergo bariatric surgery.

High Blood Cholesterol and Other Lipids (Chapter 7)

- The Healthy People 2020 target is a mean population total cholesterol level of 177.9 mg/dL for adults, which had not been achieved among the population of US adults or in any race/ethnicity subgroup as of 2015 to 2018 NHANES data. Conversely, the Healthy People 2020 target of ≤13.5% for the proportion of adults with high total cholesterol ≥240 mg/dL has been achieved as of the combined period 2015 to 2018 for adults overall and all race-sex subgroups.
- Long-term exposure to even modestly elevated cholesterol levels can lead to CHD later in life. In an analysis of time-weighted average exposures to low-density lipoprotein cholesterol (LDL-C) during young (18–39 years of age) versus later (≥40 years of age) adulthood among 36 030 participants from 6 US cohorts, CHD rates were significantly elevated among individuals who had young adult LDL-C ≥100 (versus <100) mg/dL, independently of later adult exposures (adjusted HR, 1.64). Specifically, compared with LDL-C <100 mg/dL, adjusted HRs were as follows: for LDL-C 100 to 129 mg/dL, 1.62; for LDL-C 130 to 159 mg/dL, 1.89; and for LDL-C ≥160 mg/dL, 2.03.
- In a 20-year follow-up study, early initiation of statin treatment among 214 children with familial hypercholesterolemia was associated with a decrease in LDL-C by 32%, slowed progression of subclinical atherosclerosis, and lower cumulative incidence by 39 years of age of cardiovascular events compared with affected parents (0% versus 7% and 1% versus 26% of fatal and nonfatal cardiovascular events, respectively).
- Among 5693 participants in PALM (Patient and Provider Assessment of Lipid Management), a nationwide registry of ambulatory community practices, females were less likely than males to receive statin dosing at the guideline-recommended

intensity (36.7% versus 45.2%; *P*<0.001) and were more likely to not ever have been offered statin therapy despite being eligible (18.6% versus 13.5%) compared with males.

High Blood Pressure (Chapter 8)

- Analysis of NHANES 1999 to 2002, 2007 to 2010, and 2015 to 2018 found large increases in hypertension awareness, treatment, and control (≈10%) within each race/ethnicity and sex subgroup except for Black females. Among Black females, levels of hypertension awareness, treatment, and control increased between 1999 to 2002 and 2007 to 2010 but decreased between 2007 to 2010 and 2015 to 2018.
- With the use of 2017 guidelines from the American Academy of Pediatrics, analysis of data for children and adolescents 8 to 17 years of age (n=12 249) from NHANES 2003 to 2004 through NHANES 2015 to 2016 found that the prevalence of either elevated BP or hypertension (combined) significantly declined from 16.2% in 2003 to 2004 to 13.3% in 2015 to 2016 and the prevalence of hypertension declined from 6.6% to 4.5% in this age group.
- In NHDS (National Hospital Discharge Survey) data compiled by the Centers for Disease Control and Prevention, chronic hypertension in pregnancy (defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg either before pregnancy or up to the first 20 weeks during pregnancy) increased >13-fold between 1970 and 2010. Black women had a persistent 2-fold higher rate of chronic hypertension compared with White women over the 40-year period.

Diabetes (Chapter 9)

- On the basis of data from NHANES 2013 to 2016, an estimated 26 million adults have diagnosed diabetes, 9.4 million adults (3.7%) have undiagnosed diabetes, and 91.8 million adults (37.6%) have prediabetes.
- The age-adjusted prevalence of diagnosed diabetes in adults ≥18 years of age increased from 6.4% in 1999 to 2002 to 9.4% in 2013 to 2016. In contrast, the age-adjusted prevalence of undiagnosed diabetes was similar from 1999 to 2002 (3.1%) and 2013 to 2016 (2.6%).
- Among adults with diagnosed diabetes in NHANES 2013 to 2016, 9.9% had a hemoglobin A_{1c} ≥10.0%, and this was more prevalent among adults 18 to 44 years of age (16.3%) than adults ≥65 years of age (4.3%).
- In NHIS (National Health Interview Survey) 2013 to 2017, adults with diabetes <65 years of age were more likely to report overall financial hardship from medical bills (41.1%) than adults with diabetes ≥65 years of age (20.7%). The prevalence of cost-related medication nonadherence was 34.7% and delayed medical care was 55.5% among adults with diabetes <65 years of age.
- In 2016, of 154 health conditions evaluated, diabetes had the highest public insurance spending ($55.4 billion).

Metabolic Syndrome (Chapter 10)

- Uncertainty remains concerning the definition of the obesity component of metabolic syndrome (MetS) in the pediatric population because it is age dependent. Therefore, use of body mass index percentiles and waist-height ratio has been recommended. According to the Centers for Disease Control and Prevention and FitnessGram standards for pediatric obesity, the prevalence of MetS in obese youth ranges from 19% to 35%.
- On the basis of NHANES 2007 to 2014, the overall prevalence of MetS was 34.3% and was similar for males (35.3%) and females (33.3%). The prevalence of MetS 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.
- Each 1000-steps-per-day increase is associated with lower odds of having MetS (odds ratio, 0.90) in American men.
- In a meta-analysis including 17 prospective longitudinal studies with 602 195 women and 15 945 cases of breast cancer, MetS was associated with increased risk of incident breast cancer in postmenopausal women (adjusted relative risk, 1.25) but significantly reduced breast cancer risk in premenopausal women (adjusted relative risk, 0.82). Further analyses showed that the association between MetS and increased risk of breast cancer was observed only among White and Asian women, whereas there was no association in Black women.

Adverse Pregnancy Outcomes (Chapter 11)

- Adverse pregnancy outcomes (including hypertensive disorders of pregnancy, gestational diabetes, preterm birth, and small for gestational age at birth) occur in 10% to 20% of pregnancies.
- According to a meta-analysis of individual participant data from 265 270 females from 39 European, North American, and Oceanic cohort studies, risk of adverse pregnancy outcomes was greater with higher categories of prepregnancy body mass index and greater degree of gestational weight gain, with an adjusted odds ratio of 2.51

for women with prepregnancy obesity and high gestational weight gain.
- On the basis of a meta-analysis of 9 studies, gestational hypertension was associated with a 67% higher risk of subsequent CVD, and preeclampsia was associated with a 75% higher risk of subsequent CVD-related mortality.
- Among 2 141 709 live-born singletons in the Swedish Birth Registry from 1973 to 1994 followed up through 2015 (maximum, 43 years of age), gestational age at birth was inversely associated with risk for premature CHD (adjusted HRs at 30–43 years of age versus full-term [39–41 weeks] births: for preterm [<37 weeks], 1.53; for early term [37–38 weeks], 1.19).

Kidney Disease (Chapter 12)

- Overall prevalence of chronic kidney disease (estimated glomerular filtration rate <60 mL·min^{-1}·1.73 m^{-2} or albumin-to-creatinine ratio ≥30 mg/g) was 14.8% (2013–2016).
- Incidence of end-stage kidney disease in the United States is projected to increase 11% to 18% through 2030.
- In NHANES 1999 to 2014, 34.9% of adults with chronic kidney disease used an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.
- Rates of stress testing among Medicare beneficiaries declined from 2008 to 2012, but rates were 5% to 15% higher for those with chronic kidney disease and end-stage kidney disease than for those without chronic kidney disease.

Sleep (Chapter 13)

- Analysis of 2018 BRFSS (Behavioral Risk Factor Surveillance System) data indicated that the proportion of adults reporting inadequate sleep (<7 hours) was 35.4%. Older people (>65 years of age) were less likely to report sleeping <7 hours, and younger males (<45 years of age) were more likely to report sleeping <7 hours.
- In the 2018 BRFSS, non-Hispanic Black people had the highest percentage of respondents reporting sleeping <7 hours per night (45.4%), whereas non-Hispanic White people had the lowest percentage (33.2%) of respondents reporting sleeping <7 hours.
- A meta-analysis of 15 prospective studies observed a significant association between the presence of obstructive sleep apnea and the risk of cerebrovascular disease (HR, 1.94).
- An analysis of the global prevalence and burden of obstructive sleep apnea estimated that 936 million males and females 30 to 69 years of age have mild to severe obstructive sleep apnea (apnea-hypopnea index ≥5) and 425 million have moderate to severe obstructive sleep apnea (apnea-hypopnea index ≥15) globally. The prevalence was highest in China, followed by the United States, Brazil, and India.

Total Cardiovascular Diseases (Chapter 14)

- On the basis of NHANES 2015 to 2018 data, the prevalence of CVD (comprising CHD, HF, stroke, and hypertension) in adults ≥20 years of age is 49.2% overall (126.9 million in 2018) and increases with age in both males and females. CVD prevalence excluding hypertension (CHD, HF, and stroke only) is 9.3% overall (26.1 million in 2018).
- From the combination of estimates from NHANES, REGARDS (Reasons for Geographic and Racial Differences in Stroke), and randomized controlled trials for BP-lowering treatments, it was estimated that achieving the 2017 American College of Cardiology/AHA BP goals could prevent 3.0 million (uncertainty range, 1.1 million–5.1 million) CVD events (CHD, stroke, and HF) compared with current BP levels, but achieving the 2017 American College of Cardiology/AHA BP goals could also increase serious adverse events by 3.3 million (uncertainty range, 2.2 million–4.4 million).
- The US IMPACT (International Model for Policy Analysis of Agricultural Commodities and Trade) Food Policy Model, a computer simulation model, projected that a national policy combining a 30% fruit and vegetable subsidy targeted to low-income Supplemental Nutrition Assistance Program 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%.

Stroke (Cerebrovascular Diseases and Vascular Contributions to Brain Health) (Chapter 15)

- In a county-level study, stroke mortality rates among US adults 35 to 64 years of age increased from 14.7 per 100 000 in 2010 to 15.4 per 100 000 in 2016. Rates decreased among adults ≥65 years of age from 299.3 per 100 000 in 2010 to 271.4 per 100 000 in 2016.
- In a meta-analysis of 35 studies (n=2 458 010 patients), perioperative or postoperative atrial fibrillation (AF) was associated with an increased risk of early stroke (odds ratio, 1.62) and later stroke (HR, 1.37). This risk was found in both

patients undergoing noncardiac surgery (HR, 2.00) and those undergoing cardiac surgery (HR, 1.20).
- An analysis of the NHIS demonstrated that awareness of stroke symptoms and signs among US adults improved from 2009 to 2014. In 2014, 68.3% of the survey respondents were able to recognize 5 common stroke symptoms, and 66.2% demonstrated knowledge of all 5 stroke symptoms and the importance of calling 9-1-1.
- In a meta-analysis of 9 studies, subclinical or silent brain infarcts were associated with decline in cognitive function on the Mini-Mental State Examination score (standardized mean difference, –0.47). In the same meta-analysis, among 4 studies, subclinical or silent brain infarcts were associated with cognitive dysfunction on the Montreal Cognitive Assessment Scale (standardized mean difference, –3.36).

Congenital Cardiovascular Defects and Kawasaki Disease (Chapter 16)

- In 2018, the age-adjusted death rate attributable to congenital cardiovascular defects in the United States was 0.9 per 100 000. The death rate was higher for males than females.
- In a recent study, adults with congenital cardiovascular defects requiring hospital admission for HF demonstrated higher odds of longer length of stay, incident arrhythmias, and in-hospital mortality compared with adults with HF without congenital cardiovascular defects.
- The incidence of Kawasaki disease appears to be rising worldwide, with potential contributions from improved recognition, more frequent diagnosis of incomplete Kawasaki disease, and true increasing incidence.

Disorders of Heart Rhythm (Chapter 17)

- In 2018, 53 895 deaths had arrhythmias as the primary cause of death, and 564 182 included arrhythmia as one of the causes of death.
- The prevalence of AF in the United States was estimated to be 5.2 million in 2010, increasing to 12.1 million in 2030. In the United States, 1.2 million people were newly diagnosed with AF in 2010. This number is projected to increase to 2.6 million by 2030.
- The lifetime risk of AF has been estimated to be 1 in 3 among White people and 1 in 5 among Black people.
- Hypertension accounts for the largest proportion of AF (≈22%), followed by obesity, smoking, cardiac disease, and diabetes.
- A study examining public and private health insurer records from 1996 to 2016 reported that AF was 33rd in spending for health conditions with an estimated $28.4 billion in 2016 dollars, with an annualized rate of change of 3.4% during this period.
- In a controlled trial randomizing alcohol drinkers with paroxysmal AF either to alcohol abstinence or to continue their usual alcohol consumption, AF recurred in 53% of the abstinence group and 73% of the control group. Compared with the control group, the abstinence group had a significantly longer duration without AF recurrence (HR, 0.55) and significantly lower AF burden (median percent time in AF, 0.5% versus 1.2%).

Sudden Cardiac Arrest, Ventricular Arrhythmias, and Inherited Channelopathies (Chapter 18)

- Sudden cardiac arrest and sudden cardiac death result from many different disease processes, each of which can have different risk factors. Among patients with out-of-hospital cardiac arrest (OHCA) resuscitated and hospitalized from 2012 to 2016, acute coronary syndrome and other cardiac causes accounted for the largest proportion of causes. Among patients with in-hospital cardiac arrest, respiratory failure was the most common cause.
- Among 5869 autopsied subjects with sudden cardiac death, excluding cases with noncardiac causes of death, in Finland between 1998 and 2017, ischemic cardiac disease represented 4392 (74.8%) and nonischemic cardiac diseases represented 1477 (25.2%). Over time, the proportion of ischemic sudden cardiac death declined from 78.8% (1998–2002) to 72.4% (2013–2017).
- According to multiple studies, sudden cardiac arrest is more common in males than in females. Females compared with males with OHCA are older, less likely to present with shockable rhythms, and less likely to collapse in public. Despite these factors that would reduce survival, females have equivalent or higher rates of survival to hospital discharge or to 30 days relative to males.
- Incidence of emergency medical services–treated OHCA in people of any age is 76.5 individuals per 100 000 population according to the 2019 CARES (Cardiac Arrest Registry to Enhance Survival) registry, with >2-fold variation between states (range, 41.8–126.1). Survival after emergency medical services–treated OHCA was 10.6% in the 2019 CARES registry, with variation between states reporting data.

Subclinical Atherosclerosis (Chapter 19)

- Among 1585 participants free of CHD and free of MetS, those who were obese had a higher prevalence of coronary artery calcification than individuals with a normal weight, with a prevalence ratio of 1.59.
- A single-nucleotide-polymorphism genetic risk score for type 2 diabetes composed of 48 variants was associated with carotid plaque and atherosclerotic CVD events in ≈160 000 individuals, suggesting a causal role between genetic predisposition to type 2 diabetes and atherosclerotic CVD.
- In overweight and obese children 6 to 13 years of age, greater nut consumption was associated with lower carotid intima-media thickness (β=0.135 mm) when controlled for confounders.

Coronary Heart Disease, Acute Coronary Syndrome, and Angina Pectoris (Chapter 20)

- Data from the National Center for Health Statistics on trends in CHD death rates from 1999 to 2009 indicate disparities in the trends by rural-urban status. An overall 40% decline in the rate of CHD death was observed; however, the decline was greater in urban areas (large metropolitan: 42% decline; from 284 to 164 per 100 000 from 1999–2009; medium metropolitan: 40% decline; from 244 to 147 per 100 000) compared with rural areas (35% decline; from 266 to 173 per 100 000).
- According to the Centers for Medicare & Medicaid Services Hospital Inpatient Quality Reporting Program data on 2363 hospitals in 2018, the average 30-day mortality after acute myocardial infarction was 13.6%, with higher mortality observed in rural hospitals (from 13.4% to 13.8% for the most urban to most rural hospitals).
- The rapid increase in the population ≥65 years of age has resulted in a slowing of HD mortality. According to the Centers for Disease Control and Prevention WONDER (Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research) data from 2011 through 2017, a deceleration in the decline in HD mortality was observed with a <1% annualized decrease. The increase in the growth of the population ≥65 years of age, combined with the slowing of the decrease in HD mortality, resulted in an increase in the absolute number of HD deaths since 2011 (50 880 deaths; 8.5% total increase). However, the age-adjusted mortality for CHD continued to decline (2.7% annualized decrease) and the absolute number of CHD deaths declined (2.5% total decrease over the time period) between 2011 to 2017.
- Among 366 103 Medicare fee-for-service beneficiaries eligible for cardiac rehabilitation in 2016, only 24.4% participated in cardiac rehabilitation; among those who participated, the mean number of days to initiation was 47.0, and 26.9% completed cardiac rehabilitation with ≥36 sessions. Participation decreased with increasing age and was lower in females, Hispanic individuals, Asian individuals, those eligible for dual Medicare/Medicaid coverage, and those with ≥5 comorbidities.

Cardiomyopathy and Heart Failure (Chapter 21)

- The prevalence of HF continues to rise over time, with aging of the population. An estimated 6 million American adults ≥20 years of age had HF according to 2015 to 2018 data. Prevalence is higher in women than men ≥80 years of age; overall prevalence is especially high in both Black females and Black males.
- 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 is highly variable across the world, with the lowest in sub-Saharan Africa. Prevalence of HF risk factors also varies worldwide, with hypertension being most common in Latin America, the Caribbean, Eastern Europe, and sub-Saharan Africa. Ischemic HD is most prevalent in Europe and North America. Valvular HD is more common in East Asia and Asia-Pacific countries.

Valvular Diseases (Chapter 22)

- The incidence of valvular HD is 64 per 100 000 person-years, with aortic stenosis (47.2%), mitral regurgitation (24.2%), and aortic regurgitation (18.0%) contributing most of the valvular diagnoses.
- In 1950, ≈15 000 Americans died of rheumatic fever/rheumatic HD compared with ≈3400 annually in the present era. Recent declines in mortality have been slowest in the South compared with other regions.

Venous Thromboembolism (Deep Vein Thrombosis and Pulmonary Embolism), Chronic Venous Insufficiency, Pulmonary Hypertension (Chapter 23)

- In 2016, there were an estimated ≈1 220 000 total venous thromboembolism cases in the United States.
- According to 2018 data, ≈25 000 deaths (any mention) resulted from pulmonary hypertension.

- Hospitalized patients are at particularly high risk of venous thromboembolism; asymptomatic deep vein thrombosis was associated with 3-fold greater risk of death among acutely ill hospitalized patients.
- In the ARIC study (Atherosclerosis Risk in Communities), the presence of HF was associated with a 3-fold greater venous thromboembolism risk. The association was present for HF with both preserved and reduced ejection fraction.

Peripheral Artery Disease and Aortic Diseases (Chapter 24)

- The lifetime risk (80-year horizon) of peripheral arterial disease was estimated at ≈19%, 22%, and 30% in White, Hispanic, and Black individuals, respectively, from pooled data from 6 US community-based cohorts.
- A large-scale genome-wide association study in >31 000 peripheral artery disease cases and >211 000 controls from the Million Veterans Program and the UK Biobank identified 18 new peripheral arterial disease loci. Eleven of the loci were associated with disease in 3 vascular beds, including *LDLR*, *LPA*, and *LPL*, whereas 4 of the variants were specific for peripheral arterial disease (including variants in *TCF7L2* and *F5*).
- Patients with microvascular disease, defined as retinopathy, neuropathy, and nephropathy, were at increased risk for amputation (HR, 3.7), independently of traditional risk factors and prevalent peripheral arterial disease, among 135 674 patients in the Veterans Aging Cohort Study (enrollment 2003–2014).
- Between 1999 and 2016, deaths resulting from ruptured thoracic aortic aneurysm and abdominal aortic aneurysm declined significantly from 5.5 to 1.8 million and 26.3 to 7.9 per million, respectively, according to US National Vital Statistics data.

Quality of Care (Chapter 25)

- Among hospitals that care for Medicare fee-for-service beneficiaries, the implementation of hospital readmission reduction programs for acute myocardial infarction was associated with a reduction in 30-day postdischarge mortality.
- For HF, the Hospital Readmissions Reduction Program was associated with a reduction in 1-year risk adjusted readmission rate.
- Higher quality of care for OHCA is associated with an increase in adjusted survival to discharge and adjusted rates of favorable neurological outcome.

Medical Procedures (Chapter 26)

- Data from the Society of Thoracic Surgeons Congenital Heart Surgery Database indicate that a total of 123 777 congenital heart surgeries were performed from January 2015 to December 2018 and that delayed sternal closure was the most common primary procedure.
- In 2019, 3552 heart transplantations were performed in the United States, the most ever.

Economic Cost of Cardiovascular Disease (Chapter 27)

- The average annual direct and indirect cost of CVD in the United States was an estimated $363.4 billion in 2016 to 2017.
- The estimated direct costs of CVD increased from $103.5 billion in 1996 to 1997 to $216.0 billion in 2016 to 2017.
- By event type, hospital inpatient stays accounted for the highest direct cost ($96.2 billion) in 2016 to 2017.

Conclusions

The AHA, through its Statistics Committee, continuously monitors and evaluates sources of data on HD and stroke in the United States to provide the most current information available in the Statistical Update. The 2021 annual Statistical Update is the product of a full year's worth of effort by dedicated volunteer clinicians and scientists, committed government professionals, and AHA staff members, without whom publication of this valuable resource would be impossible. Their contributions are gratefully acknowledged.

Salim S. Virani, MD, PhD, FAHA, Chair
Connie W. Tsao, MD, MPH, Vice Chair
Sally S. Wong, PhD, RD, CDN, FAHA, AHA Science and Medicine Advisor
Debra G. Heard, PhD, AHA Consultant
On behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee

ARTICLE INFORMATION

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The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

A copy of the document is available at https://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the

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Disclosures

Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Salim S. Virani	Michael E. DeBakey VA Medical Center Health Services Research and Development Center for Innovations, Baylor College of Medicine	Department of Veterans Affairs†; World Heart Federation*; Tahir and Jooma Family†	None	None	None	None	None	None
Connie W. Tsao	Beth Israel Deaconess Medical Center	NIH†	None	None	None	None	None	None
Alvaro Alonso	Emory University	American Heart Association†; National Institutes of Health†	None	None	None	None	Corify Care*	None
Hugo J. Aparicio	Boston University	None	None	None	None	None	None	None
Emelia J. Benjamin	Boston University	NIH†; American Heart Association†; Samsung*	None	None	None	None	None	None
Marcio S. Bittencourt	University Hospital, University of São Paulo, (Brazil)	Sanofi*	None	EMS*; GE HealthCare*; Novo Nordisk*	None	None	None	None
Clifton W. Callaway	University of Pittsburgh	NIH (grants to study emergency care)†	None	None	None	None	None	None
April P. Carson	University of Alabama at Birmingham	Centers for Disease Control and Prevention†; National Institutes of Health†; Amgen, Inc†	None	None	None	None	None	None
Alanna M. Chamberlain	Mayo Clinic	NIH†; EpidStrategies†	None	None	None	None	None	None
Susan Cheng	Cedars-Sinai Medical Center	NIH†	None	None	None	None	Zogenix†	None
Francesca N. Delling	University of California, San Francisco	NHLBI*	None	None	None	None	None	None
Mitchell S.V. Elkind	Columbia University Neurological Institute	BMS-Pfizer Alliance for Eliquis†; Roche†	None	None	None	None	None	None
Kelly R. Evenson	University of North Carolina	NIH†; RWJF*; CDC*; US DOT†	None	None	None	None	None	None
Jane F. Ferguson	Vanderbilt University	None	None	None	None	None	None	None
Deepak K. Gupta	Vanderbilt University	NHLBI (PI of K23, PI of R01, PI of R01, co-I of 4 R01s)†; Imara*	None	None	None	None	Imara*	None

(*Continued*)

Writing Group Disclosures Continued

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Sadiya S. Khan	Northwestern University	American Heart Association†	None	None	None	None	None	None
Brett M. Kissela	University of Cincinnati	NIH†	None	None	None	None	None	None
Kristen L. Knutson	Northwestern University	NIH†	None	None	None	None	Sleep Research Society/SRS Foundation†	None
Chong D. Lee	Arizona State University	Arizona State University/ Global Sports Institute*; Dignity Health/Arizona State University*; US Department of Veterans Affairs*; NIH R-21 (AG050084)*	None	None	None	None	None	None
Tené T. Lewis	Emory University	NIH†	None	None	None	None	None	None
Junxiu Liu	Icahn School of Medicine, Mount Sinai‡	None	None	None	None	None	None	None
Matthew Shane Loop	University of North Carolina at Chapel Hill	NHLBI†	None	None	None	None	None	None
Pamela L. Lutsey	University of Minnesota	None	None	None	None	None	None	None
Jun Ma	University of Illinois at Chicago	NIH†; AHRQ†; PCORI†; VHS†	None	None	None	None	Health Mentor, Inc*	None
Jason Mackey	Indiana University	NIH (NINDS NS30678)†; (IUSM/ IUH SRI UL1TR001108 [Shekhar])†; PCORI (BEST-MSU [Grotta])†	None	None	None	None	None	None
Seth S. Martin	Johns Hopkins University	None	None	None	None	None	None	None
David B. Matchar	Duke-NUS Medical School Health Services and Systems Research	None	None	None	None	None	None	None
Michael E. Mussolino	NIH/NHLBI	None	None	None	None	None	None	None
Sankar D. Navaneethan	Baylor College of Medicine	Keryx†	None	None	None	None	Tricida*; Bayer*; Boehringer Ingelheim†; REATA*	None
Amanda Marma Perak	Lurie Children's Hospital, Northwestern University	NHLBI†	None	None	None	None	None	None
Gregory A. Roth	University of Washington	NIH†; Cardiovascular Medical Research and Education Fund†	None	None	None	None	None	None
Zainab Samad	Duke University	None	None	None	None	None	None	None
Gary M. Satou	UCLA	None	None	None	None	None	None	None
Emily B. Schroeder	Parkview Health	Garfield Foundation*; NHLBI*; American Heart Association†; NIDDK†	None	None	None	None	None	None

(*Continued*)

Writing Group Disclosures Continued

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Svati H. Shah	Duke University	None	None	None	None	Unlicensed patent held by Duke University*	None	American Heart Association Board of Directors*
Christina M. Shay	American Heart Association	None	None	None	None	None	None	None
Andrew Stokes	Boston University	Johnson & Johnson, Inc†	None	None	None	None	None	None
Lisa B. VanWagner	Northwestern University	W.L. Gore & Associates*	American Society for Transplantation*; American Association for the Study of Liver Disease*	Salix Pharmaceuticals*; W.L. Gore & Associates*	Wilson Kehoe Winingham LLC*; Smith Haughey Rice & Roegge*; Hamilton Law Firm*	None	W.L. Gore & Associates*	None
Nae-Yuh Wang	The Johns Hopkins Medical Institutions	NIH†; NIH†	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

‡During development of the 2021 Statistical Update, Dr Liu was employed by the Friedman School of Nutrition Science & Policy, Tufts University.

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1. ABOUT THESE STATISTICS

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The AHA works with the NHLBI 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 29 of this document, the Glossary.

The surveys and data sources used are the following:

- ACC NCDR's Chest Pain–MI Registry (formerly the ACTION Registry)—quality information for AMI
- ARIC—CHD and HF incidence rates
- BRFSS—ongoing telephone health survey system

Abbreviations Used in Chapter 1

ACC	American College of Cardiology
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
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CVD	cardiovascular disease
ED	emergency department
FHS	Framingham Heart Study
GBD	Global Burden of Disease Study
GCNKSS	Greater Cincinnati/Northern Kentucky Stroke Study
GWTG	Get With The Guidelines
HALE	healthy life expectancy
HBP	high blood pressure
HCUP	Healthcare Cost and Utilization Project

(*Continued*)

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Abbreviations Used in Chapter 1 Continued

HDL-C	high-density lipoprotein cholesterol
HF	heart failure
ICD	*International Classification of Diseases*
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
ICD-10-CM	*International Classification of Diseases, 10th Revision, Clinical Modification*
LDL-C	*low-density lipoprotein cholesterol*
MEPS	Medical Expenditure Panel Survey
MI	myocardial infarction
NAMCS	National Ambulatory Medical Care Survey
NCDR	National Cardiovascular Data Registry
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
NVSS	National Vital Statistics System
NYTS	National Youth Tobacco Survey
TC	total cholesterol
USRDS	United States Renal Data System
WHO	World Health Organization
YLD	years lived with disability and injury
YLL	years of life lost
YRBSS	Youth Risk Behavior Surveillance System

- GBD—global disease prevalence, mortality, YLL, and YLD
- GCNKSS—stroke incidence rates and outcomes within a biracial population
- GWTG—quality information for resuscitation, HF, and stroke
- HCUP—hospital inpatient discharges and procedures
- 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
- NAMCS—physician office visits
- NHAMCS—hospital outpatient and ED visits
- NHANES—disease and risk factor prevalence and nutrition statistics
- NHIS—disease and risk factor prevalence
- NVSS—mortality for United States
- USRDS—kidney disease prevalence
- WHO—mortality rates by country
- YRBSS—health-risk behaviors in youth and young adults

Disease Prevalence

Prevalence is an estimate of how many people have a condition at a given point or period in time. The CDC/NCHS

conducts health examination and health interview surveys that provide estimates of the prevalence of diseases and risk factors. In this Statistical 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 from data collected from 2015 to 2018. These are applied to census population estimates for 2018. 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 be evaluated only by comparing prevalence rates estimated from surveys conducted in different years.

In the 2021 Statistical Update, there is an emphasis on social determinants of health that are built across the various chapters, and global estimates are provided when available.

Risk Factor Prevalence

The NHANES 2013 to 2016 data are used in this Statistical Update to present estimates of the percentage of people with high LDL-C and diabetes. NHANES 2015 to 2018 data are used to present estimates of the percentage of people with overweight, obesity, and high TC and HDL-C. BRFSS 2018 data are used for the prevalence of sleep issues. NHIS 2018, BRFSS 2017 and 2018, and NYTS 2018 data are used for the prevalence of cigarette smoking. The prevalence of physical inactivity is obtained from 2017 YRBSS and 2017 and 2018 NHIS.

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 2018 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 Statistical Update includes the number of deaths for which the disease is the underlying cause. Two exceptions are Chapter 8 (High Blood Pressure) and Chapter 21 (Cardiomyopathy and Heart Failure). HBP, 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 Statistical 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 obtained from the CDC WONDER website or the CDC NVSS mortality file.[1] Any-mention numbers of deaths were tabulated from the CDC WONDER website or CDC NVSS mortality file.[2]

Population Estimates

In this publication, we have used national population estimates from the US Census Bureau for 2018[3] in the computation of morbidity data. CDC/NCHS population estimates[4] for 2018 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 principal (first-listed) diagnosis, and

procedures are listed according to all-listed procedures (principal and secondary). These estimates are from the 2016 HCUP.[5] Ambulatory care visit data include patient visits to primary providers' offices and hospital outpatient departments and EDs. Ambulatory care visit data reflect the primary (first-listed) diagnosis. These estimates are from the 2016 NAMCS[6] and 2016 NHAMCS[7] of the CDC/NCHS. Data for community health centers are included in 2016 NAMCS estimates. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from *ICD-9* to *ICD-10*. This should be kept in mind because coding changes could affect some statistics, especially when comparisons are made across these years.

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 CDC/NCHS are applied as noted.[8] Effective with mortality data for 1999, *ICD-10* is used.[9] Beginning in 2016, *ICD-10-CM* is used for hospital inpatient stays and ambulatory care visit data.[10]

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.[11] International mortality data are age adjusted to the European standard population. 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 Statistical 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 2018. For disease and risk factor prevalence, most rates in this report are calculated from the 2015 to 2018 NHANES. Because NHANES is conducted only in the noninstitutionalized population, we extrapolated the rates to the total US resident population on July 1, 2018, 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 2016. Numbers of visits to primary providers' offices and hospital EDs are for 2016, whereas hospital outpatient department visits are for 2011. Except as noted, economic cost estimates are for 2016 to 2017.

Cardiovascular Disease

For data on hospitalizations, primary provider office visits, and mortality, total CVD is defined according to *ICD* codes given in Chapter 14 of the present document. This definition includes all diseases of the circulatory system. Unless otherwise specified, estimates for total CVD do not include congenital CVD. Prevalence of total CVD includes people with hypertension, CHD, stroke, and HF.

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.

Global Burden of Disease

The GBD study is an ongoing global effort to measure death and disability attributable to diseases, injuries, and risk factors for all countries from 1990 to the present day. The study seeks to produce consistent and comparable estimates of population health over time and across locations, including summary metrics such as disability-adjusted life years and HALE. Results are made available to policy makers, researchers, governments, and the public with the overarching goals of improving population health and reducing health disparities.

GBD 2019, the study's most recent iteration, was produced by the collective efforts of >5000 researchers in >150 countries. Estimates were produced for 369 diseases and injuries and 87 risk factors. Detailed methods and results can be found via the study's online data visualization tools and across a range of peer-reviewed scientific research articles that can be found cited in this publication.

During each annual cycle of the GBD study, population health estimates are reproduced for the full-time series. For GBD 2019, estimates were produced for 1990 to 2019 for 204 countries and territories, stratified by age and sex, with subnational estimates made available for an increasing number of countries. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in

results across GBD study cycles for both the most recent and earlier years.

For more information about the GBD and to access GBD 2019 resources, data visualizations, and most recent publications, please visit the study's website.[12–14]

Contacts

If you have questions about statistics or any points made in this Statistical Update, please contact the AHA National Center, Office of Science, Medicine and Health. 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 Statistical 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*.

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2. CARDIOVASCULAR HEALTH

See Tables 2-1 through 2-10 and Charts 2-1 through 2-5

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In 2010, the AHA released an Impact Goal that included 2 objectives that would guide organizational priorities over the next decade: "By 2020, to improve the cardiovascular health of all Americans by 20%, while reducing deaths from CVDs and stroke by 20%."[1]

The concept of CVH was introduced in this goal and characterized by 7 components (Life's Simple 7)[2] that include health behaviors (diet quality, PA, smoking) and health factors (blood cholesterol, BMI, BP, blood glucose). For an individual to have ideal CVH overall, they must have an absence of clinically manifest CVD and the simultaneous presence of optimal levels of all 7 CVH components, including abstinence from smoking, a healthy diet pattern, sufficient PA, normal body weight, and normal levels of TC, BP, and FPG (in the absence of medication treatment; Table 2-1). Because ideal CVH is rare, the distribution of the 7 CVH components is also described with the use of the categories poor, intermediate, and ideal.[1] Table 2-1 provides the specific definitions for these categories for each CVH component in both adults and youth.

From 2011 to 2020, this chapter in the annual Statistical Update has published national prevalence estimates for CVH to inform progress toward improvements in the prevalence of CVH. This year, updates to this chapter include prevalence estimates for components of CVH for which newly released NHANES data from 2017 to 2018 were available. New additions this year also include 10-year differences in the leading causes and risk factors for YLDs and YLLs, which

Abbreviations Used in Chapter 2

AF	atrial fibrillation
AHA	American Heart Association
AIDS	autoimmune deficiency syndrome
BMI	body mass index
BP	blood pressure
CAC	coronary artery calcification
CI	confidence interval
CKD	chronic kidney disease
CVD	cardiovascular disease
CVH	cardiovascular health
DALY	disability-adjusted life-year
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
ESRD	end-stage renal disease
F&V	fruits and vegetables
FPG	fasting plasma glucose
GBD	Global Burden of Disease Study
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)

(*Continued*)

Abbreviations Used in Chapter 2 Continued

HBP	high blood pressure
HD	heart disease
HF	heart failure
HIV	human immunodeficiency virus
HR	hazard ratio
ICH	intracerebral hemorrhage
IHD	ischemic heart disease
IMT	intima-media thickness
LDL	low-density lipoprotein
MA	Mexican American
MI	myocardial infarction
NA	not available
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHB	non-Hispanic Black
NHW	non-Hispanic White
PA	physical activity
PAF	population attributable fraction
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
svg	Servings
TC	total cholesterol
UI	uncertainty interval
VTE	venous thromboembolism
YLD	years lived with disability and injury
YLL	years of life lost

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highlight the influence of the components of CVH on premature death and disability in populations.

Relevance of Ideal CVH

- Multiple independent investigations (summaries of which are provided in this chapter) have confirmed the importance of having ideal levels of these components, along with the overall concept of CVH. Findings include strong inverse, stepwise associations in the United States of the number of CVH components at ideal levels with all-cause mortality, CVD mortality, IHD mortality, CVD, and HF; with subclinical measures of atherosclerosis such as carotid IMT, arterial stiffness, and CAC prevalence and progression; with physical functional impairment and frailty; with cognitive decline and depression; and with longevity.[6–12] Similar relationships have also been seen in non-US populations.[6,7,13–23]
- A large Hispanic/Latino cohort study in the United States confirmed the associations between CVD and status of CVH components in this population and found that the levels of CVH components compared favorably with existing national estimates; however, some of the associations varied by sex and heritage.[7]
- A study of Black people found that risk of incident HF was 61% lower among those with ≥4 ideal CVH components than among those with 0 to 2 ideal components.[8]
- Ideal health behaviors and ideal health factors are each independently associated with lower CVD risk in a stepwise fashion; across any level of health behaviors, health factors are associated with incident CVD, and conversely, across any level of health factors, health behaviors are associated with incident CVD.[24]
- Analyses from the US Burden of Disease Collaborators demonstrated that poor levels of each of the 7 CVH components resulted in substantial mortality and morbidity in the United States in 2010. The leading risk factor related to overall disease burden was suboptimal diet, followed by tobacco smoking, high BMI, raised BP, high FPG, and physical inactivity.[25]
- A meta-analysis of 9 prospective cohort studies involving 12 878 participants reported that having the highest number of ideal CVH components 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]) compared with individuals with the lowest number of ideal components.[26]
- The adjusted PAFs for CVD mortality for individual components of CVH have been reported as follows[27]:
  - 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
- Several studies have been published in which investigators have assigned individuals a CVH score ranging from 0 to 14 on the basis of the sum of points assigned to each component of CVH (poor=0, intermediate=1, ideal=2 points). With this approach, data from the REGARDS cohort were used to demonstrate an inverse stepwise association between a higher CVH score component and lower incidence of stroke. On the basis of this score, every unit increase in CVH 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.[28]
- The Cardiovascular Lifetime Risk Pooling Project showed that adults with all optimal risk factor levels (similar to having ideal CVH 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 CVH factors. 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.[29]
- Better CVH as defined by the AHA is associated with lower incidence of HF,[6,8,9,11,19] less subclinical vascular disease,[12,17,20,30,31] better global cognitive performance and cognitive function,[18,32,33] lower hazard of subsequent dementia,[34] lower prevalence[10] and incidence[35] of depressive symptoms, lower loss of physical functional status,[36] longer leukocyte telomere length,[37] less ESRD,[38] less pneumonia, less chronic obstructive pulmonary disease,[39] less VTE/PE,[40] lower prevalence of aortic sclerosis and stenosis,[41] lower risk of calcific aortic valve stenosis,[42] better prognosis after MI,[43] lower risk of AF,[44] and lower odds of having elevated resting heart rate.[45] In addition, a study among a sample of Hispanic/Latino people residing in the United States reported that greater positive psychological functioning (dispositional optimism) was associated with higher CVH scores as defined by the AHA.[46] A study in college students found that both handgrip strength and muscle mass are positively associated with greater numbers of ideal CVH components,[47] and a cross-sectional study found that greater cardiopulmonary fitness, upper-body flexibility, and lower-body muscular strength

are associated with better CVH components in perimenopausal females.[48] Furthermore, studies demonstrate that higher quality of life scores are associated with better CVH metrics,[49] providing additional evidence to support the benefits of ideal CVH on general health and quality of life.

- According to 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 CVH as measured by Life's Simple 7 scores.[50] In addition, neighborhood factors and contextual relationships have been found to be related to health disparities in CVH, but more research is needed to better understand these complex relationships.[51] Having more ideal CVH components in middle age is also associated with lower non-CVD and CVD health care costs in later life.[52] An investigation of 4906 participants in the Cooper Center Longitudinal Study reported that participants with ≥5 ideal CVH components exhibited 24.9% (95% CI, 11.7%–36.0%) lower median annual non-CVD costs and 74.5% (95% CI, 57.5%–84.7%) lower median CVD costs than those with ≤2 ideal CVH components.[52]
- A report from a large, ethnically diverse insured population found that people with 6 or 7 and those with 3 to 5 of the CVH components in the ideal category had a $2021 and $940 lower annual mean health care expenditure, respectively, than those with 0 to 2 ideal health components.[53]

CVH: Prevalence (NHANES 2015–2016 and 2017–2018) (See Table 2-2 and Charts 2-1 through 2-3)

- The national prevalence estimates for children (12–19 years of age) and adults (≥20 years of age) who meet ideal, intermediate, and poor levels of each of the 7 CVH components are displayed in Chart 2-1.[54] The most current estimates at time of publication were based on data from NHANES 2017 to 2018 for smoking, BMI, PA (for adults), TC, and BP and data from NHANES 2015 to 2016 for PA (for children), diet, and diabetes status. NHANES 2017 to 2018 survey changed the PA assessments for children, so the PA status for children was updated through 2016 only.
- For most components of CVH, prevalence of ideal levels is higher in US children (12–19 years of age) than in US adults (≥20 years of age), except for the Healthy Diet Score and PA, for which prevalence of ideal levels in children is lower than in adults.
- Among US children (12–19 years of age; Chart 2-1), the unadjusted prevalence of ideal levels of CVH components currently varies from <1% for the Healthy Diet Score (ie, <1 in 100 US children meets at least 4 of the 5 dietary components) to >86% for smoking, BP, and diabetes components (unpublished AHA tabulation).
- Among US adults (Chart 2-1), the lowest prevalence of ideal levels for CVH components is <1% for the Healthy Diet Score in adults ≥20 years of age. The highest prevalence of ideal levels for a CVH component is for smoking (79.8% of adults report never having smoked or being a former smoker who has quit for >12 months). In 2017 to 2018, 52.4% of adults had ideal levels of TC (<200 mg/dL).
- Age-standardized and age-specific prevalence estimates for ideal CVH and for ideal levels of individual CVH components for 2015 to 2016 and 2017 to 2018 are displayed in Table 2-2.
- In 2015 to 2018, all individual components of CVH among adults were highest in the youngest age groups (20–39 years of age) and were lowest in the oldest age group (≥60 years of age), except the Healthy Diet Score, for which prevalence of ideal levels was highest in older adults but still <1% according to the 2015 to 2016 NHANES data.
- Chart 2-2 displays the unadjusted prevalence estimates of ideal levels of CVH components for the population of US children (12–19 years of age) by race/ethnicity.
  - Majority of US children 12 to 19 years of age met ideal criteria for smoking (93.4%–97.4%), BP (80.1%–89.6%), and TC (73.4%–80.0%) in 2017 to 2018 across race/ethnicity subgroups.
  - Majority of US children 12 to 19 years of age met ideal criteria for diabetes (73.6%–88.0%) in 2015 to 2016 across race/ethnicity groups.
  - Of US children 12 to 19 years of age, 46.8% to 76.2% met ideal criteria for BMI in 2017 to 2018, whereas only 23.8% to 27.8% of US children met ideal criteria for PA in 2015 to 2016 across race/ethnicity categories.
  - Few US children 12 to 19 years of age (<1%) met ideal criteria for Healthy Diet Score in 2015 to 2016 across all race/ethnicity groups.
- Chart 2-3 displays the unadjusted prevalence estimates of ideal levels of CVH components for the population of US adults ≥20 years of age by race/ethnicity.
  - Majority of US adults ≥20 years of age met ideal criteria for smoking (75.9%–90.4%) in 2017 to 2018 across race/ethnicity subgroups.
  - Fewer than a quarter to a little more than half of US adults ≥20 years of age met ideal criteria for BMI (15.2%–50.5%), TC (49.8%–57.7%), PA (30.4%–42.7%), and BP (31.5%–44.4%) in 2017 to 2018 across race/ethnicity groups.

- Of US adults ≥20 years of age, 42.0% to 59.7% met ideal criteria for diabetes in 2015 to 2016 across race/ethnicity categories.
- Few US adults ≥20 years of age (0.1%–1.6%) met ideal criteria for Healthy Diet Score in 2015 to 2016 across all race/ethnicity groups.

CVH: Trends Over Time (See Charts 2-4 and 2-5)

- The trends in prevalence of meeting ideal criteria for the individual components of CVH from 1999 to 2000 to 2017 to 2018 (for diet, trends from 2003–2004 through 2015–2016) are shown in Chart 2-4 for children (12–19 years of age) and in Chart 2-5 for adults (≥20 years of age).
  - Among children 12 to 19 years of age from 1999 to 2000 to 2017 to 2018, the prevalence of meeting ideal criteria for smoking and BP has consistently improved, increasing from 76.4% to 95.7% for nonsmoking and from 83.6% to 89.1% for ideal BP. For ideal TC, the prevalence increased from 72.0% to 77.2%. However, a decline in prevalence of ideal levels was observed for BMI, from 69.8% in 1999 to 2000 to 60.1% in 2015 to 2016, although it rebounded slightly to 63.3% in 2017 to 2018.
  - From 1999 to 2000 to 2015 to 2016, declines in prevalence of ideal levels were observed for PA (38.4% to 25.4%) and diabetes (92.4% to 86.2%) among children.
  - Among adults, from 1999 to 2000 to 2017 to 2018, the prevalence of meeting ideal criteria for smoking, TC, and BP increased. For example, the prevalence of being a never smoker or having quit ≥1 year prior increased from 72.9% to 79.8%. Over the 18-year period, the prevalence of meeting criteria for ideal TC increased from 45.1% to 52.4%. However, declines in prevalence of ideal levels were observed for PA (from 40.2% to 38.3%) and BMI (from 36.3% to 26.4%) among adults during this period.
  - Similar to trends observed in children, a decline in prevalence of ideal levels was observed for diabetes among adults, from 69.1% in 1999 to 2000 to 58.4% in 2015 to 2016.

Trends in Risk Factors and Causes for YLL and YLD in the United States: 1990 to 2019 (See Tables 2-3 through 2-6)

- The leading risk factors for YLLs from 1990 to 2019 in the United States are presented in Table 2-3.
  - Smoking and high SBP remained the first and second leading YLL risk factors in both 1990 and 2019. Age-standardized rates of YLL attributable to smoking declined by 46.4%, whereas age-standardized rates attributable to high SBP declined 45.8%.
  - From 1990 to 2019, YLLs caused by drug use rose from 18th to 5th leading YLL risk factor with a 242.3% increase in the age-standardized YLL rate.
- The leading causes of YLLs from 1990 to 2019 in the United States are presented in Table 2-4.
  - IHD and tracheal, bronchus, and lung cancer were the first and second leading YLL causes in both 1990 and 2019. Age-standardized YLL rates attributable to IHD declined 50.9%, whereas age-standardized YLL rates resulting from tracheal, bronchus, and lung cancer declined 36.1%.
  - From 1990 to 2019, opioid use disorders rose from 46th to 4th leading YLL cause with a 799.2% increase in the age-standardized YLL rate. Type 2 diabetes also rose from 12th to 6th leading YLL cause, whereas Alzheimer disease and other dementias also rose from 15th to 7th leading YLL cause.
  - The leading risk factors for YLDs from 1990 to 2019 in the United States are presented in Table 2-5.
  - High BMI, high FPG, and smoking are among the first, second, and third leading YLD risk factors in both 1990 and 2019, with high BMI and high FPG rising in ranking while smoking dropped from the first to third leading YLD risk factor during this time period. Age-standardized YLD rates attributable to smoking declined by 25.8%, while age-standardized rates attributable to high BMI and high FPG increased by 44.4% and 47.4%, respectively, between 1990 and 2019.
- The leading causes of YLDs from 1990 to 2019 in the United States are presented in Table 2-6.
  - Low back pain and other musculoskeletal disorders were the first and second leading causes of YLDs in both 1990 and 2019. The age-standardized rates of YLD attributable to low back pain decreased 12.5%, whereas age-standardized YLD rates for other musculoskeletal disorders increased 44.2%.
  - From 1990 to 2019, type 2 diabetes rose from the ninth to third leading YLD cause with a 55.8% increase in the age-standardized YLD rates.
  - Opioid use disorders rose from 16th to 4th leading YLD cause between 1990 and 2019 with a 288.7% increase in age-standardized rates of YLD.

Trends in Global Risk Factors and Causes for YLL and YLD: 1990 to 2019 (See Tables 2-7 through 2-11)

- The leading global YLL risk factors from 1990 to 2019 are presented in Table 2-7.
  - High SBP and smoking were the first and second leading YLL risk factors globally in 2019. Age-standardized YLL rates attributable to HBP and smoking declined 29.0% and 41.3%, respectively, between 1990 and 2019.
  - From 1990 to 2019, high FPG rose from 14th to 5th leading risk factor of global YLLs with a 1.5% decrease in the age-standardized YLL rates over this period.
- The leading global YLL causes from 1990 to 2019 are presented in Table 2-8.
  - IHD rose from the third to first leading global YLL cause between 1990 and 2019, whereas age-standardized YLL rates declined by 29.1% during this period. This shift resulted in lower respiratory infections moving from first to second leading cause, and age-standardized YLL rates declined 62.7%.
  - ICH and ischemic stroke rose from 9th to 4th and from 13th to 8th leading cause of global YLL, respectively, between 1990 and 2019.
  - Type 2 diabetes also rose from 28th to 14th leading global YLL cause, showing a 9.1% increase in age-standardized YLL rate.
- The leading global risk factors for YLDs from 1990 to 2019 are presented in Table 2-9.
  - High FPG and high BMI were the first and second leading YLD risk factors globally in 2019, replacing iron deficiency and smoking, which ranked fourth and third, respectively, in 2019. Age-standardized YLD rates attributable to high FPG and high BMI increased 44.1% and 60.2%, respectively, whereas age-standardized global YLD rates attributable to smoking and iron deficiency deceased 22.9% and 16.7%, respectively.
  - Ambient particulate matter pollution rose from 17th to 8th leading global risk factor for YLD, resulting in a 64.9% increase in the age-standardized global YLD rates.
- The leading global causes of YLDs from 1990 to 2019 are presented in Table 2-10.
  - Low back pain and migraine were the first and second leading global causes of YLDs in both 1990 and 2019. The age-standardized rates of YLD attributable to low back pain decreased 16.3%, whereas rates for migraine increased 1.5% across the same time period.
  - From 1990 to 2019, type 2 diabetes rose from 10th to 6th leading global cause of YLD during this time period, with a 50.2% increase in the age-standardized global YLD rate.

Furthering the AHA's Impact Through Continued Efforts to Improve CVH (See Tables 2-3 through 2-6)

- Renewed efforts to maintain and improve CVH will be foundational to successful reductions in mortality and disability in the United States and globally. Individuals with more favorable levels of CVH have significantly lower risk for several of the leading causes of death, including IHD,[24] Alzheimer disease,[55] stroke,[56,57] CKD,[58] diabetes,[59,60] breast cancer,[61,62] and atrial fibrillation (Tables 2-3 and 2-4). In addition, 6 of the 10 leading US risk factors for YLL and 4 of the 10 leading risk factors for YLD in 2019 were also components of CVH (Tables 2-3 and 2-5). Taken together, these data demonstrate the tremendous importance of continued efforts to improve CVH.
- The expanding efforts of the AHA and American Stroke Association in areas of brain health are also well poised to drive toward improvement in several leading causes of death and disability that influence YLLs and YLDs, including stroke, Alzheimer disease, depression and anxiety disorders, and alcohol and substance use disorders.
- Despite improvements observed in CVH and brain health over the past decade, further progress is needed to more fully realize these benefits for all Americans. Details are described in the AHA presidential advisory on brain health.[63]

Global Efforts to Improve CVH (See Tables 2-7 through 2-10)

- Renewal of efforts to improve CVH is a continuing challenge that requires collaboration throughout the global community in ways that aim targeted skills and resources at improving the top causes and risk factors for death and disability in countries. Such efforts are required in countries at all income levels with an emphasis on efforts to halt the continued worsening of the components of CVH (Tables 2-7 through 2-10).
- Many challenges exist related to implementation of prevention and treatment programs in international settings; some challenges are unique to individual countries/cultures, whereas others are universal. Partnerships and collaborations with local, national, regional, and global partners are foundational to effectively addressing relevant national health priorities in ways that facilitate contextualization within individual countries and cultures.

Table 2-1. Definitions of Poor, Intermediate, and Ideal for Each Component of CVH

	Level of CVH 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/m^2	25–29.9 kg/m^2	<25 kg/m^2
Children 2–19 y of age	>95th percentile	85th–95th percentile	<85th percentile
PA			
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 score, No. of components‡			
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)
TC, 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
BP			
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
Diabetes§			
Adults ≥20 y of age	FPG ≥126 mg/dL or HbA_{1c} ≥6.5%	FPG 100–125 mg/dL or HbA_{1c} 5.7%–6.4% or treated to goal	FPG <100 mg/dL or HbA_{1c} <5.7%
Children 12–19 y of age	FPG ≥126 mg/dL or HbA_{1c} ≥6.5%	FPG 100–125 mg/dL or HbA_{1c} 5.7%–6.4% or treated to goal	FPG <100 mg/dL or HbA_{1c} <5.7%

BMI indicates body mass index; BP, blood pressure; CVH, cardiovascular health; DBP, diastolic blood pressure; ellipses (…), data not available; FPG, fasting plasma glucose; HbA_{1c}, glycosylated hemoglobin or hemoglobin A_{1c}; PA, physical activity; SBP, systolic blood pressure; and TC, total cholesterol.

*Age ranges in children for each metric depend on guidelines and data availability.

†Represents appropriate energy balance; that is, appropriate dietary quantity and PA to maintain normal body weight.

‡In the context of a healthy dietary pattern that is consistent with a DASH (Dietary Approaches to Stop Hypertension)–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 also be described with a continuous American Heart Association diet score, scaled from 0 to 100 (see Chapter 5, Nutrition).

§FPG is solely used to determine poor, intermediate, and ideal status for American Heart Association Strategic Impact Goal monitoring purposes. For population surveillance purposes, use of HbA_{1c} was added to define poor, intermediate, and ideal levels of this component, and the name was changed to diabetes to reflect this addition.

Source: Modified from Lloyd-Jones et al.[1] Copyright © 2010, American Heart Association, Inc.

Table 2-2. Prevalence of Ideal CVH and Its Components in the US Population in Selected Age Strata: NHANES 2015 to 2016 and 2017 to 2018

	NHANES years	Age 12–19 y	Age ≥20 y*	Age 20–39 y	Age 40–59 y	Age ≥60 y
Ideal CVH factors						
TC	2017–2018	77.2 (1.7)	52.4 (1.5)	74.0 (1.8)	44.8 (2.6)	25.5 (1.5)
BP	2017–2018	89.1 (1.3)	40.8 (1.4)	61.6 (1.9)	34.0 (2.4)	15.1 (1.3)
Diabetes	2015–2016	86.2 (1.4)	58.4 (1.4)	79.3 (1.1)	51.2 (2.5)	32.4 (1.6)
Ideal health behaviors						
PA	2017–2018	NA	38.3 (1.7)	48.4 (2.3)	33.9 (2.2)	29.3 (2.6)
Smoking	2017–2018	95.7 (1.1)	79.8 (1.3)	74.3 (2.2)	80.1 (1.7)	87.8 (1.0)
BMI	2017–2018	63.4 (1.8)	26.4 (1.3)	33.6 (2.1)	22.7 (2.0)	21.9 (1.1)
4 or 5 Healthy diet goals met†	2015–2016	0.0 (0.0)	0.3 (0.1)	0.1 (0.1)	0.1 (0.1)	0.7 (0.3)
F&V ≥4.5 cups/d	2015–2016	3.7 (0.9)	10.2 (0.6)	7.8 (0.9)	11.1 (1.4)	13.8 (1.1)
Fish ≥2 svg/wk	2015–2016	7.6 (1.0)	18.0 (1.7)	15.9 (2.5)	19.3 (2.3)	18.7 (1.6)
Sodium <1500 mg/d	2015–2016	0.6 (0.3)	0.7 (0.2)	0.8 (0.3)	0.9 (0.4)	0.2 (0.1)
SSB <450 kcal/wk	2015–2016	40.4 (2.6)	53.3 (1.7)	47.7 (2.9)	51.6 (2.3)	66.5 (2.7)
Whole grains ≥3 one-ounce svg/d	2015–2016	6.8 (0.8)	7.1 (0.6)	5.9 (1.2)	6.5 (0.9)	9.5 (1.1)
Secondary diet metrics						
Nuts/legumes/seeds ≥4 svg/wk	2015–2016	36.7 (2.4)	52.4 (1.7)	48.9 (3.0)	54.9 (2.3)	54.1 (1.8)
Processed meats ≤2 svg/wk	2015–2016	39.2 (2.8)	44.0 (0.9)	45.4 (1.1)	44.0 (1.7)	41.9 (2.6)
SFat <7% total kcal	2015–2016	4.5 (1.0)	8.4 (0.5)	8.8 (1.1)	8.9 (0.7)	6.8 (0.9)

Values are percent (standard error).

BMI indicates body mass index; BP, blood pressure; CVH, cardiovascular health; F&V, fruits and vegetables; NA, not available; NHANES, National Health and Nutrition Examination Survey; PA, physical activity; SFat, saturated fat; SSB, sugar-sweetened beverage; svg, servings; and TC, total cholesterol.

*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.

Source: Unpublished American Heart Association tabulation using NHANES 2015 to 2016 and 2017 to 2018.[54]

Table 2-3. The Leading 20 Risk Factors of YLL and Death in the United States: Rank, Number, and Percentage Change, 1990 and 2019

Risk factors for disability	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change, 1990–2019 (95% UI)		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change, 1990–2019 (95% UI)	
	1990	2019	1990	2019	Total No. of YLLs	Age-standardized YLL rate	1990	2019	Total No. of deaths	Age-standardized death rate
Smoking	1	1	11 005.06 (10 692.42 to 11 351.22)	10 371.03 (10,017.19 to 10 728.28)	−5.76% (−8.46% to −2.93%)	−46.43% (−47.91% to −44.85%)	515.41 (496.77 to 537.03)	527.74 (505.55 to 550.83)	2.39% (−1.3% to 6.28%)	−42.21% (−44.18% to −40.15%)
High SBP	2	2	8466.11 (7465.95 to 9424.27)	7815.63 (6814.38 to 8821.87)	−7.68% (−13.09% to −2.58%)	−45.76% (−48.82% to −42.81%)	503.63 (425.60 to 573.56)	495.20 (407.47 to 574.65)	−1.67% (−9.73% to 6.05%)	−45.94% (−49.57% to −42.07%)
High BMI	4	3	4994.23 (3131.76 to 6877.86)	7778.57 (5416.09 to 9912.24)	55.75% (41.31% to 80.47%)	−9.18% (−17.75% to 5.86%)	232.16 (138.00 to 334.08)	393.86 (257.61 to 528.44)	69.65% (52.54% to 98.96%)	−5.82% (−15.3% to 10%)
High FPG	5	4	4664.81 (3563.73 to 6006.04)	7121.62 (5548.50 to 9006.14)	52.67% (37.87% to 68%)	−12.25% (−20.59% to −3.79%)	263.41 (193.27 to 355.67)	439.38 (320.11 to 582.66)	66.81% (48.24% to 85.48%)	−8.01% (−17.9% to 2.09%)
Drug use	18	5	999.47 (899.54 to 1135.28)	4265.41 (4080.78 to 4494.41)	326.77% (277.64% to 372.57%)	242.34% (202.34% to 280.43%)	24.76 (22.26 to 27.73)	104.74 (100.39 to 109.98)	323.09% (280.5% to 364.71%)	214.02% (181.7% to 245.57%)
Alcohol use	6	6	2708.90 (2327.61 to 3129.89)	3936.71 (3457.94 to 4524.58)	45.33% (30.7% to 60.18%)	−5.97% (−14.74% to 2.75%)	76.48 (61.08 to 93.37)	136.66 (115.68 to 162.66)	78.69% (54.74% to 108.25%)	6.66% (−6.18% to 22.33%)
High LDL cholesterol	3	7	6291.91 (5210.65 to 7354.85)	3863.72 (3077.21 to 4730.88)	−38.59% (−43.38% to −34.18%)	−63.6% (−66.17% to −61.13%)	353.09 (267.44 to 443.65)	226.34 (158.85 to 304.37)	−35.9% (−43.1% to −29.38%)	−64.86% (−68.02% to −61.77%)
Kidney dysfunction	7	8	2138.32 (1781.84 to 2527.38)	3159.52 (2795.42 to 3536.01)	47.76% (37.73% to 60.92%)	−13.36% (−19.3% to −5.75%)	138.81 (111.85 to 167.70)	214.74 (182.32 to 248.84)	54.71% (43.24% to 69.01%)	−15% (−20.89% to −6.95%)
Diet low in whole grains	9	9	1897.21 (868.61 to 2445.35)	1778.79 (855.23 to 2258.78)	−6.24% (−10% to 0.74%)	−44.83% (−47.05% to −40.69%)	103.24 (46.57 to 133.79)	102.25 (48.18 to 131.55)	−0.96% (−5.31% to 6.17%)	−45.32% (−47.42% to −41.37%)
Low temperature	13	10	1320.06 (1079.50 to 1579.76)	1734.12 (1488.09 to 1989.52)	31.37% (21.84% to 42.8%)	−28.03% (−33.6% to −21.47%)	92.53 (76.50 to 108.86)	123.09 (104.13 to 141.28)	33.02% (24.01% to 42.4%)	−28.1% (33.15% to 22.91%)
Diet low in legumes	12	11	1471.67 (348.59 to 2464.41)	1299.03 (337.88 to 2145.69)	−11.73% (−15.97% to 2.02%)	−48.26% (−50.62% to −39.91%)	80.91 (20.30 to 134.49)	76.84 (19.83 to 126.33)	−5.03% (−10.1% to 8.8%)	−48.05% (−50.45% to −41.09%)
Diet high in red meat	16	12	1258.35 (677.77 to 1830.45)	1268.70 (754.94 to 1787.30)	0.82% (−7.68% to 16.14%)	−40.06% (−45.03% to −30.7%)	59.84 (31.13 to 88.85)	65.65 (37.01 to 94.39)	9.71% (−0.52% to 29.65%)	−38.55% (−44.31% to −27.11%)
Diet high in *trans* fatty acids	14	13	1311.91 (77.03 to 1776.96)	1097.24 (55.44 to 1490.02)	−16.36% (−24.34% to −12.35%)	−50.97% (−55.84% to −48.6%)	71.37 (4.33 to 97.34)	64.39 (3.44 to 88.07)	−9.78% (−18.55% to −4.86%)	−50.56% (−55.32% to −48.06%)
Diet high in processed meat	19	14	850.40 (283.64 to 1366.73)	969.35 (405.97 to 1459.61)	13.99% (−0.22% to 53.8%)	−32.69% (−41.36% to −9.36%)	42.16 (13.90 to 69.60)	50.90 (20.97 to 78.62)	20.71% (5.93% to 59.18%)	−32.15% (−40.76% to −9.05%)
Ambient particulate matter pollution	8	15	2001.60 (842.72 to 3490.50)	931.95 (526.95 to 1361.42)	−53.44% (−76.57% to 3.52%)	−71.21% (−84.9% to −39.42%)	95.26 (37.62 to 171.26)	47.79 (26.06 to 71.53)	−49.84% (−75.93% to 18.1%)	−71.29% (−85.9% to −33.4%)
Diet high in sodium	24	16	574.46 (36.43 to 1999.45)	914.24 (61.08 to 2622.57)	59.15% (25.57% to 270.02%)	−4.75% (−25.72% to 132.21%)	31.62 (2.16 to 113.50)	48.50 (3.26 to 151.35)	53.38% (23.18% to 208.55%)	−13.04% (−30.53% to 82.94%)
Low birth weight	10	17	1512.98 (1436.65 to 1601.27)	853.24 (778.57 to 935.91)	−43.61% (−49.31% to −37.44%)	−38.47% (−44.69% to −31.75%)	17.04 (16.18 to 18.03)	9.61 (8.77 to 10.54)	−43.62% (−49.32% to −37.46%)	−38.49% (−44.71% to −31.77%)
Short gestation	11	18	1492.43 (1415.76 to 1577.76)	830.26 (756.11 to 909.70)	−44.37% (−49.91% to −38.33%)	−39.3% (−45.36% to −32.72%)	16.81 (15.94 to 17.77)	9.35 (8.51 to 10.24)	−44.38% (−49.92% to −38.35%)	−39.32% (−45.37% to −32.74%)
Secondhand smoke	17	19	1072.52 (858.49 to 1288.00)	765.32 (597.81 to 943.60)	−28.64% (−35.48% to −21.24%)	−58.57% (−62.38% to −54.53%)	44.43 (35.48 to 53.61)	35.58 (27.27 to 44.12)	−19.92% (−28.44% to −10.64%)	−55.34% (−59.81% to −50.32%)
Diet low in fruits	21	20	845.55 (505.63 to 1141.76)	745.10 (463.85 to 1006.64)	−11.88% (−21.92% to 0.05%)	−47.98% (−53.6% to −41.37%)	42.79 (25.00 to 57.89)	40.17 (24.61 to 54.38)	6.13% (−18.07% to 9.22%)	−47.6% (−53.99% to −39.31%)

BMI indicates body mass index; FPG, fasting plasma glucose; LDL, low-density lipoprotein; SBP, systolic blood pressure; UI, uncertainty interval; and YLLs, years of life lost to premature mortality.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[66] Printed with permission.

Table 2-4. The Leading 20 Causes of YLL and Death in the United States: Rank, Number, and Percent Change, 1990 and 2019

Diseases and injuries	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change, 1990–2019 (95% UI)		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change, 1990–2019 (95% UI)	
	1990	2019	1990	2019	Total No. of YLLs	Age-standardized YLL rate	1990	2019	Total No. of deaths	Age-standardized death rate
IHD	1	1	10 181.09 (9690.92 to 10 439.15)	8651.61 (8081.02 to 9124.13)	−15.02% (−17.54% to −11.72%)	−50.89% (−52.28% to −48.96%)	604.09 (558.11 to 627.32)	557.65 (496.86 to 594.41)	−7.69% (−11.14% to −3.43%)	−49.86% (−51.39% to −47.6%)
Tracheal, bronchus, and lung cancer	2	2	3559.62 (3479.49 to 3617.41)	4124.65 (3950.45 to 4261.93)	15.87% (11.75% to 19.93%)	−36.1% (−38.35% to −33.86%)	156.26 (151.01 to 159.34)	206.20 (193.72 to 214.28)	31.96% (26.46% to 37.09%)	−26.83% (−29.74% to −24.01%)
Chronic obstructive pulmonary disease	4	3	1592.74 (1505.38 to 1778.28)	3100.42 (2620.31 to 3305.63)	94.66% (63.07% to 109.95%)	11.21% (−6.25% to 19.76%)	90.48 (83.71 to 103.20)	195.83 (161.22 to 212.29)	116.42% (72.76% to 137.51%)	21.67% (−2.03% to 33%)
Opioid use disorders	46	4	219.00 (209.51 to 229.51)	286.80 (2182.91 to 2418.61)	944.2% (875.88% to 1027.46%)	799.2% (738.44% to 878.48%)	4.35 (4.18 to 4.55)	47.34 (45.39 to 49.24)	987.66% (922.91% to 1054.34%)	795.34% (741.01% to 859.05%)
Colon and rectum cancer	7	5	1291.48 (1249.20 to 1320.46)	1640.65 (1574.85 to 1689.21)	27.04% (23.7% to 30.48%)	−24.11% (−26.08% to −21.94%)	65.58 (61.89 to 67.69)	84.03 (77.99 to 87.52)	28.12% (24.34% to 31.56%)	−26.31% (−28.25% to −24.39%)
Type 2 diabetes	12	6	856.92 (809.02 to 882.74)	1365.65 (1299.49 to 1422.98)	59.37% (54.2% to 65.34%)	−7.31% (−10.46% to −3.84%)	43.92 (40.93 to 45.55)	73.41 (67.73 to 76.76)	67.15% (61.31% to 72.93%)	−5.46% (−8.66% to 2.26%)
Alzheimer disease and other dementias	15	7	743.80 (180.25 to 2011.60)	139.08 (333.70 to 3431.38)	80.03% (65.82% to 99.45%)	−3.65% (−10.86% to 5.5%)	73.08 (18.40 to 194.71)	143.92 (37.07 to 354.96)	96.94% (80.52% to 119.01%)	−1.92% (−9.65% to 7.87%)
Motor vehicle road injuries	3	8	1836.51 (1812.57 to 1864.76)	1231.24 (1152.15 to 1272.09)	−32.96% (−37.75% to −30.48%)	−46.42% (−50.42% to −44.35%)	35.67 (35.13 to 36.27)	28.25 (26.71 to 29.14)	−20.82% (−25.88% to −18.17%)	−42.5% (−46.41% to −40.47%)
Breast cancer	9	9	1199.58 (1165.78 to 1222.05)	1212.43 (1157.03 to 1261.82)	1.07% (−3% to 4.94%)	−40.05% (−42.49% to −37.71%)	48.21 (45.76 to 49.51)	55.02 (51.01 to 57.90)	14.12% (9.23% to 18.83%)	−35.5% (−38.05% to −33.07%)
Lower respiratory infections	8	10	1223.88 (1159.84 to 1261.53)	1210.65 (1124.89 to 1262.59)	−1.08% (−4.06% to 1.99%)	−40.39% (−42.03% to −38.65%)	72.72 (66.22 to 76.44)	81.92 (72.24 to 87.40)	12.66% (8.1% to 16.85%)	−38.93% (−40.75% to −36.94%)
Ischemic stroke	6	11	1324.40 (1218.20 to 1381.45)	1185.52 (1045.83 to 1295.90)	−10.49% (−15.56% to −3.94%)	−50.06% (−52.58% to −46.54%)	103.35 (92.02 to 109.29)	108.95 (92.44 to 120.30)	5.42% (−1.45% to 14.3%)	−44.68% (−47.72% to −40.18%)
Pancreatic cancer	17	12	587.36 (568.59 to 599.72)	1134.93 (1078.47 to 1178.70)	93.23% (85.27% to 100.27%)	10.36% (5.85% to 14.28%)	28.60 (27.10 to 29.43)	57.49 (53.67 to 60.25)	101.03% (92.1% to 109.18%)	14.29% (9.49% to 18.74%)
ICH	14	13	772.31 (741.63 to 799.80)	1099.70 (1033.09 to 1188.13)	42.39% (35.89% to 50.11%)	−16.7% (−20.47% to −12.21%)	38.33 (35.84 to 39.86)	59.73 (54.34 to 64.89)	55.82% (47.69% to 66.31%)	−12.28% (−16.49% to −6.65%)
Self-harm by other specified means	16	14	686.74 (629.95 to 767.19)	961.37 (835.09 to 1004.91)	39.99% (28.48% to 45.86%)	12.77% (3.34% to 17.66%)	14.65 (13.31 to 16.22)	21.98 (19.00 to 23.04)	50.1% (40.1% to 55.9%)	12.88% (4.55% to 17.5%)
Hypertensive HD	23	15	447.65 (373.87 to 469.58)	957.73 (599.24 to 1027.23)	113.95% (43.15% to 126.64%)	29.98% (−15.61% to 38.05%)	23.73 (20.11 to 25.47)	52.96 (35.45 to 57.78)	123.18% (58.64% to 136.08%)	23.67% (−13.76% to 30.56%)
Self-harm by firearm	13	16	853.20 (767.29 to 906.88)	895.00 (844.35 to 1014.78)	4.9% (1.11% to 13.45%)	−20.52% (−23.51% to −13.82%)	19.32 (17.67 to 20.57)	23.36 (22.13 to 26.18)	20.95% (17.12% to 28.48%)	−16.01% (−18.8% to −10.1%)
Cirrhosis and other chronic liver diseases caused by hepatitis C	24	17	434.18 (390.04 to 483.14)	839.29 (746.47 to 938.91)	93.3% (82.11% to 103.87%)	19.63% (14.07% to 25.01%)	14.46 (12.96 to 16.10)	29.91 (26.55 to 33.43)	106.84% (97.17% to 116.53%)	23.07% (18.06% to 28.21%)
Endocrine, metabolic, blood, and immune disorders	35	18	272.90 (226.89 to 362.60)	772.39 (598.36 to 893.98)	183.04% (139% to 197.28%)	77.55% (62.97% to 84.21%)	8.68 (7.45 to 12.18)	34.54 (24.72 to 37.44)	297.78% (180.95% to 332.08%)	123.05% (67.99% to 138.77%)
Physical violence by firearm	11	19	980.04 (963.97 to 993.74)	735.86 (682.89 to 761.54)	−24.92% (−29.57% to −22.24%)	−34.98% (−39.02% to −32.65%)	16.74 (16.47 to 16.96)	13.00 (12.12 to 13.43)	−22.33% (−26.91% to −19.9%)	−35.1% (−39.01% to −32.96%)
Prostate cancer	18	20	581.18 (403.13 to 650.19)	712.79 (628.11 to 1037.53)	22.65% (9.65% to 66.94%)	−29.34% (−36.77% to −4.07%)	36.24 (25.66 to 40.65)	48.32 (41.35 to 70.59)	33.36% (19.07% to 78.37%)	−24.46% (−32.33% to 1.1%)

HD indicates heart disease; ICH, intracerebral hemorrhage; IHD, ischemic heart disease; UI, uncertainty interval; and YLLs, years of life lost to premature mortality.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[67] Printed with permission. Copyright © 2020, University of Washington.

Table 2-5. The Leading 20 Risk Factors for YLDs in the United States: Rank, Number, and Percentage Change, 1990 and 2019

Risk factors for disability	YLD rank (for total number)		Total No. of YLDs, in thousands (95% UI)		Percent change, 1990–2019 (95% UI)	
	1990	2019	1990	2019	Total No. of YLDs	Age-standardized YLD rate
High BMI	2	1	2014.44 (1191.63 to 3041.53)	4757.53 (3035.97 to 6728.53)	136.17% (116.67% to 171.6%)	44.45% (32.86% to 65.18%)
High FPG	3	2	1473.97 (1043.23 to 1958.70)	3705.54 (2636.55 to 4926.74)	151.4% (140.32% to 165.13%)	47.37% (40.86% to 54.89%)
Smoking	1	3	2927.37 (2152.15 to 3726.22)	3580.31 (2711.48 to 4421.59)	22.3% (15.58% to 30.13%)	–25.75% (–29.66% to –21.37%)
Drug use	5	4	1031.70 (712.04 to 1385.17)	3009.85 (2080.84 to 4025.99)	191.74% (158.71% to 224.78%)	148.76% (118.72% to 178.48%)
High SBP	6	5	884.49 (639.70 to 1142.32)	1287.04 (929.96 to 1667.98)	45.51% (35.52% to 55.15%)	–13.11% (–18.82% to –7.75%)
Alcohol use	4	6	1102.64 (760.00 to 1520.68)	1259.73 (879.63 to 1722.34)	14.25% (4.96% to 25.06%)	–16.46% (–21.27% to –11.03%)
Occupational ergonomic factors	7	7	769.12 (531.07 to 1052.57)	909.32 (640.04 to 1206.98)	18.23% (8.01% to 30.5%)	–14.3% (–21.29% to –6.44%)
Low bone mineral density	8	8	411.39 (289.23 to 569.28)	782.17 (549.97 to 1077.01)	90.13% (85.32% to 95.57%)	6.66% (4.03% to 9.54%)
Kidney dysfunction	9	9	399.32 (297.80 to 524.36)	775.02 (582.79 to 1002.90)	94.08% (83.38% to 105.14%)	19.75% (14.04% to 25.57%)
Diet high in red meat	14	10	230.60 (158.70 to 317.03)	485.27 (322.95 to 687.22)	110.44% (91.62% to 126.96%)	25.76% (15.64% to 34.5%)
Diet high in processed meat	17	11	172.86 (104.84 to 255.78)	471.02 (287.52 to 692.65)	172.5% (148.34% to 205.98%)	58.21% (44.23% to 76.99%)
Short gestation	10	12	371.84 (284.50 to 469.16)	468.88 (365.55 to 581.92)	26.1% (16.16% to 36.48%)	4.21% (–3.87% to 12.88%)
Low birth weight	11	13	371.84 (284.50 to 469.16)	468.88 (365.55 to 581.92)	26.1% (16.16% to 36.48%)	4.21% (–3.87% to 12.88%)
High LDL cholesterol	13	14	297.03 (185.95 to 446.89)	303.55 (190.21 to 472.68)	2.19% (–8.4% to 12.75%)	–37.09% (–43.62% to –30.57%)
Ambient particulate matter pollution	12	15	308.85 (111.01 to 556.89)	291.90 (139.49 to 500.08)	–5.49% (–55.19% to 120.72%)	–44.15% (–73.38% to 30.06%)
Bullying victimization	22	16	132.13 (29.00 to 322.15)	268.38 (58.82 to 613.61)	103.12% (81.47% to 133.27%)	81.82% (61.43% to 105.89%)
Occupational injuries	15	17	196.96 (134.56 to 279.88)	265.30 (176.61 to 390.65)	34.7% (5.8% to 73.94%)	0.01% (–21.72% to 29.35%)
Childhood sexual abuse	19	18	164.32 (72.88 to 313.28)	251.15 (121.67 to 443.14)	52.84% (27.67% to 94.68%)	22.66% (3.32% to 54.56%)
Intimate partner violence	20	19	161.94 (26.50 to 326.56)	250.12 (31.52 to 514.75)	54.45% (27.68% to 63.76%)	23.3% (–4.55% to 30.31%)
Secondhand smoke	16	20	173.12 (106.23 to 245.30)	246.72 (146.07 to 362.41)	42.51% (23% to 59.97%)	–16.37% (–27.46% to –6.05%)

BMI indicates body mass index; FPG, fasting plasma glucose; LDL, low-density lipoprotein; SBP, systolic blood pressure; UI, uncertainty interval; and YLDs, years of life lived with disability or injury.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[66] Printed with permission. Copyright © 2020, University of Washington.

Table 2-6. The Leading 20 Causes for YLDs in the United States: Rank, Number, and Percent Change, 1990 and 2019

Diseases and injuries	YLD rank (for total number)		Total number of YLDs, in thousands (95% UI)		Percent change, 1990–2019 (95% UI)	
	1990	2019	1990	2019	Total No. of YLDs	Age-standardized YLD rate
Low back pain	1	1	4504.86 (3168.68 to 6039.64)	5697.15 (4114.14 to 7474.69)	26.47% (18.72% to 34.96%)	–12.46% (–17.42% to –7.02%)
Other musculoskeletal disorders	2	2	1731.90 (1200.59 to 2420.19)	3530.50 (2522.22 to 4747.29)	103.85% (83.83% to 126.23%)	44.17% (30.42% to 59.6%)
Type 2 diabetes	9	3	1030.39 (715.25 to 1387.82)	2761.76 (1939.08 to 3738.03)	168.03% (153.55% to 185.2%)	55.84% (47.58% to 65.14%)
Opioid use disorders	16	4	554.70 (366.80 to 787.88)	2489.58 (1684.54 to 3394.11)	348.82% (308.52% to 396.89%)	288.67% (253.85% to 332.48%)
Major depressive disorder	4	5	1341.83 (930.71 to 1837.66)	2242.30 (1552.73 to 3056.52)	67.11% (62.83% to 72.26%)	33.07% (29.58% to 36.62%)
Age-related and other hearing loss	5	6	1340.58 (932.94 to 1865.97)	2187.37 (1524.78 to 3048.08)	63.17% (58.93% to 67.46%)	–1.4% (–3.46% to 0.7%)
Migraine	3	7	1671.80 (241.76 to 3778.40)	2078.81 (333.85 to 4660.27)	24.35% (18.96% to 37.7%)	–2.61% (–5.89% to 1.17%)
Neck pain	7	8	1201.62 (792.53 to 1709.09)	2043.52 (1392.66 to 2886.40)	70.06% (55.99% to 82.82%)	18.41% (9.89% to 27.58%)
Chronic obstructive pulmonary disease	8	9	1111.88 (924.35 to 1262.67)	1921.11 (1606.46 to 2147.99)	72.78% (66.73% to 79.98%)	–0.62% (–3.94% to 3.51%)
Anxiety disorders	6	10	1331.27 (932.18 to 1816.40)	1872.34 (1314.62 to 2530.62)	40.64% (37% to 44.94%)	8.41% (6.85% to 10.06%)
Falls	10	11	971.06 (690.51 to 1336.57)	1594.64 (1136.33 to 2190.22)	64.22% (57.72% to 71.62%)	0.07% (–2.87% to 3.35%)
Asthma	11	12	904.55 (587.17 to 1330.72)	1296.66 (857.41 to 1849.88)	43.35% (31.26% to 56.15%)	11.01% (1.8% to 21.71%)
Schizophrenia	13	13	767.43 (562.88 to 970.69)	993.34 (732.79 to 1243.07)	29.44% (25.28% to 34.45%)	–1.22% (–3.13% to 0.79%)
Osteoarthritis hand	18	14	486.85 (249.46 to 1017.65)	930.08 (466.70 to 1964.92)	91.04% (74.27% to 108.64%)	7.82% (–0.72% to 17.23%)
Ischemic stroke	15	15	559.93 (399.70 to 724.14)	870.59 (628.48 to 1114.77)	55.48% (47.94% to 63.39%)	–5.16% (–9.35% to –0.14%)
Alcohol use disorders	12	16	785.98 (523.84 to 1106.57)	784.98 (538.64 to 1092.19)	–0.13% (–5.58% to 5.53%)	–21.58% (–24.39% to –18.84%)
Osteoarthritis knee	19	17	450.96 (227.51 to 906.41)	759.11 (380.59 to 1527.66)	68.33% (62.62% to 75.07%)	–2.68% (–6.62% to 1.66%)
Endocrine, metabolic, blood, and immune disorders	14	18	629.50 (428.40 to 868.36)	726.71 (500.66 to 990.69)	15.44% (6.81% to 23.95%)	–23.84% (–29.21% to –18.2%)
Alzheimer's disease and other dementias	22	19	391.77 (276.91 to 523.54)	687.80 (497.57 to 889.29)	75.56% (59.97% to 94.86%)	–3.82% (–12.02% to 6.33%)
Edentulism	17	20	491.91 (304.02 to 742.02)	668.95 (424.02 to 985.05)	35.99% (29.73% to 43.73%)	–17.13% (–22.52% to –10.71%)

UI indicates uncertainty interval; and YLDs, years of life lived with disability or injury.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[67] Printed with permission. Copyright © 2020, University of Washington.

Table 2-7. The Leading 20 Global Risk Factors of YLL and Death: Rank, Number, and Percentage Change, 1990 and 2019

Risk factors for disability	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change, 1990–2019 (95% UI)		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change, 1990–2019 (95% UI)	
	1990	2019	1990	2019	Total Number of YLLs	Age-standardized YLL rate	1990	2019	Total No. of deaths	Age-standardized death rate
High SBP	6	1	143603.62 (129333.91 to 157734.25)	214260.28 (191165.39 to 236748.61)	49.2% (38.51% to 59.21%)	−28.96% (−33.93% to −24.37%)	6787.71 (6072.71 to 7495.92)	10845.60 (9514.14 to 12130.85)	59.78% (49.19% to 69.4%)	−29.81% (−34.25% to −25.76%)
Smoking	7	2	140203.56 (132792.85 to 147036.56)	168238.03 (155801.16 to 180393.21)	20% (10.41% to 30.71%)	−41.31% (−45.98% to −36.16%)	5868.49 (5578.08 to 6152.89)	7693.37 (7158.45 to 8200.59)	31.1% (21.21% to 42.07%)	−38.67% (−43.11% to −33.68%)
Low birth weight	2	3	269478.56 (250822.80 to 288996.54)	151317.48 (128528.30 to 179613.60)	−43.85% (−52.35% to −33.52%)	−43.1% (−51.71% to −32.64%)	3033.43 (2823.41 to 3253.23)	1703.12 (1446.63 to 2021.58)	−43.85% (−52.35% to −33.53%)	−43.11% (−51.72% to −32.65%)
Short gestation	3	4	221314.76 (206273.76 to 238540.80)	128741.23 (109481.34 to 153683.78)	−41.83% (−50.32% to −30.76%)	−41.05% (−49.66% to −29.84%)	2491.34 (2321.98 to 2685.26)	1449.04 (1232.27 to 1729.80)	−41.84% (−50.33% to −30.77%)	−41.06% (−49.67% to −29.85%)
High FPG	14	5	61627.96 (51459.07 to 74728.01)	126654.90 (104234.74 to 153148.03)	105.52% (91.63% to 119.7%)	−1.5% (−7.92% to 5.66%)	2910.09 (2340.62 to 3753.67)	6501.40 (5110.28 to 8363.05)	123.41% (108.53% to 138.04%)	−1.46% (−7.48% to 5.12%)
High BMI	16	6	54375.58 (30163.43 to 84361.01)	119383.76 (79596.11 to 163875.52)	119.55% (88.91% to 166.91%)	8.27% (−6.61% to 31.18%)	2198.13 (1205.50 to 3432.16)	5019.36 (3223.36 to 7110.74)	128.35% (101.34% to 170.06%)	4.93% (−7.26% to 24.58%)
Ambient particulate matter pollution	13	7	66492.55 (44569.97 to 94108.79)	104895.28 (84911.25 to 123445.01)	57.75% (20.29% to 113.82%)	−4.23% (−24.76% to 26.13%)	2047.17 (1454.74 to 2739.85)	4140.97 (3454.41 to 4800.29)	102.28% (60.27% to 160.61%)	−0.92% (−19.85% to 26.25%)
High LDL cholesterol	12	8	66683.88 (56074.15 to 79392.34)	92904.81 (75590.22 to 111436.78)	39.32% (28.6% to 48.91%)	−33.26% (−37.98% to −28.66%)	3002.61 (2350.83 to 3761.88)	4396.98 (3301.26 to 5651.79)	46.44% (35.21% to 55.63%)	−36.74% (−40.61% to −33.09%)
Household air pollution from solid fuels	4	9	200169.50 (154731.29 to 248560.54)	83565.87 (60754.11 to 108481.62)	−58.25% (−66.65% to −48.52%)	−69.1% (−74.78% to −62.42%)	4358.21 (3331.29 to 5398.69)	2313.99 (1631.34 to 3118.14)	−46.91% (−58.07% to −34.49%)	−69.88% (−75.85% to −63.27%)
Child wasting	1	10	292012.74 (241855.36 to 351715.87)	79187.22 (61262.34 to 100812.43)	−72.88% (−78.47% to −66.32%)	−73.89% (−79.28% to −67.54%)	3430.42 (2851.24 to 4125.93)	993.05 (786.46 to 1245.24)	−71.05% (−76.85% to −64.32%)	−73.05% (−78.35% to −66.7%)
Alcohol use	15	11	55971.37 (49934.31 to 62781.18)	75813.95 (66966.44 to 85498.40)	35.45% (23.85% to 47.91%)	−25.69% (−32.08% to −18.91%)	1639.87 (1442.38 to 1845.20)	2441.97 (2136.99 to 2784.90)	48.91% (35.99% to 63.1%)	−23.77% (−30.55% to −16.4%)
Kidney dysfunction	19	12	37087.06 (32724.00 to 41606.93)	65204.46 (57219.63 to 73512.12)	75.81% (64.57% to 87.42%)	−11.26% (−17.07% to −5.57%)	1571.72 (1344.42 to 1805.60)	3161.55 (2723.36 to 3623.81)	101.15% (88.45% to 112.88%)	−10.02% (−15.49% to −4.64%)
Unsafe water source	5	13	153905.20 (115315.56 to 190197.92)	57641.09 (41786.87 to 75887.40)	−62.55% (−71.19% to −49.83%)	−68.27% (−75.24% to −57.55%)	2442.07 (1764.95 to 3147.03)	1230.15 (817.82 to 1788.90)	−49.63% (−61.95% to −29.85%)	−65.76% (−73.6% to −53.37%)
Unsafe sex	25	14	18492.16 (14813.00 to 23832.65)	41999.23 (37398.24 to 49078.72)	127.12% (100.78% to 162.48%)	35.87% (21.91% to 54.45%)	429.99 (356.20 to 533.21)	984.37 (904.99 to 1106.17)	128.93% (102.2% to 164.15%)	27.64% (13.89% to 44.6%)
Diet high in sodium	20	15	31285.63 (10435.19 to 63583.27)	40722.69 (11550.13 to 86326.74)	30.16% (−3.03% to 47.85%)	−36.45% (−52.02% to −28.15%)	1320.34 (412.33 to 2796.87)	,885.36 (476.84 to 4194.71)	42.79% (4.76% to 61.05%)	−34.18% (−50.81% to −26.58%)
Diet low in whole grains	22	16	26467.42 (12815.63 to 33041.82)	38954.84 (19130.31 to 49094.51)	47.18% (37.22% to 57.73%)	−28.99% (−33.76% to −24.05%)	1178.22 (579.63 to 1474.66)	1844.84 (921.29 to 2338.61)	56.58% (47.07% to 65.85%)	−31.16% (−35.14% to −27.26%)
Unsafe sanitation	9	17	115547.43 (92118.35 to 138980.27)	37183.90 (29008.07 to 48393.08)	−67.82% (−75.33% to −56.89%)	−72.65% (−78.73% to −63.04%)	1836.46 (1390.57 to 2325.10)	756.58 (542.45 to 1095.44)	−58.8% (−68.54% to −43.12%)	−71.89% (−78.23% to −62.13%)
No access to handwashing facility	10	18	80929.22 (58183.31 to 102881.65)	32224.40 (22228.24 to 42981.39)	−60.18% (−67.34% to −51.09%)	−65.26% (−71.61% to −57.2%)	1200.09 (854.11 to 1553.29)	627.92 (427.17 to 846.29)	−47.68% (−56.38% to −36.7%)	−62.55% (−68.93% to −54.77%)
Secondhand smoke	18	19	44029.71 (31252.42 to 57353.06)	31489.25 (24218.79 to 38792.35)	−28.48% (−39.18% to −15.29%)	−54.89% (−60.57% to −48.97%)	1161.96 (878.27 to 1431.85)	1304.32 (1006.96 to 1605.39)	12.25% (1.01% to 25.04%)	−42.45% (−47.47% to −36.76%)
Low temperature	21	20	26827.37 (20973.96 to 33715.52)	25954.68 (21667.68 to 30902.49)	−3.25% (−18.13% to 13.86%)	−51.56% (−57.31% to −45.99%)	1276.64 (1092.81 to 1461.24)	1652.98 (1413.03 to 1913.43)	29.48% (18.11% to 41.67%)	−43.63% (−47.8% to −38.92%)

BMI indicates body mass index; FPG, fasting plasma glucose; LDL, low-density lipoprotein; SBP, systolic blood pressure; UI, uncertainty interval; and YLLs, years of life lost because of premature mortality.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[66] Printed with permission. Copyright © 2020, University of Washington.

Table 2-8. The Leading 20 Global Causes of YLL and Death: Rank, Number, and Percentage Change, 1990 and 2019

Diseases and injuries	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change, 1990–2019 (95% UI)		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change, 1990–2019 (95% UI)	
	1990	2019	1990	2019	Total No. of YLLs	Age-standardized YLL rate	1990	2019	Total No. of deaths	Age-standardized death rate
IHD	3	1	118 399.43 (113 795.23 to 122 787.19)	176 634.92 (165 028.83 to 188 453.38)	49.19% (38.17% to 59.29%)	−29.14% (−34.13% to −24.56%)	5695.89 (5405.19 to 5895.40)	9137.79 (8395.68 to 9743.55)	60.43% (50.23% to 69.14%)	−30.8% (−34.83% to −27.17%)
Lower respiratory infections	1	2	223 807.88 (198 291.93 to 258 361.55)	96 536.65 (84 197.05 to 112 404.97)	−56.87% (−64.43% to −47.7%)	−62.66% (−69.13% to −55.03%)	3320.01 (3018.49 to 3715.06)	2493.20 (2268.18 to 2736.18)	−24.9% (−34.42% to −15.39%)	−48.54% (−53.95% to −42.93%)
Diarrheal diseases	2	3	182 456.67 (146 519.78 to 217 965.17)	69 887.49 (54 617.33 to 92 161.23)	−61.7% (−70.34% to −49.12%)	−67.6% (−74.63% to −56.89%)	2896.27 (2222.66 to 3644.59)	1534.44 (1088.68 to 2219.10)	−47.02% (−59.64% to −27.06%)	−64.05% (−72.05% to −51.35%)
ICH	9	4	52 648.78 (48 739.14 to 57 507.05)	65 306.22 (60 073.84 to 70 392.27)	24.04% (10.38% to 35.4%)	−37.37% (−44.17% to −31.5%)	2099.76 (1932.53 to 2328.41)	2886.20 (2644.48 to 3099.35)	37.45% (21.73% to 50.92%)	−35.61% (−42.76% to −29.23%)
Neonatal preterm birth	4	5	112 709.17 (103 574.46 to 122 915.10)	58 942.91 (49 829.35 to 70 084.83)	−47.7% (−56.13% to −37.42%)	−47.02% (−55.56% to −36.61%)	1269.04 (1166.14 to 1383.98)	663.52 (560.96 to 788.95)	−47.71% (−56.14% to −37.44%)	−47.04% (−55.57% to −36.63%)
Chronic obstructive pulmonary disease	11	6	48 769.20 (40 770.89 to 52 860.94)	54 594.90 (48 711.47 to 59 513.37)	11.95% (−0.47% to 35.12%)	−46.81% (−52.61% to −36.11%)	2520.22 (2118.06 to 2719.39)	3280.64 (2902.85 to 3572.37)	30.17% (15.74% to 55.05%)	−41.74% (−48.03% to −31.07%)
Neonatal encephalopathy caused by birth asphyxia and trauma	6	7	71 832.72 (64 553.03 to 80 228.20)	50 368.25 (42 242.80 to 59 745.92)	−29.88% (−41.7% to −15.68%)	−28.91% (−40.9% to −14.52%)	808.68 (726.80 to 903.20)	566.98 (475.54 to 672.55)	−29.89% (−41.71% to −15.69%)	−28.92% (−40.91% to −14.54%)
Ischemic stroke	13	8	34 004.54 (31 954.95 to 37 258.43)	50 349.74 (46 232.45 to 54 066.67)	48.07% (32.31% to 61.3%)	−33.35% (−40% to −27.56%)	2049.67 (1900.02 to 2234.21)	3293.40 (2973.54 to 3536.08)	60.68% (45.83% to 74.65%)	−33.64% (−39.16% to −28.15%)
Tracheal, bronchus, and lung cancer	19	9	26 859.81 (25 598.42 to 28 199.92)	45 313.75 (41 866.20 to 48 831.01)	68.7% (52.68% to 85.03%)	−16.34% (−24.19% to −8.38%)	1065.14 (1019.22 to 1117.18)	2042.64 (1879.24 to 2193.27)	91.77% (74.52% to 108.97%)	−7.77% (−15.93% to 0.23%)
Malaria	8	10	63 480.60 (34 802.94 to 103 091.05)	43 824.70 (21 055.36 to 77 962.79)	−30.96% (−58.84% to 6.4%)	−39.03% (−63.65% to −6.42%)	840.55 (463.32 to 1356.07)	643.38 (301.60 to 1153.66)	−23.46% (−54.89% to 18.46%)	−37.93% (−63.46% to −4.52%)
Drug-susceptible tuberculosis	5	11	74 658.58 (68 441.13 to 81 346.25)	38 431.33 (33 206.79 to 43 219.46)	−48.52% (−55.92% to −40.77%)	−67.54% (−72.12% to −62.69%)	1760.71 (,610.86 to 1908.32)	1061.29 (924.21 to 1186.12)	−39.72% (−48.03% to −30.36%)	−66.82% (−71.34% to −61.52%)
Other neonatal disorders	12	12	47 950.24 (40 831.64 to 57 251.83)	33 099.91 (27 646.20 to 40 129.55)	−30.97% (−48% to −11.34%)	−30.12% (−47.35% to −10.26%)	539.95 (459.81 to 644.56)	372.68 (311.26 to 451.84)	−30.98% (−48% to −11.37%)	−30.13% (−47.36% to −10.29%)
HIV/AIDS resulting in other diseases	32	13	12 728.09 (9716.63 to 17 727.71)	32 470.01 (26 796.66 to 40 802.58)	155.11% (119.22% to 204.68%)	77.01% (51.97% to 111.74%)	216.91 (162.89 to 308.68)	646.76 (551.85 to 780.47)	198.17% (147.74% to 269.45%)	94.13% (61.07% to 141.2%)
Type 2 diabetes	28	14	13 851.47 (13 104.90 to 14 647.61)	31 149.12 (29 302.02 to 33 148.25)	124.88% (110.14% to 141.3%)	9.11% (2.06% to 16.65%)	606.41 (573.07 to 637.51)	1472.93 (1371.94 to 1565.86)	142.9% (128.32% to 158.37%)	10.77% (4.42% to 17.44%)
Self-harm by other specified means	15	15	32 879.52 (29 065.89 to 35 287.35)	30 986.82 (27 870.17 to 34 246.63)	−5.76% (−14.84% to 4.31%)	−38.8% (−44.56% to −32.43%)	687.85 (607.61 to 736.36)	706.33 (633.90 to 777.33)	2.69% (−6.38% to 13.66%)	−38.83% (−43.96% to −32.27%)
Colon and rectum cancer	34	16	12 013.14 (11 481.93 to 12 503.78)	23 218.75 (21 662.64 to 24 591.16)	93.28% (79.51% to 106.26%)	−5.29% (−11.8% to 0.81%)	518.13 (493.68 to 537.88)	1085.80 (1002.80 to 1149.68)	109.56% (96.2% to 121.74%)	−4.37% (−10.03% to 0.93%)
Motor vehicle road injuries	21	17	22 260.33 (19 219.44 to 25 401.32)	21 982.25 (19 334.80 to 24 633.49)	−1.25% (−14.6% to 15.23%)	−30.61% (−39.82% to −19.51%)	399.99 (349.88 to 452.26)	448.73 (396.67 to 500.41)	12.19% (−2.49% to 28.58%)	−27.7% (−37.11% to −17.51%)
Stomach cancer	24	18	20 241.69 (19 030.22 to 21 513.16)	21 872.43 (19 972.71 to 23 712.52)	8.06% (−2.52% to 19.94%)	−45.85% (−51.1% to −39.99%)	788.32 (742.79 to 834.00)	957.19 (870.95 to 1034.65)	21.42% (10.17% to 33.59%)	−41.98% (−47.18% to −36.33%)
Neonatal sepsis and other neonatal infections	20	19	23 105.79 (18 521.37 to 26 599.32)	20 118.04 (16 896.71 to 24 474.48)	−12.93% (−29.92% to 11.86%)	−11.91% (−29.12% to 13.14%)	260.15 (208.54 to 299.46)	226.52 (190.25 to 275.55)	−12.93% (−29.93% to 11.86%)	−11.91% (−29.12% to 13.15%)
Hypertensive HD	31	20	13 303.40 (10 669.61 to 14 984.15)	19 991.58 (14 951.10 to 22 179.67)	50.27% (31.09% to 74.64%)	−28.13% (−38.1% to −17.04%)	654.91 (530.57 to 732.73)	1156.73 (859.83 to 1278.56)	76.63% (49.7% to 103.4%)	−21.49% (−35.18% to −10.13%)

HD indicates heart disease; ICH, intracerebral hemorrhage; IHD, ischemic heart disease; UI, uncertainty interval; and YLLs, years of life lost to premature mortality.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[67] Printed with permission. Copyright © 2020, University of Washington.

Table 2-9. The Leading 20 Global Risk Factors for YLDs: Rank, Number, and Percentage Change, 1990 and 2019

Risk factors for disability	YLD rank (for total number)		Total No. of YLDs, in thousands (95% UI)		Percent change, 1990–2019 (95% UI)	
	1990	2019	1990	2019	Total No. of YLDs	Age-standardized YLD rate
High FPG	3	1	15 581.99 (11 024.37 to 20 775.85)	45 413.83 (31 849.57 to 60 894.87)	191.45% (186.87% to 196.13%)	44.07% (41.68% to 46.29%)
High BMI	4	2	12 907.42 (6901.43 to 20 969.73)	40 881.60 (24 508.83 to 60 876.50)	216.73% (178.46% to 276.78%)	60.16% (41.28% to 90.24%)
Smoking	2	3	20 484.09 (15 154.19 to 26 177.63)	31 556.71 (23 686.35 to 40 009.32)	54.05% (49.57% to 59.1%)	–22.88% (–24.83% to –20.74%)
Iron deficiency	1	4	25 379.25 (16 986.41 to 36 524.20)	28 798.47 (19 425.22 to 41 491.77)	13.47% (10.15% to 16.89%)	–16.67% (–19.02% to –14.23%)
High SBP	7	5	10 128.23 (7295.78 to 13 093.83)	21 164.35 (15 195.78 to 27 235.49)	108.96% (102.17% to 116.39%)	0.98% (–2.31% to 4.4%)
Alcohol use	5	6	11 836.52 (8147.05 to 16 305.10)	17 182.28 (12 000.25 to 23 497.81)	45.16% (39.58% to 51.25%)	–13.47% (–15.96% to –10.79%)
Occupational ergonomic factors	6	7	11 784.36 (8098.99 to 15 893.42)	15 310.68 (10 544.90 to 20 762.41)	29.92% (24.65% to 34.57%)	–24.61% (–26.93% to –22.45%)
Ambient particulate matter pollution	17	8	3985.80 (2637.74 to 5634.02)	13 320.10 (9643.12 to 17 166.65)	234.19% (172.63% to 322.4%)	64.91% (34.85% to 107.76%)
Drug use	9	9	7479.41 (5163.69 to 10 042.08)	12 664.94 (8804.75 to 16 725.98)	69.33% (60.93% to 78.15%)	14.49% (9.59% to 19.37%)
Kidney dysfunction	14	10	5003.27 (3651.06 to ,508.03)	11 282.48 (8232.55 to 14 676.40)	125.5% (118.26% to 132.74%)	20.24% (16.89% to 23.23%)
Short gestation	12	11	5054.73 (3854.95 to 6433.30)	9673.88 (7598.43 to 12 021.19)	91.38% (75.26% to 106.94%)	43.44% (31.94% to 54.79%)
Low birth weight	13	12	5054.73 (3854.95 to 6433.30)	9673.88 (7598.43 to 12 021.19)	91.38% (75.26% to 106.94%)	43.44% (31.94% to 54.79%)
Low bone mineral density	16	13	4082.06 (2923.34 to 5511.96)	8620.52 (6115.78 to 11 640.10)	111.18% (108.01% to 114.56%)	–1.7% (–2.77% to –0.66%)
Household air pollution from solid fuels	8	14	8277.99 (5837.95 to 11 127.29)	7908.60 (5254.80 to 11 299.35)	–4.46% (–20.63% to 15.04%)	–52.14% (–60.18% to –42.55%)
Unsafe water source	11	15	6054.63 (3781.50 to 8815.37)	7455.38 (4530.39 to 10 914.15)	23.14% (16.02% to 29.05%)	–11.82% (–16.58% to –8.1%)
Occupational noise	18	16	3933.44 (2688.10 to 5599.97)	7001.45 (4760.56 to 10 059.34)	78% (71.39% to 83.61%)	–1.71% (–4.07% to 0.35%)
Occupational injuries	10	17	6779.60 (4833.81 to 9123.27)	6842.83 (4831.64 to 9300.85)	0.93% (–10.59% to 13.14%)	–39.26% (–46.08% to –31.85%)
High LDL cholesterol	22	18	3035.02 (1990.11 to 4342.73)	5713.21 (3677.82 to 8268.24)	88.24% (82.75% to 94.36%)	–7.77% (–9.68% to –6.05%)
Secondhand smoke	24	19	2652.31 (1685.26 to 3741.03)	5512.81 (3246.56 to 8105.45)	107.85% (84.4% to 123.61%)	6.66% (–4.51% to 14.89%)
Unsafe sex	32	20	1609.09 (1135.71 to 2172.24)	4646.23 (3296.41 to 6215.68)	188.75% (161.84% to 225.83%)	80.75% (63.79% to 103.78%)

BMI indicates body mass index; FPG, fasting plasma glucose; LDL, low-density lipoprotein; SBP, systolic blood pressure; UI, uncertainty interval; and YLDs, years of life lived with disability or injury.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[66] Printed with permission. Copyright © 2020, University of Washington.

Table 2-10. The Leading 20 Global Causes for YLDs: Rank, Number, and Percentage Change, 1990 and 2019

Diseases and injuries	YLD rank (for total number)		Total No. of YLDs, in thousands (95% UI)		Percent change, 1990–2019 (95% UI)	
	1990	2019	1990	2019	Total No. of YLDs	Age-standardized YLD rate
Low back pain	1	1	43 361.65 (30 529.53 to 57 934.97)	63 685.12 (44 999.20 to 85 192.92)	46.87% (43.31% to 50.52%)	−16.34% (−17.12% to −15.55%)
Migraine	2	2	26 863.35 (3969.24 to 61 445.23)	42 077.67 (6418.38 to 95 645.21)	56.64% (52.61% to 62.08%)	1.54% (−4.43% to 3.27%)
Age-related and other hearing loss	5	3	22 008.10 (14 914.22 to 31 340.37)	40 235.30 (27 393.19 to 57 131.94)	82.82% (75.22% to 88.94%)	−1.82% (−3.65% to −0.14%)
Other musculoskeletal disorders	7	4	16 608.89 (11 264.34 to 23 176.10)	38 459.70 (26 253.49 to 53 553.79)	131.56% (124.6% to 139.54%)	32.24% (28.82% to 36.45%)
Major depressive disorder	4	5	23 461.28 (16 026.05 to 32 502.66)	37 202.74 (25 650.21 to 51 217.04)	58.57% (53.61% to 62.96%)	−2.83% (−4.06% to −1.63%)
Type 2 diabetes	10	6	11 626.63 (7964.90 to 15 799.45)	35 150.63 (23 966.55 to 47 810.13)	202.33% (197.13% to 207.63%)	50.23% (48.08% to 52.22%)
Anxiety disorders	6	7	18 661.02 (12 901.15 to 25 547.29)	28 676.05 (19 858.08 to 39 315.12)	53.67% (48.76% to 59.06%)	−0.12% (−0.95% to 0.74%)
Dietary iron deficiency	3	8	25 069.79 (16 835.78 to 36 058.21)	28 534.68 (19 127.59 to 41 139.28)	13.82% (10.49% to 17.17%)	−16.39% (−18.72% to −14%)
Neck pain	9	9	12 393.48 (8128.87 to 17 740.32)	22 081.32 (14 508.24 to 31 726.93)	78.17% (69.45% to 87.06%)	−0.34% (−2.47% to 1.85%)
Falls	8	10	12 639.31 (8965.44 to 17 334.90)	21 383.29 (15 161.79 to 29 501.22)	69.18% (65.42% to 73.71%)	−7% (−8.56% to −5.35%)
Chronic obstructive pulmonary disease	13	11	10 472.74 (8682.19 to 11 830.68)	19 837.47 (16 596.49 to 22 441.73)	89.42% (85.38% to 93.59%)	−4.85% (−6.64% to −2.98%)
Endocrine, metabolic, blood, and immune disorders	11	12	11 022.44 (7513.64 to 15 340.32)	18 000.31 (12 249.60 to 24 962.91)	63.31% (59.14% to 67.48%)	−4.64% (−6.09% to −3.38%)
Other gynecological diseases	12	13	10 812.95 (7041.93 to 15 340.80)	16 382.52 (10 628.96 to 23 352.28)	51.51% (48.55% to 54.4%)	−9.37% (−11.11% to −7.59%)
Schizophrenia	14	14	9131.34 (6692.14 to 11 637.63)	15 107.25 (11 003.87 to 19 206.79)	65.44% (62.36% to 68.86%)	−0.56% (−1.57% to 0.38%)
Ischemic stroke	18	15	6499.45 (4626.50 to 8367.19)	13 128.53 (9349.92 to 16 930.38)	101.99% (97.41% to 106.95%)	0.07% (−1.76% to 1.95%)
Osteoarthritis knee	25	16	5184.78 (2569.34 to 10 565.52)	11 534.02 (5719.12 to 23 489.98)	122.46% (120.76% to 124.08%)	7.8% (7.1% to 8.44%)
Diarrheal diseases	16	17	8035.21 (5544.86 to 11 122.17)	11 030.29 (7631.54 to 15 146.75)	37.27% (33.79% to 41.16%)	−2.63% (−4.19% to −1.02%)
Alcohol use disorders	17	18	7875.53 (5287.35 to 11 122.36)	10 732.01 (7253.40 to 15 212.46)	36.27% (31.35% to 41.08%)	−15.49% (−16.83% to −14.07%)
Asthma	15	19	8832.45 (5776.18 to 13 071.58)	10 196.26 (6654.65 to 15 061.36)	15.44% (12.66% to 18.69%)	−23.4% (−26.63% to −20.2%)
Neonatal preterm birth	26	20	5054.73 (3854.95 to 6433.30)	9673.88 (7598.43 to 12 021.19)	91.38% (75.26% to 106.94%)	43.44% (31.94% to 54.79%)

UI indicates uncertainty interval; and YLDs, years of life lived with disability or injury.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[67] Printed with permission. Copyright © 2020, University of Washington.

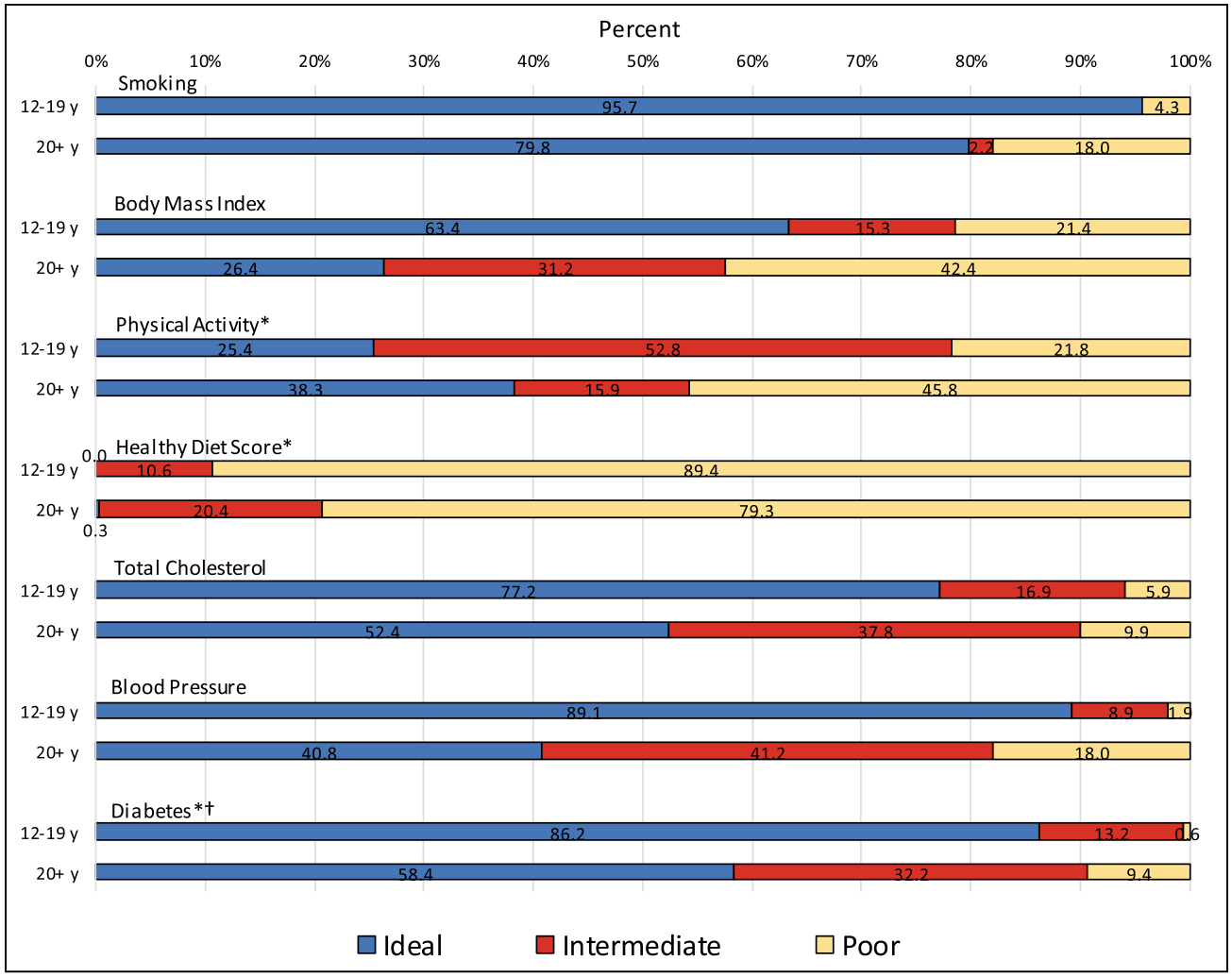

Chart 2-1. Prevalence estimates of poor, intermediate, and ideal cardiovascular health (CVH) for each component of CVH among US children 12 to 19 years of age and US adults ≥20 years of age, 2015 to 2016 and 2017 to 2018.

*2015 to 2016 data for both age groups for healthy diet score and diabetes and for 12 to 19 years of age for physical activity. All other data are from 2017 to 2018. Data collection methodology for physical activity was changed in 2017 to 2018 for participants <18 years of age, resulting in an inability to estimate prevalence of ideal physical activity levels in this age group during this cycle.

†Categories defined by either fasting plasma glucose or hemoglobin A_{1c} on the basis of data availability. Prevalence estimates for adults ≥20 years of age are age adjusted.

Source: Unpublished American Heart Association tabulation using National Health and Nutrition Examination Survey, 2015 to 2016 and 2017 to 2018.[54]

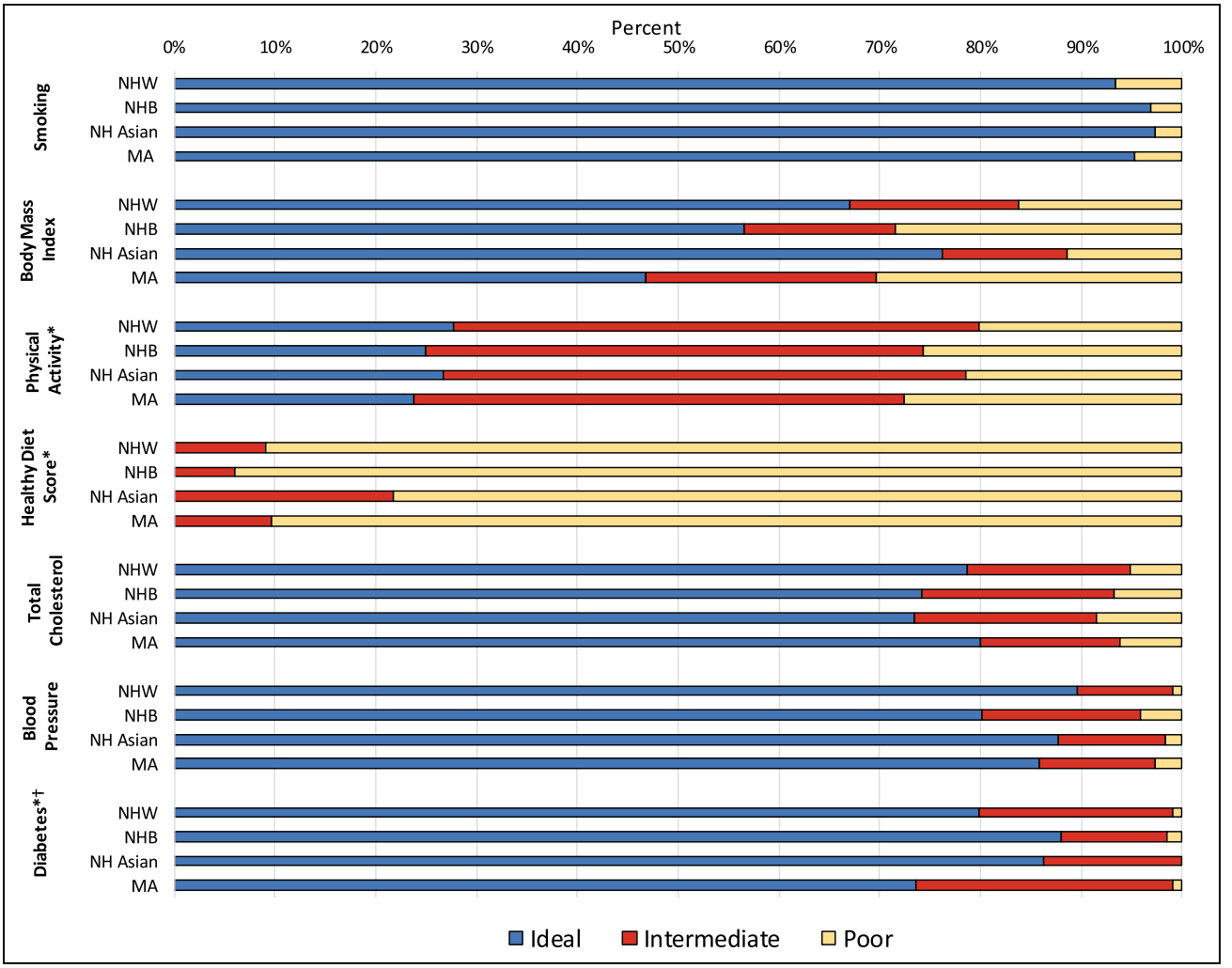

Chart 2-2. Prevalence estimates of poor, intermediate, and ideal cardiovascular health (CVH) for each component of CVH by race/ethnicity among US children 12 to 19 years, 2015 to 2016 and 2017 to 2018.

MA indicates Mexican American; NH, non-Hispanic; NHB, non-Hispanic Black; and NHW, non-Hispanic White.

*Data from 2015 to 2016. All other data are from 2017 to 2018.

†Categories defined by either fasting plasma glucose or hemoglobin A_{1c} on the basis of data availability. Prevalence estimates for adults ≥20 years of age are age adjusted.

Source: Unpublished American Heart Association tabulation using National Health and Nutrition Examination Survey, 2015 to 2016 and 2017 to 2018.[54]

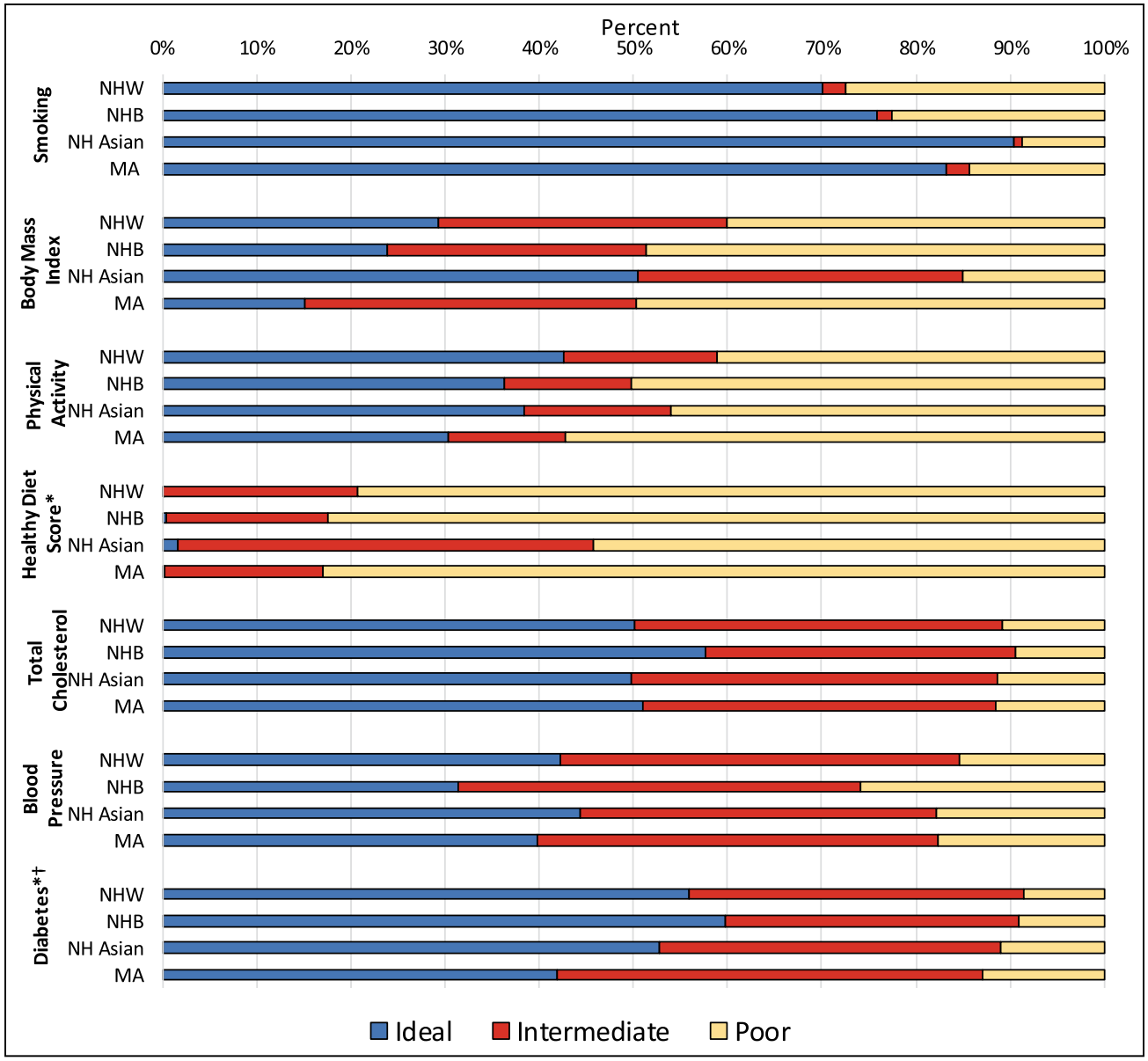

Chart 2-3. Age-adjusted prevalence estimates of poor, intermediate, and ideal cardiovascular health (CVH) for each component of CVH by race/ethnicity among US adults ≥20 years of age, 2015 to 2016 and 2017 to 2018.

MA indicates Mexican American; NH, non-Hispanic; NHB, non-Hispanic Black; and NHW, non-Hispanic White.

*Data from 2015 to 2016. All other data are from 2017 to 2018.

†Categories defined by either fasting plasma glucose or hemoglobin A_{1c} on the basis of data availability.

Source: Unpublished American Heart Association tabulation using National Health and Nutrition Examination Survey, 2015 to 2016 and 2017 to 2018.[54]

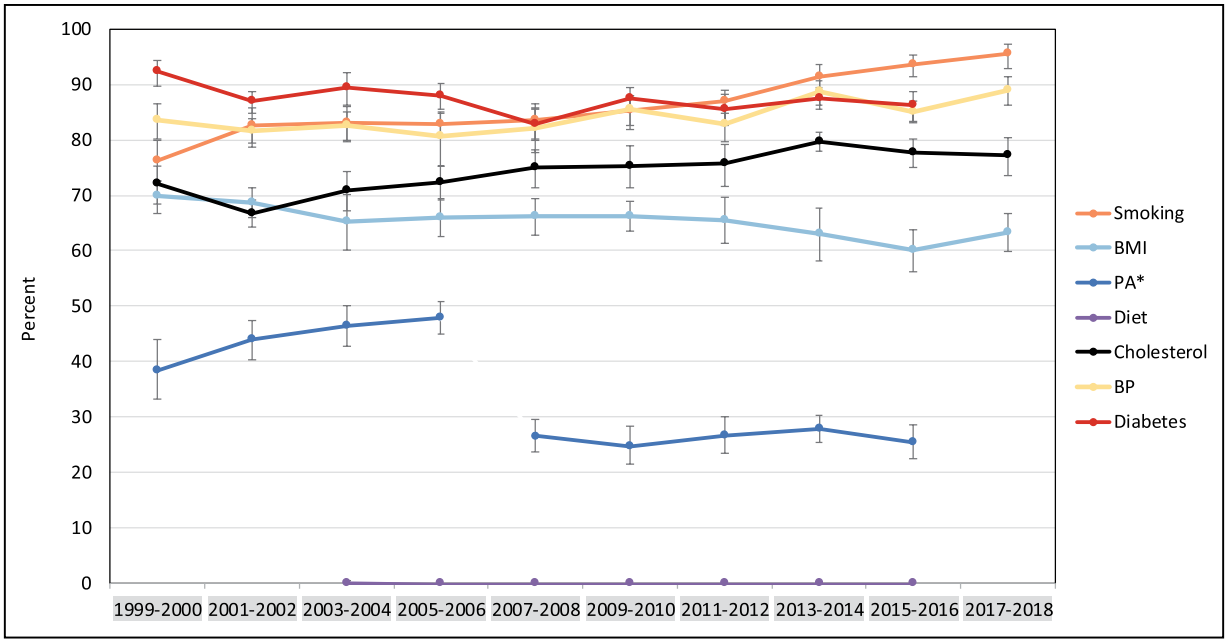

Chart 2-4. Trends in prevalence (unadjusted) of meeting ideal criteria for individual components of cardiovascular health (CVH) among US children 12 to 19 years of age, 1999 to 2000 through 2017 to 2018.

Error bars represent 95% CI. Data for the Healthy Diet Score, based on a 2-day average intake, were available only for the 2003 to 2004, 2005 to 2006, 2007 to 2008, 2009 to 2010, 2011 to 2012, 2013 to 2014, and 2015 to 2016 National Health and Nutrition Examination Survey (NHANES) cycles at the time of this analysis. Data on diet and diabetes were not available for NHANES 2017 to 2018 at the time of these analyses.

BMI indicates body mass index; BP, blood pressure; and PA, physical activity.

*Because of changes in the PA questionnaire between NHANES cycles 1999 to 2006 and 2007 to 2016, prevalence trends over time for this CVH component should be interpreted with caution, and statistical comparisons should not be attempted. Trend lines are absent between these time frames as an indicator of this issue. Data collection methodology for PA was changed in 2017 to 2018 for participants <18 years of age, resulting in an inability to estimate prevalence of ideal PA levels in this age group during this cycle.

Source: Unpublished American Heart Association tabulation using NHANES, 1999 to 2000 through 2017 to 2018.[54]

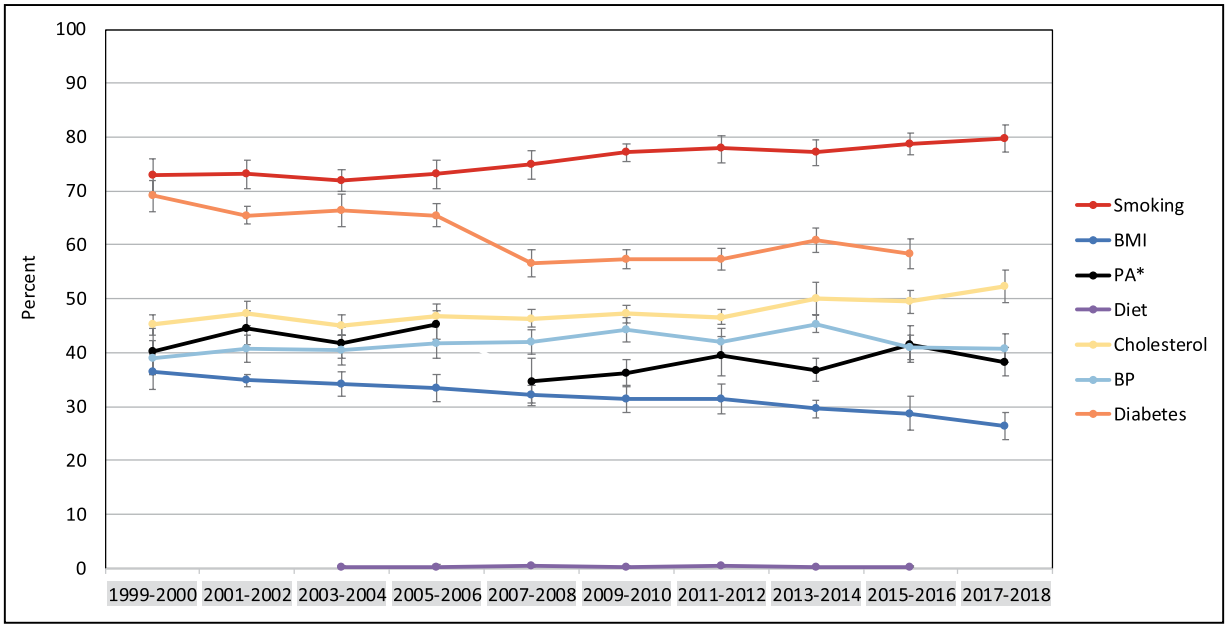

Chart 2-5. Age-standardized trends in prevalence of meeting ideal criteria for individual components of cardiovascular health (CVH) among US adults ≥20 years of age, 1999 to 2000 through 2017 to 2018.

Error bars represent 95% CI. Data for the Healthy Diet Score, based on a 2-day average intake, were available only for the 2003 to 2004, 2005 to 2006, 2007 to 2008, 2009 to 2010, 2011 to 2012, 2013 to 2014, and 2015 to 2016 National Health and Nutrition Examination Survey (NHANES) cycles at the time of this analysis. Data on diet and diabetes were not available for NHANES 2017 to 2018 at the time of this analysis.

BMI indicates body mass index; BP, blood pressure; and PA, physical activity.

*Because of changes in the PA questionnaire between NHANES cycles 1999 to 2006 and 2007 to 2018, prevalence trends over time for this CVH component should be interpreted with caution, and statistical comparisons should not be attempted. Trend lines are absent between these time frames as an indicator of this issue.

Source: Unpublished American Heart Association tabulation using NHANES, 1999 to 2000 through 2017 to 2018.[54]

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3. Deleted in proof.
4. Deleted in proof.
5. Deleted in proof.
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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. Cigarette smoking, the most common form of tobacco use, is a major risk factor for CVD and stroke.[1] 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 CVH in Life's Simple 7.[2] Unless otherwise stated, throughout the rest of this chapter, we report tobacco use and smoking estimates from the NYTS[3] for adolescents and from the NHIS[4] for adults (≥18 years of age) because these data sources have more recent data. As a survey of middle and high school students, the NYTS may not be generalizable to youth who are not enrolled in school; however, in 2016, 97% of youth 10 to 17 years of age were enrolled in school, which indicates that the results of the NYTS are likely broadly applicable to US youth.[3]

Other forms of tobacco use are becoming increasingly common. 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*.[5] A notable evolution in electronic nicotine delivery systems technology and marketing has occurred recently with the advent of pod mods, small rechargeable devices that deliver high levels of nicotine derived from nicotine salts in loose-leaf tobacco.[6] Use of cigars, cigarillos, filtered cigars, and hookah also has become increasingly common in recent years. Thus, each section below addresses 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

ABI	ankle-brachial index
ACS	acute coronary syndrome
AHA	American Heart Association
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
CVH	cardiovascular health
DALY	disability-adjusted life-year
DBP	diastolic blood pressure
EAGLES	Study Evaluating the Safety and Efficacy of Varenicline and Bupropion for Smoking Cessation in Subjects With and Without a History of Psychiatric Disorders
e-cigarette	electronic cigarette
EVITA	Evaluation of Varenicline in Smoking Cessation for Patients Post-Acute Coronary Syndrome
FDA	US Food and Drug Administration
GBD	Global Burden of Disease Study
HD	heart disease
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
HR	hazard ratio
MEPS	Medical Expenditure Panel Survey
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
MPOWER	Monitor tobacco use and prevention policies
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NSDUH	National Survey on Drug Use and Health
NYTS	National Youth Tobacco Survey
OR	odds ratio
PAD	peripheral artery disease
PAF	population attributable fraction
PAR	population attributable risk
PATH	Population Assessment of Tobacco and Health
QALY	quality-adjusted life-year
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
YRBSS	Youth Risk Behavior Survey

(*Continued*)

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Prevalence (See Chart 3-1)

Youth

- Prevalence of cigarette use in the past 30 days for middle and high school students by sex and race/ethnicity in 2019 is shown in Chart 3-1.

- In 2019[7]:
  - 31.2% (95% CI, 29.1%–33.5%) of high school students (corresponding to 4.7 million users) and 12.5% (95% CI, 11.2%–13.9%) of middle school students (corresponding to 1.5 million users) used any tobacco products. In addition, 5.8% (95% CI, 4.6%–7.3%) of high school students (860 000 users) and 2.3% (95% CI, 1.8%–2.9%) of middle school students (270 000 users) smoked cigarettes in the past 30 days.
  - 4.8% (95% CI, 3.7%–6.3%) of high school students (720 000 users) and 1.8% (95% CI, 1.4%–2.2%) of middle school students (210 000) used smokeless tobacco in the past 30 days.
  - 7.6% (95% CI, 6.6%–8.8%) of high school students (1.1 million users) and 2.3% (95% CI, 1.9%–2.9%) of middle school students (270 000 users) used cigars in the past 30 days.
- Of youth who smoked cigarettes in the past 30 days in 2019, 28.9% (95% CI, 23.1%–35.5%) of middle and high school students (corresponding to 330 000 users) reported smoking cigarettes on 20 to 30 days of the past 30 days.[7]
- In 2019, tobacco use within the past month for middle and high school students varied by race/ethnicity: The prevalence of past 30-day cigarette use was 5.0% (95% CI, 3.9%–6.4%) in NH White youth compared with 3.1% (95% CI, 2.3–4.1%) in NH Black youth and 3.6% (95% CI, 2.8%–4.5%) in Hispanic youth. For cigars, the respective percentages were 5.1% (95% CI, 4.3%–6.1%), 8.6% (7.0%–10.6%), and 4.8% (95% CI, 3.9%–5.9%).[7]
- The percentage of high school (27.5% or 4 110 000 users) and middle school (10.5% or 1 240 000 users) students who used e-cigarettes in the past 30 days exceeded the proportion using cigarettes in 2019 (Chart 3-1).

Adults
(See Charts 3-2 and 3-3)

- According to the NHIS 2018 data, among adults ≥18 years of age[4]:
  - 13.7% (95% CI, 13.1%–14.3%) of adults reported cigarette use every day or some days.
  - 15.6% (95% CI, 14.8%–16.5%) of males and 12.0% (95% CI, 11.2%–12.7%) of females reported cigarette use every day or some days.
  - 7.8% of those 18 to 24 years of age, 16.5% of those 25 to 44 years of age, 16.3% of those 45 to 64 years of age, and 8.4% of those ≥65 years of age reported cigarette use every day or some days.
  - 22.6% of NH American Indian or Alaska Native adults, 14.6% of NH Black adults, 7.1% of NH Asian adults, 9.8% of Hispanic adults, and 15.0% of NH White adults reported cigarette use every day or some days.
  - By annual household income, reported cigarette use every day or some days was 21.3% of people with <$35 000 income compared with 14.9% of those with income of $35 000 to $74 999, 13.3% of those with income of $75 000 to $99 999, and 7.3% of those with income ≥$100 000.
  - In adults ≥25 years of age, the percentage reporting current cigarette use was 21.8% for those with <12 years of education, 36.0% in those with a General Educational Development high school equivalency, 19.7% among those with a high school diploma, 18.3% among those with some college, 14.8% among those with an associate's degree, and 7.1% among those with an undergraduate degree compared with 3.7% among those with a graduate degree.
  - 20.6% of lesbian/gay/bisexual individuals were current smokers compared with 13.5% of heterosexual/straight individuals.
  - By region, the prevalence of current cigarette smokers was highest in the Midwest (16.2%) and South (14.8%) and lowest in the Northeast (12.5%) and West (10.7%).[4]
- According to data from BRFSS 2018, the state with the highest age-adjusted percentage of current cigarette smokers was West Virginia (26.8%). The states with the lowest age-adjusted percentage of current cigarette smokers were Utah (9.0%) and California (11.4%; Chart 3-2).[8]
- In 2018, smoking prevalence was higher among adults ≥18 years of age who reported having a disability or activity limitation (19.2%) than among those reporting no disability or limitation (13.1%).[4]
- Among individuals reporting serious psychological distress, 31.6% were current smokers compared with 13.0% of those without serious psychological distress.[4]
- Among females who gave birth in 2016, 7.2% smoked cigarettes during pregnancy. Smoking prevalence during pregnancy was greatest for females 20 to 24 years of age (10.7%), followed by females 15 to 19 years of age (8.5%) and 25 to 29 years of age (8.2%).[9] 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%).
- e-Cigarette prevalence in 2017 is shown in Chart 3-3. Comparing e-cigarette prevalence across the 50 states shows that the average age-adjusted prevalence

was 5.3%. The lowest age-adjusted prevalence was observed in California (3.2%), and the highest prevalence was observed in Oklahoma (7.5%). The age-adjusted prevalence was 1.3% in Puerto Rico.

Incidence

- According to the 2018 NSDUH, ≈1.83 million people ≥12 years of age had smoked cigarettes for the first time within the past 12 months compared with 1.90 million in 2017 (2018 NSDUH Table 4.2B).[10] Of new smokers in 2018, 571 000 were 12 to 17 years of age, 781 000 were 18 to 20 years of age, and 360 000 were 21 to 25 years of age; only 113 000 were ≥26 years of age when they first smoked cigarettes.
- The number of new smokers 12 to 17 years of age in 2018 (571 000) decreased from 2017 (604 000). The number of new smokers 18 to 25 years of age in 2018 (1.14 million) also decreased from 2017 (1.15 million) (2018 NSDUH Table 4.2B).[10]
- According to data from the PATH Study between 2013 and 2016, in youth 12 to 15 years of age, use of an e-cigarette was independently associated with new ever use of combustible cigarettes (OR, 4.09 [95% CI, 2.97–5.63]) and past 30-day use (OR, 2.75 [95% CI, 1.60–4.73]) at 2 years of follow-up. For youth who tried another non–e-cigarette tobacco product, a similar strength of association for cigarette use at 2 years was observed.[11]

Lifetime Risk

Youth

- Per NSDUH data for individuals 12 to 17 years of age, overall, the lifetime use of tobacco products declined from 14.9% to 13.4% between 2017 and 2018, with lifetime cigarette use declining from 10.8% to 9.6% during the same time period (2018 NSDUH Tables 2.2B and 2.3B).[10]
  - The lifetime use of tobacco products among adolescents 12 to 17 years of age varied by the following:
    - Sex: Lifetime use was higher among males (14.7%) than females (12.0%; 2018 NSDUH Table 2.8B).[10]
    - Race/ethnicity: Lifetime use was highest among American Indian and Alaska Native adolescents (18.7%), followed by NH White adolescents (16.3%), Hispanic or Latino adolescents (10.8%), NH Black adolescents (9.8%), and NH Asian adolescents (4.6%; 2018 NSDUH Table 2.8B).[10]

Adults

- According to NSDUH data, the lifetime use of tobacco products in individuals ≥18 years of age did not decline significantly between 2017 (67.5%) and 2018 (66.3%). Lifetime cigarette use declined in a similar interval from 61.8% to 60.3% (2018 NSDUH Tables 2.2B and 2.3B).[10] Similar to the patterns in youth, lifetime risk of tobacco products varied by demographic factors (2018 NSDUH Table 2.8B)[10]:
  - Sex: Lifetime use was higher in males (75.0%) than females (58.2%).
  - Race/ethnicity: Lifetime use was highest in American Indian or Alaska Native adults (78.2%) and NH White adults (74.1%), followed by Native Hawaiian or Other Pacific Islander adults (69.7%), Hispanic or Latino adults (51.6%), NH Black adults (55.1%), and NH Asian adults (40.1%).
- In 2018, the lifetime use of smokeless tobacco for adults ≥18 years of age was 16.7% (2018 NSDUH Table 2.1B).

Secular Trends (See Chart 3-4)

Youth

The percentage of adolescents (12–17 years of age) who reported smoking cigarettes in the past month declined from 13.0% in 2002 to 2.7% in 2018 (NSDUH Table 7.6B[10]; Chart 3-4). The percentages for daily cigarette use among those with past-month cigarette smoking in 12- to 17-year-olds were 31.5% in 2002 and 14.8% in 2018.[10,12] Trends in e-cigarette use and other tobacco product use among high school students between 2011 and 2018 are shown in Chart 3-5.

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 15.6% in 2018 and from 34% of females in 1965 to 12.0% in 2018, according to NHIS data.[4,13] 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.[14]

- On the basis of weighted NHIS data, the current smoking status among 18- to 24-year-old males declined 47.5%, from 28.0% in 2005 to 14.7% in 2016; for 18- to 24-year-old females, smoking declined 44.4%, from 20.7% to 11.5%, over the same time period.[15]
- According to data from the BRFSS, the prevalence of e-cigarette use increased from 4.3% to 4.8% between 2016 and 2018 in US adults. Increases in e-cigarette use over this period were significant for middle-aged adults, women, and former smokers.[16]

- 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%.[15]

CVH 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.[17] 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 were reported in a systematic review of regular cigar smoking.[18]
- 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 diabetes.[17]
- Cigarette smoking and other traditional CHD risk factors might have a synergistic interaction in HIV-positive individuals.[19]
- Among the US Black population, cigarette use is associated with elevated measures of subclinical PAD in a dose-dependent manner. Current smokers had an increased adjusted odds of ABI <1 (OR, 2.2 [95% CI, 1.5–3.3]).[20]
- 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]).[21]
- Cigarette smoking is a risk factor for both ischemic stroke and SAH in adjusted analyses and has a synergistic effect on other stroke risk factors such as oral contraceptive use.[22]
- 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.[23]
- Current smokers have a 2 to 4 times increased risk of stroke compared with nonsmokers or those who have quit for >10 years.[22,24]
- A meta-analysis of 26 studies reported that compared with never smoking, current smoking (RR, 1.75 [95% CI, 1.54–1.99]) and former smoking (RR, 1.16 [95% CI, 1.08–1.24]) were associated with increased risk of HF.[25] In MESA, compared with never smoking, current smoking was associated with an adjusted doubling in incident HF (HR, 2.05 [95% CI, 1.36–3.09]). The increased risk was similar for HFpEF (HR, 2.51) and HFrEF (HR, 2.58).[26]
- Short-term exposure to water pipe smoking is associated with a significant increase in SBP, DBP, and heart rate compared with nonsmoking control subjects,[27] but long-term effects remain unclear. Current use of smokeless tobacco was associated with an adjusted 1.27-fold increased risk of CVD events compared with never using. The CVD rate was 11.3 per 1000 person-years in never users and 21.4 in current users of smokeless tobacco.[28]
- The long-term CVD risks associated with e-cigarette use are not known because of a lack of longitudinal data.[29,30] However, e-cigarette use has been linked to elevated levels of preclinical biomarkers associated with cardiovascular injury such as markers for sympathetic activation, oxidative stress, inflammation, thrombosis, and vascular dysfunction.[31] In addition, daily and some-day use of e-cigarettes may be associated with MI and CHD.[32,33]
- Dual use of e-cigarettes and combustible cigarettes was associated with significantly higher odds of CVD (OR, 1.36 [95% CI, 1.18–1.56]) compared with exclusive combustible cigarette use.[33] The association of dual use (relative to exclusive cigarette use) with CVD was 1.57 (95% CI, 1.18–2.07) for daily e-cigarette users and 1.31 (95% CI, 1.13–1.53) for occasional e-cigarette users.

Family History and Genetics

- Genetic factors contribute to smoking behavior; common and rare variants in several loci have been found to be associated with smoking initiation, number of cigarettes smoked per day, and smoking cessation.[34,35]
- Genetics might also modify adverse CVH outcomes among smokers, with variation in *ADAMTS7* associated with loss of cardioprotection in smokers.[36]

Smoking Prevention

Tobacco 21 legislation was signed into law on December 20, 2019, increasing the federal minimum age for sale of tobacco products from 18 to 21 years.[37]

- Such legislation is likely to 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.
  - For instance, investigators compared smoking rates in Needham, MA, after introduction of an ordinance that raised the minimum purchase age to 21 years. The 30-day smoking rate in Needham declined from 13% to 7% between 2006 and 2010 compared with a decline from 15% to 12% (P<0.001) in 16 surrounding communities.[38]

— Another study using BRFSS 2011 to 2016 data before the federal legislation found that metropolitan and micropolitan statistical areas with local Tobacco 21 policies yielded significant reductions in smoking among youth 18 to 20 years of age.[39]

- In addition, in several towns where Tobacco 21 laws were enacted before federal legislation, reductions of up to 47% in smoking prevalence among high school students have been reported.[40] Furthermore, the National Academy of Medicine estimates that the nationwide Tobacco 21 law could result in 249 000 fewer premature deaths, 45 000 fewer lung cancer deaths, and 4.2 million fewer life-years lost among Americans born between 2010 and 2019.[40]
- Before the federal minimum age of sale increase, 19 states (Hawaii, California, New Jersey, Oregon, Maine, Massachusetts, Illinois, Virginia, Delaware, Arkansas, Texas, Vermont, Connecticut, Maryland, Ohio, New York, Washington, Pennsylvania, and Utah), Washington, DC, and at least 470 localities (including New York City, NY; Chicago, IL; San Antonio, TX; Boston, MA; Cleveland, OH; and both Kansas Cities [Kansas and Missouri]) passed legislation setting the minimum age for the purchase of tobacco to 21 years.[41]

Awareness, Treatment, and Control

Smoking Cessation

- According to NHIS 2017 data, 61.7% of adult ever smokers had stopped smoking; the quit rate has increased 6 percentage points since 2012 (55.1%).[42]
  - — Between 2011 and 2017, according to BRFSS surveys, quit attempts varied by state, with quit attempts increasing in 4 states (Kansas, Louisiana, Virginia, and West Virginia), declining in 2 states (New York and Tennessee), and not changing significantly in 44 states. In 2017 the quit attempts over the past year were highest in Guam (72.3%) and lowest in Wisconsin (58.6%), with a median of 65.4%.[43]
  - — According to NHIS 2015 data, 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 health care provider advice to quit.[44] Receiving advice to quit smoking was lower among uninsured smokers (44.1%) than among those with health insurance coverage through Medicaid or those who were dual eligible for coverage (both Medicaid and Medicare; 59. 9%).
- Data from clinical settings suggest wide variation in counseling practices related to smoking cessation. In a study based on national registry data, only 1 in 3 smokers who visited a cardiology practice received smoking cessation assistance.[45]
- According to cross-sectional MEPS data from 2006 to 2015, receiving advice to quit increased over time from 60.2% in 2006 to 2007 to 64.9% in 2014 to 2015. In addition, in 2014 to 2015, use of prescription smoking cessation medicine was significantly lower among NH Black (OR, 0.51 [95% CI, 0.38–0.69]), NH Asian (OR, 0.31 [95% CI, 0.10–0.93]), and Hispanic (OR, 0.53 [95% CI, 0.36–0.78]) individuals compared with White individuals. Use of prescription smoking cessation medicine was also significantly lower among those without health insurance (OR, 0.58 [95% CI, 0.41–0.83]) and higher among females (OR, 1.28 [95% CI, 1.10–1.52]).[46] In 2014 to 2015, receipt of doctor's advice to quit among US adult smokers was significantly lower in NH Black (59.7 [95% CI, 56.1–63.1]) and Hispanic (57.9 [95% CI, 53.5–62.2]) individuals compared with NH White individuals (66.6 [95% CI, 64.1–69.1]).
  - — 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.[44]
  - — In 2015, fewer 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).[44]
- Smoking cessation reduces the risk of cardiovascular morbidity and mortality for smokers with and without CHD.
  - — In several studies, a dose-response relationship has been seen among current smokers between the number of cigarettes smoked per day and CVD incidence.[47,48]
  - — Quitting smoking at any age significantly lowers mortality from smoking-related diseases, and the risk declines with the time since quitting smoking.[1] Cessation appears to have both short-term (weeks to months) and long-term (years) benefits for lowering CVD risk.[49]
  - — Smokers who quit smoking at 25 to 34 years of age gained 10 years of life compared with those who continued to smoke. Those 35 to 44 years of age gained 9 years, those 45 to 54 years of age gained 6 years, and those 55 to 64 years of age gained 4 years of life, on average, compared with those who continued to smoke.[47]

— Among those with a cumulative smoking history of at least 20 pack-years, individuals who quit smoking had a significantly lower risk of CVD within 5 years of smoking cessation compared with current smokers. However, former smokers' CVD risks remained significantly higher than risks for never smokers beyond 5 years after smoking cessation.[50]

- Cessation medications (including sustained-release bupropion, varenicline, nicotine gum, lozenge, nasal spray, and patch) are effective for helping smokers quit.[51,52]
- 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. The abstinence rates at 24 weeks were higher in the varenicline (47.3%) than the placebo (32.5%) group (P=0.012; number needed to treat, 6.8). Continuous abstinence rates and reduction rates (≥50% of daily cigarette consumption) were also higher in the varenicline group.[53]
- The EAGLES trial[54] demonstrated the efficacy and safety of 12 weeks of varenicline, bupropion, or nicotine patch in motivated-to-quit patients who smoked 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.[54]
- Extended use of a nicotine patch (24 weeks compared with 8 weeks) has been demonstrated to be safe and efficacious in randomized clinical trials.[55]
- An RCT demonstrated the effectiveness of individual- and group-oriented financial incentives for tobacco abstinence through at least 12 months of follow-up.[56]
- In addition to medications, smoke-free policies, increases in tobacco prices, cessation advice from health care professionals, and quit lines and other counseling have contributed to smoking cessation.[44,57]
- 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. Investigators estimated that the Tips campaign cost about $48 million, saved ≈179 099 QALYs, and prevented ≈17 000 premature deaths in the United States.[58]
- 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.[59]
- A randomized trial of e-cigarettes and behavioral support versus nicotine-replacement therapy and behavioral support in adults attending the UK National Health Service stop-smoking services found that 1-year cigarette abstinence rates were 18% in the e-cigarette group compared with 9.9% in the nicotine-replacement therapy group (RR, 1.83 [95% CI, 1.30–2.58]; P<0.001). However, among participants abstinent at 1 year, in the nicotine-replacement therapy group, only 9% were still using nicotine-replacement therapy, whereas 80% of those in the e-cigarette group were still using e-cigarettes.[60]
- Observational evidence suggests that daily use of e-cigarettes is associated with increased likelihood of combustible cigarette smoking abstinence. However, some-day use of e-cigarettes is not associated with smoking abstinence or reduction.[61]

Mortality

- According to the 2020 Surgeon General's report on smoking cessation, >480 000 Americans die as a result of cigarette smoking and >41 000 die of secondhand smoke exposure each year, ≈1 in 5 deaths annually.
- 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.[62] Overall mortality among US smokers is 3 times higher than that for never smokers.[47]
- On average, on the basis of 2016 data, male smokers die 12 years earlier than male never smokers, and female smokers die 11 years earlier than female never smokers.[14,63]
- Increased CVD mortality risks persist for older (≥60 years of age) smokers as well. A meta-analysis of 25 studies 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.[64]
- In a sample of Native American individuals (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.[65]
- 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.[66]
- If current smoking trends continue, 5.6 million US children will die of smoking prematurely during adulthood.[17]

Electronic Cigarettes (See Charts 3-1 and 3-4)

- Electronic nicotine delivery systems, more commonly called e-cigarettes, are battery-operated devices that deliver nicotine, flavors, and other chemicals to the user in an aerosol. Although e-cigarettes were introduced into the United States only around 2007, there are currently >450 e-cigarette brands on the market, and sales in the United States were projected to be $2 billion in 2014. In 2015, Juul came on the market and has rapidly become the most popular e-cigarette product sold in the United States. The popularity of the Juul likely relates to several factors, including its slim and modern design, appealing flavors, and intensity of nicotine delivery, which approximates the experience of combustible cigarettes.[67]
- e-Cigarette use has become prevalent among never smokers. In 2016, an estimated 1.9 million tobacco users exclusively used e-cigarettes in the United States. Of these exclusive e-cigarette users, 60% were <25 years of age.[68]
- Current e-cigarette user prevalence for 2017 in the United States is shown in Chart 3-3.
- According to the NYTS, in 2019, e-cigarettes were the most commonly used tobacco products in youth: In the past 30 days, 10.5% (1.2 million) of middle school and 27.5% (4.1 million) of high school students endorsed use (Chart 3-1).[7] A significant nonlinear increase in current e-cigarette use in high school students was observed between 2011 (1.5%) and 2019 (27.4%).[7,69] A significant increase in current e-cigarette use also was observed for middle school students, for whom the corresponding values were 0.6% and 10.5% in the 2 periods.[3,7] Among high school students, rates of use were approximately equal between males (27.6%) and females (27.4%) and most pronounced among NH White students (32.4%). In middle school students, slightly higher rates were observed in females (10.8%) and in Hispanic students (13.1%).[7]
- Frequent use of e-cigarettes among high school students who were current e-cigarette users increased from 27.7% in 2018 to 34.2% in 2019. In middle school students, the percentage using frequently among current e-cigarette users increased from 16.2% in 2018 to 18.0% in 2019.[3,7]
- In 2016, 20.5 million US middle and high school students (80%) were exposed to e-cigarette advertising.[70]
- Among US adults, awareness and use of e-cigarettes have increased considerably.[71] In 2018, the prevalence of current e-cigarette use in adults, defined as use every day or on some days, was 3.2% according to data from the NHIS. The prevalence of current e-cigarette use was highest in individuals 18 to 24 years of age (7.6%) and in those with serious psychological distress (6.2%).[4]
- According to BRFSS 2016, current use of e-cigarettes in adults ≥18 years of age was higher in sexual and gender minority individuals. With respect to sexual orientation, 9.0% of bisexual and 7.0% of lesbian/gay individuals were current e-cigarette users compared with 4.6% of heterosexual people. Individuals who were transgender (8.7%) were current e-cigarette users at a higher rate than cisgender individuals (4.7%). Across US states, the highest prevalence of current e-cigarette use was observed in Oklahoma (7.0%) and the lowest in South Dakota (3.1%).[72]
- e-Cigarettes contain lower levels of most tobacco-related toxic constituents compared with traditional cigarettes,[73] including volatile organic compounds.[74,75] However, nicotine levels have been found to be consistent across long-term cigarette and long-term e-cigarette users.[31,76]
- e-Cigarette use has a significant cross-sectional association with a less favorable perception of physical and mental health and with depression.[77,78]
- According to the BRFSS 2016 and 2017, e-cigarettes are associated with a 39% increased odds of self-reported asthma (OR, 1.39 [95% CI, 1.15–1.68]) and self-reported chronic obstructive pulmonary disease (OR, 1.75 [95% CI, 1.25–2.45]) among never users of combustible cigarette.[79,80] There is a dose-response relationship such that higher frequency of e-cigarette use was associated with more asthma or chronic obstructive pulmonary disease.
- An outbreak of e-cigarette or vaping product use–associated lung injury peaked in September 2019 after increasing rapidly between June and August 2019. Surveillance data and product testing indicate that tetrahydrocannabinol-containing e-cigarettes or vaping products are linked to most e-cigarette or vaping product use–associated lung injury cases. In particular, vitamin E acetate, an additive in some tetrahydrocannabinol-containing e-cigarettes or vaping, has been identified as the primary source of risk, although exposure to other e-cigarette– or vaping-related toxicants may also play a role. As of February 18, 2020, a total of 2807 hospitalized e-cigarette or vaping product use–associated lung

injury cases or deaths have occurred in the United States.[81]
- Effective August 8, 2016, the FDA's Deeming Rule prohibited sale of e-cigarettes to individuals <18 years of age.[82]
- In January 2020, the FDA issued a policy prioritizing enforcement against the development and distribution of certain unauthorized flavored e-cigarette products such as fruit and mint flavors (ie, any flavors other than tobacco and menthol).[83]

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%.[17]
  - 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.[84]
- 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.[85]
- A meta-analysis of 24 studies demonstrated that secondhand smoke can increase risks for preterm birth by 20%.[86]
- A study using the Framingham Offspring cohort found that there was an 18% increase in AF among offspring for every 1–cigarette pack per day increase in parental smoking. In addition, offspring with parents who smoked had 1.34 (95% CI, 1.17–1.54) times the odds of smoking compared with offspring with nonsmoking parents.[87]
- As of December 31, 2019, 14 states (California, Colorado, Delaware, Hawaii, Massachusetts, New Jersey, New Mexico, New York, North Dakota, Oregon, Rhode Island, South Dakota, 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 worksites, restaurants, and bars.[41,88]
- 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% (RR, 0.90 [95% CI, 0.86–0.94]).[89]
- 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 Black individuals (46.8%) than for NH White individuals (21.8%) and Mexican American individuals (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).[90]

Cost

According to the Surgeon General's 50th anniversary report on the health consequences of smoking, the estimated annual cost attributable to smoking from 2009 to 2012 was between $289 and $332.5 billion: Direct medical care for adults accounted for $132.5 to $175.9 billion; lost productivity because of premature death accounted for $151 billion (estimated from 2005–2009); and lost productivity resulting from secondhand smoke accounted for $5.6 billion (in 2006).[14]

- In the United States, cigarette smoking was associated with 8.7% of annual aggregated health care spending from 2006 to 2010, which represented roughly $170 billion per year, 60% of which was paid by public programs (eg, Medicare and Medicaid).[91]
- According to the CDC and Federal Trade Commission, the tobacco industry spends about $9.06 billion on cigarette and smokeless tobacco advertising annually, equivalent to $25 million per day.[92]
- In 2018, 216.9 billion cigarettes were sold by major manufacturers in the United States, which represents a 5.3% decrease (12.2 billion units) from 2017.[93]
- Cigarette prices in the United States increased steeply between the early 1970s and 2018, in large part because of excise taxes on tobacco products. Per pack in 1970, the average cost was $0.38 and tax was $0.18, whereas in 2018, the average cost was $6.90 and average tax $2.82.[94]
- From 2012 through 2016, e-cigarette sales significantly increased while national e-cigarette prices significantly decreased. Together, these trends highlight the rapidly changing landscape of the US e-cigarette marketplace.[94]
- Despite the morbidity and mortality resulting from tobacco use, Dieleman et al[95] estimated that tobacco interventions were among the bottom third of health care expenditures of the 154 health conditions they analyzed. They estimated that in 2019 the United States spent $1.9 billion (95% CI,

$1.5–$2.3 billion) on tobacco interventions, the majority (75.6%) on individuals 20 to 64 years of age. Almost half of the funding (48.5%) for the intervention came from public insurance.

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

- According to the GBD synthesis of >2800 data sources, the age-standardized global prevalence of daily smoking in 2017 was 8.7% (95% UI, 7.72%–9.79%) in males and 1.76% (95% UI, 1.52%–2.02%) in females. The investigators estimate that since 1990 smoking rates have declined globally by 23% in males and 42% in females.[96]
- The GBD 2019 study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 369 diseases and injuries and 87 risk factors in 204 countries and territories. Oceania, East and Central Asia, and Eastern Europe have the highest mortality rates attributable to tobacco (Chart 3-6).
- In 2015, there were a total of 933.1 million (95% UI, 831.3–1054.3 million) smokers globally, of whom 82.3% were male. The annualized rate of change in smoking prevalence between 1990 to 2015 was –1.7% in females and –1.3% in males.[97]
- Worldwide, ≈80% of smokers live in low- and middle-income countries.[98]
- Tobacco (including smoking, secondhand smoke, and chewing tobacco) caused an estimated 8.7 million deaths globally in 2019 (6.6 million males and 2.1 million females; Table 3-1).[99] GBD investigators estimated that in 2019 tobacco was the second leading risk of mortality (high SBP was number 1), and tobacco ranked third in DALYs globally.[99]
- The WHO estimated that the economic cost of smoking-attributable diseases accounted for US $422 billion in 2012, which represented ≈5.7% of global health expenditures.[100] 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.[72,101] In 2018, population cost coverage (either partial or full) for quit interventions increased to 78% in middle-income countries and to 97% in high-income countries; 5 billion people are now covered by at least 1 MPOWER measure. However, only 23 countries offered comprehensive cessation support in the same year.[102]
- The CDC examined data from 28 countries from the 2008 to 2016 Global Adult Tobacco Survey and reported that the median prevalence of tobacco smoking was 22.5% with wide heterogeneity (3.9% in Nigeria to 38.2% in Greece). Among current smokers, quit attempts over the prior 12 months also varied with a median of 42.5% (ranging from 14.4% in China to 59.6% in Senegal). Knowledge that smoking causes heart attacks (median, 83.6%; range, 38.7% in China to 95.5% in Turkey) and stroke (median 73.6%; range, 27.2% in China to 89.2% in Romania) varied widely across countries.[103]

Table 3-1. Deaths Caused by Tobacco Worldwide by Sex, 2019

	Both sexes (95% UI)	Males (95% UI)	Females (95% UI)
Total No. of deaths, millions	8.7 (8.1 to 9.3)	6.6 (6.0 to 7.1)	2.1 (2.0 to 2.3)
Percent change in total number 1990–2019	28.6 (19.5 to 38.8)	31.7 (20.2 to 45.0)	19.8 (10.2 to 29.6)
Percent change in total number 2010–2019	10.0 (3.3 to 17.2)	9.8 (1.6 to 18.7)	10.7 (3.8 to 18.1)
Mortality rate per 100 000, age-standardized	108.6 (101.3 to 115.9)	180.6 (166.1 to 194.8)	49.2 (44.8 to 53.7)
Percent change in rate, age standardized 1990–2019	–38.9 (–43.2 to –34.2)	–39.2 (–44.4 to –33.4)	–42.6 (–47.0 to –38.1)
Percent change in rate, age standardized 2010–2019	–15.1 (–20.1 to –9.7)	–15.6 (–21.8 to –9.0)	–14.9 (–20.1 to –9.3)
PAF, all ages, %	15.4 (14.6 to 16.2)	21.4 (20.5 to 22.3)	8.3 (7.7 to 8.9)
Percent change in PAF, all ages 1990–2019	6.1 (0.8 to 12.1)	7.5 (2.5 to 13.7)	0.1 (–5.4 to 6.4)
Percent change in PAF, all ages 2010–2019	2.6 (–1.3 to 6.6)	3.4 (–0.6 to 7.1)	2.1 (–1.1 to 5.5)

PAF indicates population attributable fraction; and UI, uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[99] Printed with permission. Copyright © 2020, University of Washington.

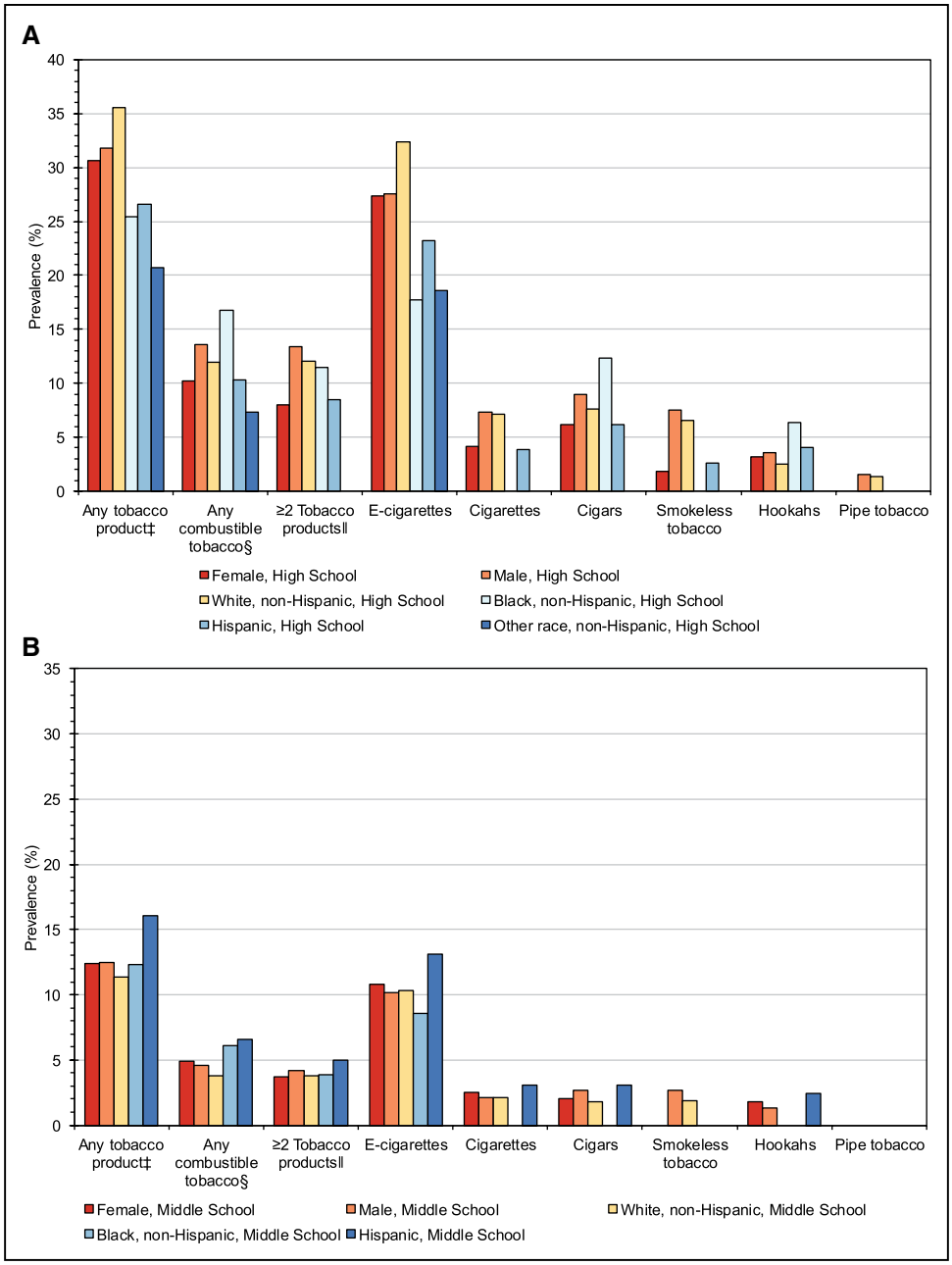

Chart 3-1. Prevalence (percent) of tobacco use in the United States in the past 30 days by product,* school level, sex, and race/ethnicity† (NYTS, 2019).
Data in (**A**) relate to high school students and (**B**) relate to middle school students. Because of methodological differences among the NSDUH, the YRBSS, the NYTS, 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 of age, who are legally permitted to smoke and have higher rates of smoking.
e-Cigarette indicates electronic cigarette; NSDUH, National Survey on Drug Use and Health; NYTS, National Youth Tobacco Survey; and YRBSS, Youth Risk Behavior Survey.
*Past 30-day use of e-cigarettes was determined by asking, "During the past 30 days, on how many days did you use e-cigarettes?" Past 30-day use of cigarettes was determined by asking, "During the past 30 days, on how many days did you smoke cigarettes?" Past 30-day use of cigars was determined by asking, "During the past 30 days, on how many days did you smoke cigars, cigarillos, or little cigars?" Past 30-day use of hookah was determined by asking, "During the past 30 days, on how many days did you smoke tobacco in a hookah or waterpipe?" Smokeless tobacco was defined as use of chewing tobacco, snuff, dip, snus, or dissolvable tobacco products. Past 30-day use of smokeless tobacco was determined by asking the following question for use of chewing tobacco, snuff, and dip: "During the past 30 days, on how many days did you use chewing tobacco, snuff, or dip?" and the following question for use of snus and dissolvable tobacco products: "In the past 30 days, which of the following products did you use on at least 1 day?" Responses from these questions were combined to derive overall smokeless tobacco use. Past 30-day use of pipe tobacco (not hookahs) was determined by asking, "In the past 30 days, which of the following products have you used on at least 1 day?"
†Hispanic people could be of any race.
‡Any tobacco product use was defined as use of any tobacco product (e-cigarettes, cigarettes, cigars, smokeless tobacco, hookahs, pipe tobacco, or bidis) on ≥1 days in the past 30 days.
§Any combustible tobacco product use was defined as use of cigarettes, cigars, hookahs, pipe tobacco, or bidis on ≥1 days in the past 30 days.
‖Use of ≥2 tobacco products was defined as use of ≥2 tobacco products (e-cigarettes, cigarettes, cigars, smokeless tobacco, hookahs, pipe tobacco, or bidis) on ≥1 days in the past 30 days.
Source: Data derived from Wang et al.[7]

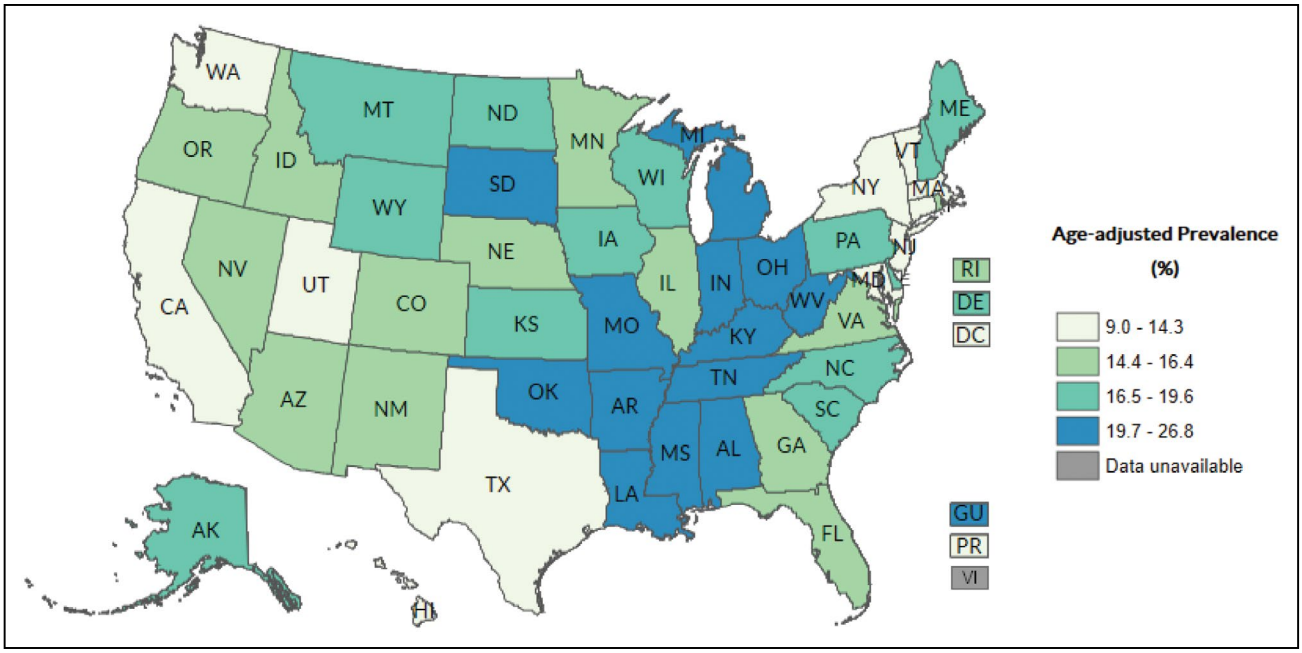

Chart 3-2. Age-adjusted prevalence (%) of current cigarette smoking for US adults by state (BRFSS, 2018).
White space between the map and legend has been removed. Icons and drop-down menus for interactive tools have been removed.
BRFSS indicates Behavior Risk Factor Surveillance System.
Source: BRFSS prevalence and trends data, 2018.[8]

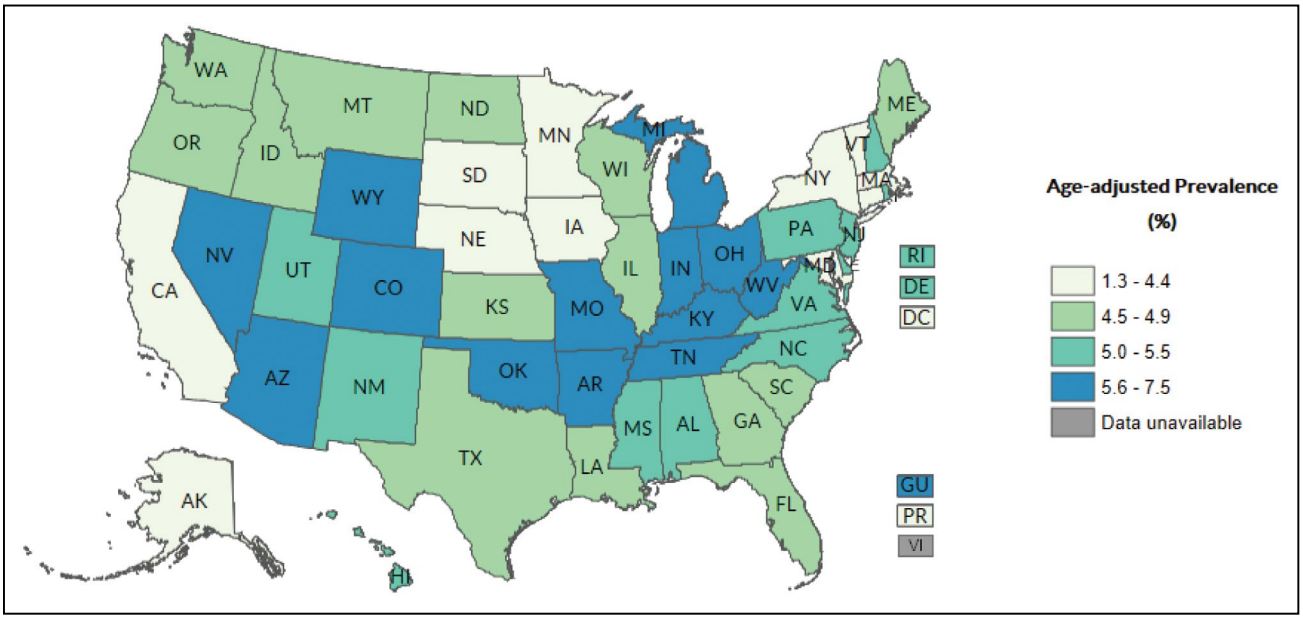

Chart 3-3. Prevalence (age-adjusted) of current electronic cigarette use, United States (BRFSS, 2017).
White space between the map and legend has been removed. Icons and drop-down menus for interactive tools have been removed.
BRFSS indicates Behavior Risk Factor Surveillance System.
Source: BRFSS prevalence and trends data, 2017.[8]

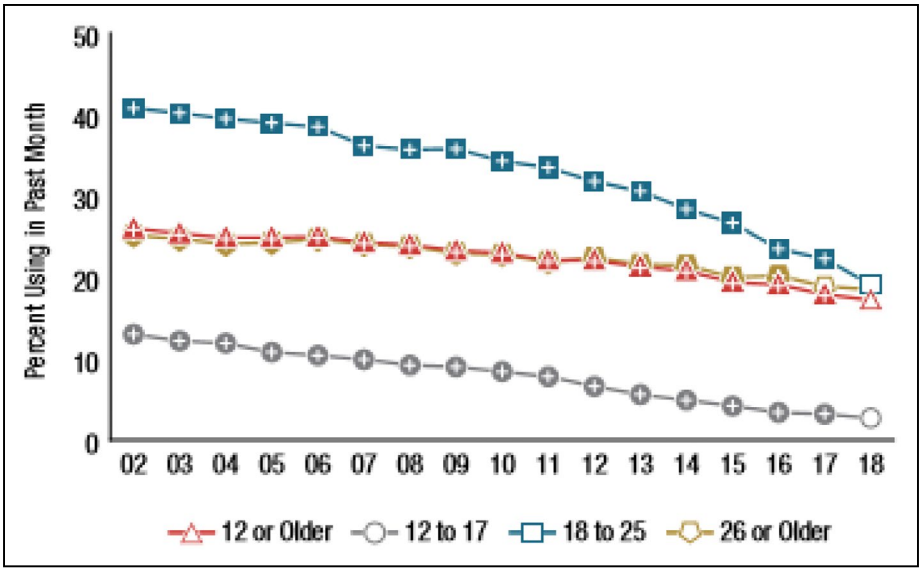

Chart 3-4. Past-month cigarette use among people ≥12 years of age, by age group: percentages, 2002 to 2018, United States (NHIS, 2002–2018; NSDUH, 2002–2018).
NHIS indicates National Health Interview Survey; and NSDUH, National Survey on Drug Use and Health.
Source: Reprinted from NSDUH.[104]

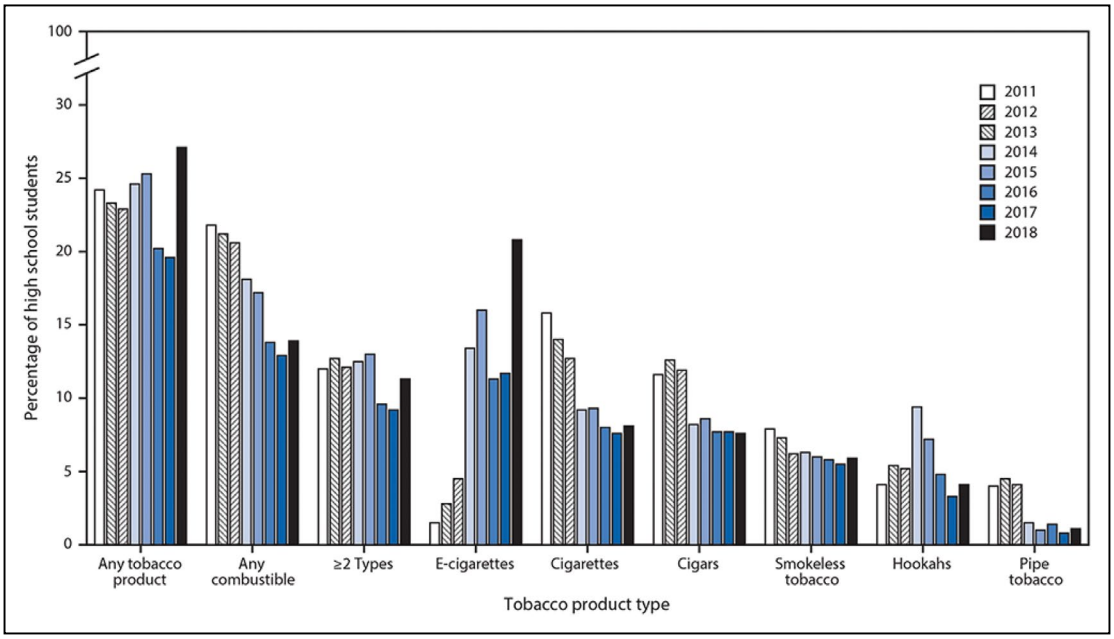

Chart 3-5. Estimated percentage of US high school students who currently use any tobacco product,* any combustible tobacco product,† ≥2 tobacco product types,‡ and selected tobacco products (NYTS, 2011–2018).§‖¶
e-Cigarette indicates electronic cigarettes; and NYTS, National Youth Tobacco Survey.
*Any tobacco product use was defined as use of e-cigarettes, cigarettes, cigars, hookahs, smokeless tobacco, pipe tobacco, or bidis (small brown cigarettes wrapped in a leaf) on ≥1 days in the past 30 days.
†Any combustible tobacco product use was defined as use of cigarettes, cigars, hookahs, pipe tobacco, or bidis on ≥1 days in the past 30 days.
‡Use of ≥2 tobacco product types was defined as use of ≥2 of the following tobacco products: e-cigarettes, cigarettes, cigars, hookahs, smokeless tobacco, pipe tobacco, or bidis on ≥1 days in the past 30 days.
§During 2017 to 2018, current use of any tobacco product, ≥2 types of tobacco products, and e-cigarettes significantly increased ($P<0.05$).
‖During 2011 to 2018, current use of combustible tobacco products, ≥2 types of tobacco products, cigars, smokeless tobacco, and pipe tobacco exhibited linear decreases ($P<0.05$). Current use of cigarettes exhibited a nonlinear decrease ($P<0.05$). Current use of hookahs exhibited a nonlinear change ($P<0.05$). Current use of e-cigarettes exhibited a nonlinear increase ($P<0.05$). No significant trend in use of any tobacco product overall was observed.
¶Beginning in 2015, the definition of smokeless tobacco included chewing tobacco/snuff/dip, snus, and dissolvable tobacco to better reflect this class of tobacco products. Thus, estimates for individual smokeless tobacco products (chewing tobacco/snuff/dip, snus, and dissolvable tobacco) are not reported. This definition was applied across all years (2011–2018) for comparability purposes.
Source: Reprinted from Gentzke et al.[3]

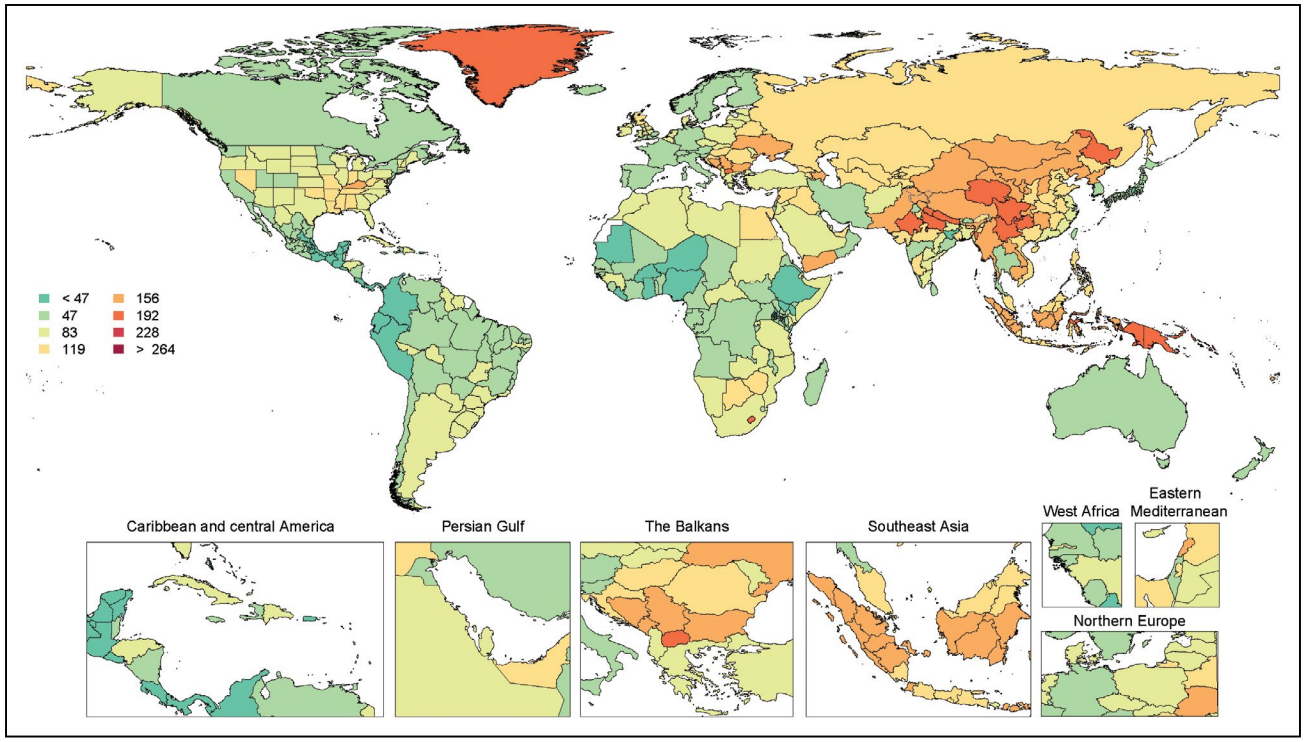

Chart 3-6. Age-standardized global mortality rates attributable to tobacco per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[99] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the GBD website.[105]

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4. PHYSICAL INACTIVITY

See Charts 4-1 through 4-13

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Physical inactivity is defined as an insufficient level to meet the current PA recommendations.[1] Physical inactivity is a major risk factor for incident CVD (eg, CHD, stroke, PAD, HF).[2] Achieving the guideline recommendations for PA is one of the AHA's 7 components of ideal CVH for both children and adults.[3]

Abbreviations Used in Chapter 4

AHA	American Heart Association
AMI	acute myocardial infarction
app	application
ARIC	Atherosclerosis Risk in Communities study
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CHD	coronary heart disease
CI	confidence interval
CPS-II	Cancer Prevention Study II
CVD	cardiovascular disease
CVH	cardiovascular health
DBP	diastolic blood pressure
ED	emergency department
FPG	fasting plasma glucose
GBD	Global Burden of Disease Study
HBP	high blood pressure
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
LDL-C	low-density lipoprotein cholesterol
LIFE	Lifestyle Interventions and Independence for Elders

(*Continued*)

Abbreviations Used in Chapter 4 Continued

MET	metabolic equivalent
MetS	metabolic syndrome
MI	myocardial infarction
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NIH-AARP	National Institutes of Health–American Association of Retired Persons
OR	odds ratio
PA	physical activity
PAD	peripheral artery disease
PAF	population attributable fraction
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	relative risk
SBP	systolic blood pressure
SE	standard error
SES	socioeconomic status
WC	waist circumference
WHI	Women's Health Initiative
WHO	World Health Organization
WHS	Women's Health Study
YRBSS	Youth Risk Behavior Surveillance System

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

The 2018 Physical Activity Guidelines for Americans recommend that children and adolescents accumulate at least 60 minutes of PA daily (including aerobic and muscle- and bone-strengthening activity).[4] In 2017, on the basis of survey interviews,[5] only 26.1% of high school students reported achieving at least 60 minutes of daily PA, which is likely an overestimation of those actually meeting the guidelines.[6]

The 2018 Physical Activity Guidelines for Americans[4] and the 2019 CVD Primary Prevention Clinical Practice Guidelines[7] recommend that adults accumulate at least 150 min/wk of moderate-intensity or 75 min/wk of vigorous-intensity aerobic activity (or an equivalent combination) and perform muscle-strengthening activities at least 2 d/wk. For many people, examples of moderate-intensity activities include walking briskly or raking the yard, and examples of vigorous-intensity activities include jogging, carrying loads upstairs, or shoveling snow. In a nationally representative sample of adults in 2018, only 24.0% reported participating in adequate leisure-time aerobic and muscle-strengthening activity to meet these criteria (Chart 4-1).[8]

Being physically active is an important aspect of overall health. Meeting recommendations for PA not only reduces premature mortality but also improves risk factors for CVD (such as HBP, diabetes, and obesity) and reduces the likelihood of diseases related to CVD,

including CHD, HF, stroke, and aging-related diseases such as dementia.[7,9–11] Benefits from PA are observed across the life span, including for children and older adults, pregnant females, and people with disabilities and chronic conditions. Therefore, the 2018 Physical Activity Guidelines for Americans recommend being as physically active as abilities and conditions allow and that some PA is better than none.[4] Even small increases in moderate-intensity PA or replacing sedentary behavior (defined as "any waking behavior characterized by an energy expenditure ≤1.5 METs while in a sitting, reclining, or lying posture"[1]) with light-intensity PA could provide health benefits.[4,9]

Defining and Measuring PA

There are several PA dimensions (eg, mode or type, frequency, duration, and intensity) and PA domains (eg, occupational, domestic, transportation, and leisure time). There are additional considerations of where PA occurs such as in homes, worksites, schools, and communities. The federal guidelines specify the suggested frequency, duration, and intensity of PA and focus on 2 types: aerobic and strengthening.

There are 2 broad categories of methods to assess PA: (1) self-reported methods that use questionnaires and diaries/logs and (2) device-based methods that use wearables (eg, pedometers, accelerometers). Studies that compare the findings between methods show that there is marked discordance between self-reported and measured PA, with respondents often overstating their PA compared with device-based measures.[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. For example, 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 when assessments focused only on leisure-time PA are used.[12]

PA and cardiorespiratory fitness provide distinct metrics in assessment of CVD risk.[13] Poor cardiorespiratory (or aerobic) fitness might be a stronger predictor of adverse cardiovascular outcomes than traditional risk factors.[14] Although many studies have shown that increasing the amount and quality of PA can improve cardiorespiratory fitness, other factors such as a genetic predisposition to perform aerobic exercise can contribute.[15] 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 often stronger than the relationship of PA to clinical outcomes.[13] The WHO created an action plan to improve cardiorespiratory fitness globally with a goal to reduce the prevalence of insufficient PA by 15% by 2030.[16]

Prevalence

Youth

(See Charts 4-2 through 4-5)

- On the basis of self-reported PA (YRBSS, 2017)[5]:
  - The prevalence of high school students who met aerobic activity recommendations of ≥60 minutes of PA on all 7 days of the week was 26.1% nationwide and was lower with each successive grade (from 9th [30.6%] to 12th [22.9%] grades). At each grade level, the prevalence was higher in boys than in girls.
  - The prevalence of high school students who met PA recommendations on all 7 d/wk or on at least 5 of 7 d/wk was higher among boys than girls overall and stratified by race/ethnicity (Chart 4-2).
  - Among high school students, 15.4% 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 not meeting recommendations on any day (19.5% versus 11.0%), with NH Black girls reporting the highest prevalence of inactivity (26.6%; Chart 4-3).
  - Among high school students, 28.5% of heterosexual students, 14.7% of gay, lesbian, and bisexual students, and 19.0% of students not sure about their sexual identity reported being physically active for at least 60 min/d on all 7 days. The difference between prevalence of being physically active in heterosexual versus gay, lesbian, and bisexual students was larger among male students than among female students (Chart 4-4).
- With the use of accelerometry (NHANES, 2003–2006),[17] youth 6 to 19 years of age had a median of 53 min/d of moderate to vigorous PA.
  - These levels of moderate to vigorous PA in youth were lower in girls and lower with greater age, with median values ranging from 82 to 138 min/d in boys 6 to 9 years of age and 64 to 111 min/d in girls 6 to 9 years of age, 39 to 67 min/d in boys 10 to 13 years of age and 20 to 49 min/d in girls 10 to 13 years of age, and 29 to 33 min/d in boys 14 to 17 years of age and 14 to 16 min/d in girls 14 to 17 years of age.
- With regard to measured cardiorespiratory fitness (NHANES, 2012)[18]:
  - For adolescents 12 to 15 years of age, boys in all age groups were more likely to have

adequate levels of cardiorespiratory fitness than girls (Chart 4-5).

- With regard to self-reported muscle-strengthening activities (YRBSS, 2017)[5]:
  - The proportion of high school students who participated in muscle-strengthening activities on ≥3 d/wk was 51.1% nationwide and was lower with successively higher grades (9th grade: males, 66.4%, females, 49.3%; 12th grade: males, 56.6%, females, 36.1%).
  - More high school boys (62.1%) than girls (40.8%) reported having participated in muscle-strengthening activities on ≥3 d/wk.

Structured Activity Participation in Schools and Sports

- Only 29.9% of students attended physical education classes in school daily (34.7% of boys and 25.3% of girls; YRBSS, 2017).[5]
- Daily physical education class participation was lower with successively higher grades from the 9th grade (45.5% for boys, 39.2% for girls) through the 12th grade (26.5% for boys, 15.9% for girls; YRBSS, 2017).[5]
- Just over half (54.3%) of high school students played on at least 1 school or community sports team in the previous year: 49.3% of girls and 59.7% of boys (YRBSS, 2017).[5]
- Data from the 2017 SummerStyles survey demonstrated that only 16.5% of parents (n=1137) reported that their child walked to school and reported safety concerns and living too far away as barriers limiting commuting as a means of engaging in an active lifestyle.[19]

Television/Video/Computers (See Chart 4-6)

- Research suggests that screen time (watching television or using a computer) can lead to less PA among children.[20] In addition, television viewing time is associated with poor nutritional choices, overeating, and weight gain (Chapter 5, Nutrition).
  - Nationwide, 43.0% of high school students used a computer, tablet, or smartphone for activities other than school work (eg, video games, texting, YouTube, or social media) for ≥3 h/d on an average school day (YRBSS, 2017).[5]
  - Among high school students, the prevalence of watching television ≥3 h/d was highest among NH Black boys (37.8%) and girls (32.8%), followed by Hispanic boys (21.9%) and girls (19.5%) and NH White girls (18.4%) and boys (16.9%) (YRBSS, 2017).[5] The prevalence of playing video games or using a computer ≥3 h/d (for activities other than schoolwork) was higher among boys and girls (Chart 4-6) (YRBSS, 2017).[5]
- A nationally representative survey conducted in 2015 of 2658 US children 8 to 18 years of age indicated that tweens (8–12 years of age) use entertainment media (eg, television, video games, internet, music, social media) on average 5 hours 55 minutes per day whereas teenagers (13–18 years of age) average 8 hours 56 minutes per day outside of school or homework.[21] Total screen time is higher for teenagers (6 hours 40 minutes) than for tweens (4 hours 36 minutes).[21]
- A nationally representative survey conducted in 2017 of 1454 parents of US children ≤8 years of age indicated that on average children spend 2 hours 19 minutes per day on screen media.[22] Children ≤2 years of age spend on average 42 min/d on screen media.[22] Despite recommendations by the American Academy of Pediatrics[23] to refrain from media use 1 hour before bedtime, 49% of children ≤8 years of age watched television or videos or played video games in the hour before bedtime.[22]

Adults (See Charts 4-7 through 4-13)

- For self-reported leisure-time aerobic PA (NHIS, 2018)[8,24]:
  - The age-adjusted proportion who reported meeting the 2018 aerobic PA guidelines for Americans (≥150 minutes of moderate PA, ≥75 minutes of vigorous PA, or an equivalent combination each week) through leisure-time activities is shown in Chart 4-7. Among both males and females, NH White adults were more likely to meet the PA aerobic guidelines with leisure-time activity than NH Black and Hispanic adults. For each racial/ethnic group, males had higher PA than females.[25]
- Adults with disabilities were less likely to meet the federal aerobic PA guidelines through leisure-time activities than those without disabilities (Chart 4-11).[8] This pattern was similar for meeting recommendations for both aerobic and strengthening.
- In 2018, 25.4% of adults did not engage in leisure-time PA (no sessions of leisure-time PA of ≥10 minutes in duration; Chart 4-12).[8]
- From accelerometer-assessed PA (NHANES, 2005–2006),[26] US adults were estimated to participate in 45.1 min/wk (SE, 4.6 min/wk) of moderate PA and 18.6 min/wk (SE, 6.6 min/wk) of vigorous PA. Levels of moderate and vigorous PA were lower in older adults (60–69 years of age; moderate, 32.7 min/wk [SE, 3.6 min/wk]; vigorous, 1.4 min/wk [SE, 0.7 min/wk]) compared with adults in younger age groups (eg, 40–49 years of age; moderate, 54.1 min/wk [SE, 12.8 min/wk]; vigorous, 24.9 min/wk [SE, 16.6 min/wk]).
  - Accelerometer data (2003–2006) also revealed that rural US adults performed less moderate to vigorous PA than urban adults, but rural

adults spent more time in lighter-intensity PA (accelerometer counts per minute, 760–2020) than their urban adult counterparts.[27]
  - In contrast to self-reported PA, which suggested that NH White individuals had higher levels of PA,[28] data from accelerometer-assessed PA revealed that Mexican American adults had higher total PA and moderate to vigorous PA than NH White or Black adults (≥20 years of age).[26]
- In a study of almost 5000 British males, among 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. However, for males who were more active in middle age, retirement is associated with higher PA.[29]
- A report using data from 2018 indicated that US adults spent on average 10.5 h/d connected to media (eg, television, radio, smartphone, tablet, internet on computer), with adults 50 to 64 years of age spending the most time per day on media compared with any other age group.[30] This same report estimated that on average Black adults spent 12 hours 58 minutes, Hispanic adults spent 9 hours 17 minutes, and Asian American adults spent 6 hours 46 minutes per day connected to media. These habits affect time available for PA and contribute to sedentary behavior.

Pregnancy and Postpartum

- PA is recommended for pregnant females without obstetric or medical complications.[4,31,32] Several reviews of the literature that supported these guidelines indicate that PA during pregnancy can decrease the odds of excessive gestational weight gain,[33,34] gestational diabetes,[33,35] preeclampsia and gestational hypertension,[35] and depressive symptoms.[36] PA also can assist with postpartum weight retention[34] and postpartum depressive symptoms.[33]
- US estimates from NHANES (2007–2014) indicate that 12.7% to 45.0% of pregnant females meet the 2015 American College of Obstetrics and Gynecology guidelines.[37] Accelerometer-assessed PA measures from NHANES (2003–2006) indicate that the population of US pregnant females averaged 12 min/d of moderate activity and 57% of their monitored day in sedentary behavior (average, 424 min/d).[38]
- For more information, see Chapter 11 on pregnancy.

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

- Individuals from urban areas who participated in NHANES (2003–2006) 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 accelerometry.[27]
  - The prevalence of walking for transportation also varies by geographic location, ranging from 43.5% of individuals living in New England reporting any walking for transportation compared with 17.8% of individuals living in the East South Central region of the United States.[39]
- A 1-day assessment indicated that the mean prevalence of any active transportation was 10.3% on the basis of 2012 data from the American Time Use Study. NH White individuals reported the lowest active transport (9.2%), followed by 11.0% of Hispanic individuals, 13.4% of NH Black individuals, and 15.0% of other NH individuals.[40]

Sitting Time

- According to data from the 2015 to 2016 NHANES, prevalence of time spent sitting >8 h/d was reported at 25.7% and was successively higher with older age.[41]

Secular Trends

Youth

Physical Activity

- Among students nationwide, there was a significant increase in the proportion reporting participation in muscle-strengthening activities on ≥3 d/wk, from 47.8% in 1991 to 51.1% in 2017; however, the prevalence did not change substantively from 2011 (55.6%) to 2017 (51.1%).[5,42]
- Nationwide, the number of high school students who reported attending physical education classes at least once per week (on an average week while in school) did not change substantively between 1991 (48.9%) and 2017 (51.7%).[5,42] Similar patterns were observed for attending physical education classes on all 5 days.
- The prevalence of high school students playing ≥1 team sport in the past year did not substantively change between 1999 (55.1%) and 2017 (54.3%).[5,42]

Cardiorespiratory Fitness

- In 2012, the prevalence of adolescents 12 to 15 years of age with adequate levels of cardiorespiratory fitness (based on age- and sex-specific standards) was 42.2%, down from 52.4% in the combined years from 1999 to 2000.[18]

Television/Video/Computers

- According to NHANES, sitting and watching television or videos at least 2 h/d remained high over

time for youth 5 to 11 years of age (65.5% in 2001–2002 to 62.2% in 2015–2016) and youth 12 to 19 years of age (64.2% in 2003–2004 to 59.4% in 2015–2016).[43]
- A significant increase occurred in the number of youth reporting having used computers for something other than schoolwork for ≥3 h/d in 2017 (43.0%) compared with 2003 (22.1%).[5,42]
- A nationally representative survey of parents to children ≤8 years of age indicated that smartphone ownership in the home has risen from 41% in 2011 to 95% in 2017; tablet ownership also rose from 8% in 2011 to 78% in 2017.[22] Among children ≤8 years of age, the amount of screen time was similar for 2011 (2 hours 16 minutes) and 2017 (2 hours 19 minutes), but the type of media accessed was shifting.[22]

Adults

- The prevalence of physical inactivity among adults ≥18 years of age, overall and by sex, has decreased from 1998 to 2018 (Chart 4-12).[44]
- The age-adjusted percentage of US adults who reported meeting both the muscle-strengthening and aerobic guidelines increased from 18.2% in 2008 to 24.0% in 2018.[44] The percentage of US adults who reported meeting the aerobic guidelines increased from 43.5% in 2008 to 54.2% in 2018.[44]
- The increase in those meeting the aerobic guidelines may be explained in part by the increased prevalence in self-reported transportation walking from 28.4% to 31.7% and leisure walking from 42.1% to 52.1% (2005–2015).[45]
- According to NHANES, sitting and watching television or videos at least 2 h/d remained high over time for adults ≥20 years of age (64.7% in 2003–2004 to 65.1% in 2015–2016).[43] Nielsen reports of adult smartphone app/web use comparing data collected in 2012 (48 min/d)[46] to 2017 (2 hours 28 minutes per day)[47] suggest large increases in use over the past few years. Although they acknowledge that there were inconsistent methods of data collection among these different reports, the reported changes in technology behavior over such a short period of time are striking.

Social Determinants

- The proportion of adults ≥25 years of age who met the 2018 PA guidelines for aerobic PA through leisure-time activities was higher with successively higher educational attainment (Chart 4-8).[8] This pattern was similar for meeting recommendations for both aerobic and strengthening activities.
- Adults residing in urban areas (metropolitan statistical areas) were more likely to meet the federal aerobic PA guidelines through leisure-time activities than those residing in rural areas (55.2% versus 47.5%; Chart 4-9).[8] This pattern was similar for meeting recommendations for both aerobic and strengthening activities.
- Categories of adults living above the poverty level were successively more likely to meet the federal aerobic PA guidelines through leisure-time activities than those living below the poverty level (<100%) (Chart 4-10).[8] When considering meeting both the aerobic and strengthening PA recommendations, the stepwise pattern persisted, with a higher percent of adults meeting recommendations the further away from the poverty line of 100%.
- In an analysis from the NIH-AARP Diet and Health Study, severe neighborhood socioeconomic deprivation was prospectively associated with less exercise time in hours (highest quintile versus lowest quintile, –0.85 [95% CI, –0.95 to –0.75]) among 136 526 participants 51 to 70 years of age.[48]

Family History and Genetics

- Genetic factors contribute to the propensity to exercise.[49-51] More work is needed to identify genetic factors that contribute to higher PA or physical inactivity.[49]

Prevention of 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.[52] There are roles for communities, schools, and worksites.

Communities

- Community-level interventions are effective in promoting PA. Communities can encourage walking with street design that includes sidewalks and improved street lighting and landscaping design that reduces traffic speed to improve pedestrian safety.[53]
- Higher neighborhood walkability has been associated with lower prevalence of overweight and obesity and lower incidence of diabetes.[54] Moving to a walkable neighborhood was associated with a lower risk for incident hypertension in the Canadian Community Health Survey.[55]

Schools

- Schools can provide opportunities for PA through physical education, recess, before- and after-school activity programs, and PA breaks, as well as offering a place for PA for the community.[56]

- Requiring daily physical education in US middle schools decreased from 10.5% in 2006 to 3.4% in 2014 and in US high schools increased from 2.1% in 2006 to 4.0% in 2014.[57] The proportion of students in grades 9 to 12 who participated in daily physical education did not meaningfully change between 2009 (33.3%) and 2013 (29.4%).[57]
- In 2012, the School Health Policies and Practices Study also reported that 58.9% of school districts required regular elementary school recess, a proportion similar to that in 2006 (57.1%).[57]

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.[58,59]

Mortality

Self-Reported PA, Sedentary Behavior, and Mortality

- In an analysis from NHIS, among 67 762 adults with >20 years of follow-up, 8.7% of all-cause mortality was attributed to a PA level of <150 min/wk of moderate-intensity PA.[60]
- A meta-analysis of 9 cohort studies, representing 122 417 adults ≥60 years of age, found that as little as 15 minutes of daily moderate to vigorous PA reduced all-cause mortality.[61] 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 below the amount recommended by the federal guidelines.
- In a pooled study of >600 000 adults,[62] 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]). There was no evidence of harm associated with performing ≥10 times the recommended minimum (HR, 0.68 [95% CI, 0.59–0.78]).[62]
- In the WHS (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, 0.73 [95% CI, 0.65–0.82]; HR, 0.71 [95% CI, 0.62–0.82]; and HR, 0.81 [95% CI, 0.67–0.97], respectively), but performing ≥150 min/wk of strength training was not associated with lower risk of all-cause mortality (HR, 1.10 [95% CI, 0.77–1.56]).[63] The HRs were adjusted for potential confounders and aerobic activity.
- A meta-analysis of 23 studies revealed an association between participating in more transportation-related PA and lower all-cause mortality, CVD, and diabetes.[64]
- In the UK Biobank of 263 540 participants, 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.[65]
- A meta-analysis including 193 696 adults reported that high occupational PA was associated with a greater risk of all-cause mortality in males (HR, 1.18 [95% CI, 1.05–1.34]) compared with low occupational PA.[66] However, a nonsignificant decrease in all-cause mortality was observed among females with high occupational PA (HR, 0.90 [95% CI, 0.80–1.01]) compared with those with low occupational PA. It is unclear whether factors such as fitness, SES, preexisting CVD, type of occupation, and other domains of PA may modify this relationship.
- In a meta-analysis of 13 studies, higher sedentary behavior 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 of PA.[67]
- 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.[68]
- In a prospective US cohort study (CPS-II) of 127 544 adults, prolonged leisure-time sitting (≥6 h/d versus <3 h/d) was associated with higher risk of mortality from all causes and CVD (including CHD and stroke-specific mortality).[69]
- With the use of an isotemporal substitution approach in a subsample of the CPS-II, among participants with the lowest level of PA, replacing 30 min/d of sitting with light-intensity PA or moderate- to vigorous-intensity PA was associated with 14% (HR, 0.86 [95% CI, 0.81–0.89]) or 45% (HR,

0.55 [95% CI, 0.47–0.62]) lower mortality, respectively. For the individuals with the highest PA levels, substitution was not associated with differences in mortality risk.[70]

Device-Measured PA, Sedentary Behavior, and Mortality

- Among 3029 NHANES adults 50 to 79 years of age in 2003 to 2006, 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 10 min/d of light activity was associated with lower all-cause mortality (HR, 0.91 [95% CI, 0.86–0.96]).[71]
- In a landmark harmonization effort of 8 prospective studies with accelerometry, over a median of 5.8 years of follow-up, the highest quartile of light (HR, 0.38–0.60) and moderate to vigorous (HR, 0.52–0.64) PA compared with the lowest quartile (least active) was associated with a lower risk of all-cause mortality.[72] Time in sedentary behavior was associated with a higher risk of all-cause mortality (HR, 1.28–2.63 across quartiles) compared with the lowest quartile (least sedentary).
- Step counting is recommended as an effective method for translating PA guidelines and monitoring PA levels because of its simplicity and the increase in step-counting devices.[9] All longitudinal studies included in a systematic review reported a favorable dose-response relationship between daily step counts and all-cause mortality (HR, 0.94 [95% CI, 0.90–0.98] per 1000–steps per day increase).[73] Among older females, having as few as 4400 steps per day was associated with lower mortality.[74] More evidence is needed to set target volumes of PA based on steps per day and to determine the role of cadence (steps per minute; a proxy for intensity of ambulation) in these relationships.[9,73]

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.[75]
- Among a Swedish cohort of 266 109 adults 18 to 74 years of age, risk of CVD morbidity and all-cause mortality decreased 2.6% and 2.3% per 1–mL·min^{-1}·kg^{-1} increase, respectively, in cardiorespiratory fitness estimated from a submaximal bicycle test.[76] The risk reduction with higher cardiorespiratory fitness was observed for both males and females across ages.
- In the UK Biobank, 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.[77]

Benefits of PA and Complications of Inactivity

Youth

Benefits

- In a study of 36 956 Brazilian adolescents, higher self-reported moderate to vigorous PA levels and lower amounts of 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.[78]
- In a prospective study of 700 Norwegian 10-year-old children, higher levels of accelerometer-assessed moderate PA at baseline were associated with lower triglyceride levels and lower insulin resistance at the 7-month follow-up. In contrast, sedentary duration was not associated with cardiometabolic risk factors at follow-up.[79]
- Among the NHANES 2003 to 2006 cohort of youths 6 to 17 years of age, those with the highest levels of accelerometer-assessed PA had lower SBP, lower glucose levels, and lower insulin levels than youths in the lowest PA group.[80]

Complications

- A higher amount of accelerometer-measured sedentary duration among children 0 to 14 years of age is associated with greater odds of hypertriglyceridemia and cardiometabolic risk.[81]

Adults

Cardiovascular and Metabolic Risk Factors

Benefits

- In a meta-analysis of 11 studies investigating the role of exercise among individuals with MetS, aerobic exercise significantly improved DBP (–1.6 mm Hg; *P=0*.01), WC (–3.4 cm; *P<0*.01), fasting glucose (–0.15 mmol/L; *P=0*.03), and HDL-C (0.05 mmol/L; *P=0*.02).[82]
- 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 the 10-year follow-up compared with using passive modes of transportation.[83]
- Even lighter-intensity activities such as yoga were reported to improve BMI, BP, triglycerides, LDL-C,

and HDL-C but not FPG in a meta-analysis of 32 RCTs comparing yoga with nonexercise control.[84]
- In a dose-response meta-analysis of 29 studies with 330 222 participants that evaluated 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]).[85]
- A systematic review reported favorable dose-response relationships between daily step counts and both type 2 diabetes (25% reduction in 5-year dysglycemia incidence per 2000-step/d increase) and MetS (29% reduction in 6-year metabolic score per 2000-step/d increase).[73]
- Intermittent breaks of 10 minutes of standing or desk pedaling during each hour of sitting were insufficient to prevent endothelial dysfunction that developed over a period of 4 hours of sitting.[86]

Complications
- 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%).[87]
- In a population-based study of Hispanic/Latino adults, higher levels of sedentary time were associated cross-sectionally with lower levels of HDL-C, 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.[88,89]

Pregnancy
- In a meta-analysis including 7 trials with 2517 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]).[90]

Cardiovascular Events

Benefits
- A study of the factors related to declining CVD among Norwegian adults ≥25 years of age found that increased PA (≥1 h/wk of strenuous PA) accounted for 9% of the decline in hospitalized and nonhospitalized fatal and nonfatal CHD events.[91]
- In a prospective cohort study of 130 843 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) intensity levels of PA were associated with a graded lower risk of major cardiovascular events (HR for high versus low, 0.75 [95% CI, 0.69–0.82]; moderate versus low, 0.86 [95% CI, 0.78–0.93]; high versus moderate, 0.88 [95% CI, 0.82–0.94]) over an average 6.9 years of follow-up.[92]
- In the 2-year LIFE study of older adults (mean age, 78.9 years), higher levels of accelerometer-assessed PA and daily steps were associated with lower risk of adverse cardiovascular events.[93]
- A systematic review reported a favorable dose-response relationship between daily step counts and cardiovascular events (defined as cardiovascular death, nonfatal MI, or nonfatal stroke; 8% yearly rate reduction per 2000–steps per day increase).[73]
- In the WHI, every 1-h/d increase in accelerometer-assessed light-intensity PA was associated with a lower risk of CHD (HR, 0.86 [95% CI, 0.73–1.00]) and lower CVD (HR, 0.92 [95% CI, 0.85–0.99]).[94]
- Domains of PA other than leisure time are understudied. A meta-analysis reported a protective relationship between transportation activity and cardiovascular risk, which was greater in females.[95] However, higher occupational PA has been associated with higher MI incidence in males 19 to 70 years of age.[96,97] These relationships require further investigation because a protective association of occupational activity with MI has been reported in young males (19–44 years of age).[97]
- The Rotterdam Study evaluated the contribution of specific PA types to 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 levels of domestic work in females (2.4 years) and high levels of gardening in males (2 years) were also associated with an increased CVD-free life span.[98]
- With an average of 27 years of follow-up, estimates from 13 534 ARIC participants indicated that those who engaged in past-year leisure-time PA at least at median levels had a longer life expectancy free of nonfatal CHD (1.5–1.6 years), stroke (1.8 years), and HF (1.6–1.7 years) compared with those who did not engage in leisure-time PA.[99] In addition, those watching less television had longer life expectancy free of CHD, stroke, and HF of close to 1 year.

Complications
- In a dose-response meta-analysis of 9 prospective cohort studies (n=720 425), higher levels of sedentary behavior were associated with greater risk of CVD in a nonlinear relationship (HR for highest versus lowest sedentary behavior, 1.14 [95% CI, 1.09–1.19]).[100]

Heart Failure
- In a meta-analysis of 12 prospective cohort studies (n=370 460), there was an inverse dose-dependent association between self-reported PA 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 2 and 4 times the guideline-recommended levels was associated with 19% and 35% lower risk of HF, respectively.[101]

- Furthermore, an individual-level pooled analysis of 3 large cohort studies demonstrated that the strong, dose-dependent association between higher self-reported leisure-time PA and lower risk of HF is driven largely by lower risk of HFpEF but not HFrEF.[102]
- In a prospective study that monitored 902 patients with HF (with HFpEF or HFrEF) 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 h/d versus >4 h/d) also was associated with lower all-cause death.[103]
- Lower levels of cardiorespiratory fitness have also been associated with higher risk of HF in a study of 21 080 veterans, with a 91% higher risk of HF noted among low-fitness participants (HR, 1.91 [95% CI, 1.74–2.09]).[104]

Secondary Prevention

- Cardiac rehabilitation, a multicomponent intervention that includes aerobic exercise and strengthening, is recommended for those with CVD to reduce hospital admissions, secondary events, and mortality.[105,106] Underuse of cardiac rehabilitation remains a persistent problem; newer approaches such as home-based cardiac rehabilitation are being explored.[106] 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.[107]
- In a prospective cohort study of 15 486 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.[108]
  - Among 1746 patients with CAD 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.[109]
  - 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]).[110]
- Using data from a registry of stable outpatients with symptomatic coronary disease, cerebrovascular disease, or PAD showed that 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.[111]
- 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, 90, and 365 days after MI.[112] 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]).[113]
- A study of women in the WHI observational study who experienced a clinical MI demonstrated that 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]) compared with those who maintained low PA levels after an MI.[114]
- Among 2370 individuals with CVD who responded to the Taiwan NHIS, achieving more total PA, leisure-time PA, and domestic and work-related PA was associated with lower mortality at the 7-year follow-up.[115]

Brain Health

- Growing evidence suggests a link between vascular risk factors, cardiovascular/cerebrovascular disease, and poor brain health, leading to cognitive and motor dysfunction. The AHA proposed to use the Life's Simple 7 strategy not only to decrease cardiovascular risk but also to maintain optimal brain health.[10]
- One of the Life's Simple 7 strategies promotes achievement of adequate PA.[10] Results from a meta-analysis including >33 000 participants suggest that individuals who self-report high PA levels have a 38% lower risk of cognitive decline.[116] Results from intervention trials have been more inconsistent.[117–120] However, there have been some promising results from a study that observed better executive function in those who adhered to a multidomain (exercise, cognitive training, and Mediterranean diet) intervention for 2 years.[117]
- Evidence from meta-analyses in patients with stroke suggests that PA rehabilitation may also improve cognitive and motor function outcomes. An overall positive effect of PA training on cognitive performance was observed in patients with stroke (Hedges g, 0.30 [95% CI, 0.14–0.47]) in a meta-analysis representing data from 736 participants.[121] Another meta-analysis of studies involving patients with stroke observed that treadmill training improved motor function compared with no training (standard mean difference, 0.60 [95% CI, 0.55–0.66]), with similar results in both low- and high-intensity and volume rehabilitation programs.[122]

Costs

- The economic consequences of physical inactivity are substantial. A global analysis of 142 countries (93.2% of the world's population) concluded that

physical inactivity cost health care systems $53.8 billion in 2013, including $9.7 billion paid by individual households.[123]

- 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 health care expenditures (including expenditures for inpatient, outpatient, ED, office-based, dental, vision, home health, prescription drug, and other services).[124]
- An evaluation of health care costs based on the cardiovascular risk factor profile (including ≥30 minutes of moderate to vigorous PA ≥5 times per week) found that among adults ≥40 years of age with CVD, the highest marginal expenditures ($2853 per person in 2012) were for those not meeting the PA guidelines. Health care 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).[125]
- Interventions and community strategies to increase PA have been shown to be cost-effective in terms of reducing medical costs[126,127]:
  - Nearly $3 in medical cost savings is realized for every $1 invested in building bicycling and walking trails.
  - The ICER 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.

Global Burden (See Chart 4-13)

- Prevalence of physical inactivity in 2016 was reported to be 27.5% (95% CI, 25.0%–32.2%) of the population globally. These rates have not changed substantially since 2001, at which time prevalence of physical inactivity was 28.5% (95% CI, 23.9%–33.9%). Critically, it appears that the number of females reporting insufficient PA is 8% higher than males, globally.[128]
- The GBD 2019 study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 369 diseases and injuries and 87 risk factors in 204 countries and territories.[129] Mortality rates attributable to low PA are highest in North Africa and the Middle East (Chart 4-13).
- Physical inactivity was responsible for 831 502 deaths in 2019.[129] Other leading risk factors include diet, alcohol, tobacco, and child and maternal malnutrition. The adjusted PAF 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.[92]

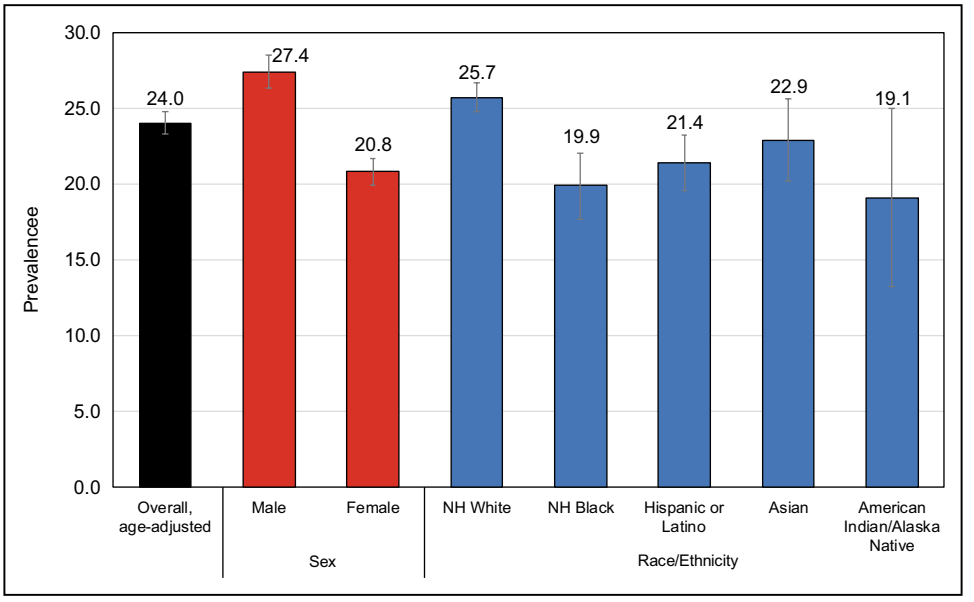

Chart 4-1. Prevalence of meeting both the aerobic and muscle-strengthening guidelines among US adults ≥18 years of age, overall and by sex and race/ethnicity, 2018.

Error bars represent 95% confidence intervals.

Data are age adjusted to the year 2000 standard population for adults ≥18 years of age. The 2018 Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time physical activity for ≥150 min/wk, vigorous activity for ≥75 min/wk, or an equivalent combination (eg, aerobic guideline). The 2018 Physical Activity Guidelines for Americans also recommend engaging in muscle-strengthening activities ≥2 d/wk (eg, muscle-strengthening guideline).

NH indicates non-Hispanic.

Source: Data derived from Healthy People 2020[8] using National Health Interview Survey, 2018.[24]

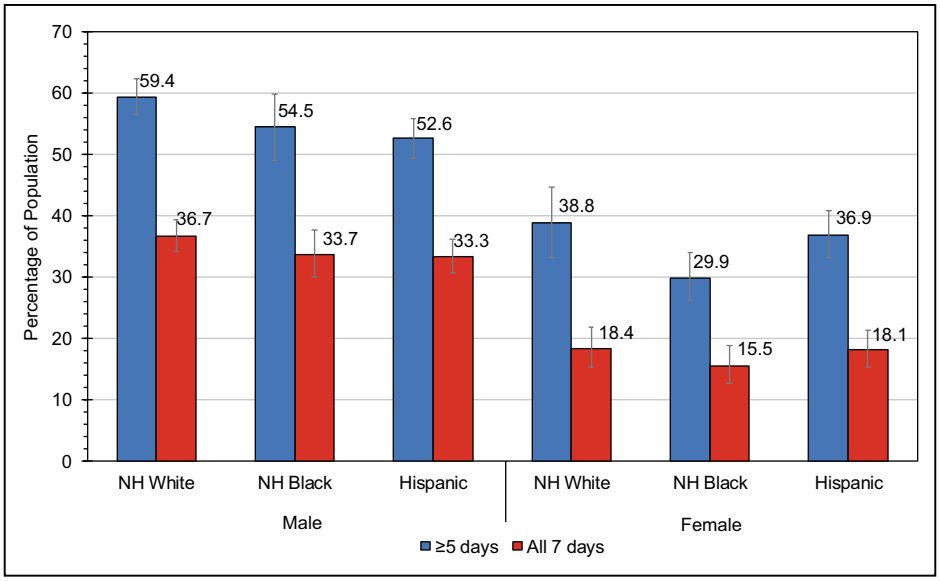

Chart 4-2. Prevalence of US students in grades 9 to 12 who were active at least 60 min/d on at least 5 and all 7 days by race/ethnicity and sex, 2017.
Error bars represent 95% confidence intervals.
This time included physical activity that increased heart rate and breathing some of the time during the 7 days before the survey.
NH indicates non-Hispanic.
Source: Data derived from Kann et al[5] using Youth Risk Behavior Surveillance System, 2017.[130]

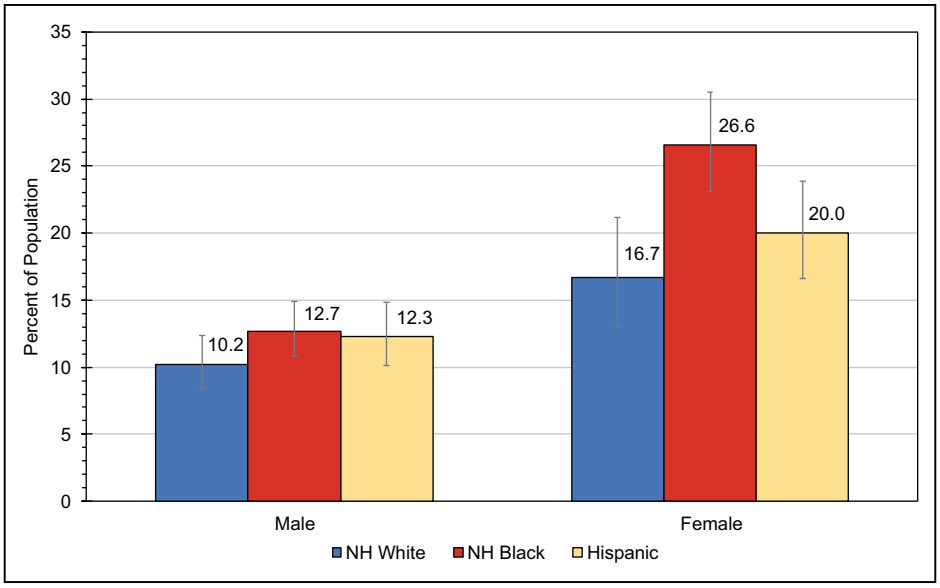

Chart 4-3. Prevalence of US students in grades 9 to 12 who did not participate in ≥60 minutes of physical activity on any day in the past 7 days by race/ethnicity and sex, 2017.
Error bars represent 95% confidence intervals.
This time included physical activity that increased heart rate and breathing some of the time during the 7 days before the survey.
NH indicates non-Hispanic.
Source: Data derived from Kann et al[5] using Youth Risk Behavior Surveillance System, 2017.[130]

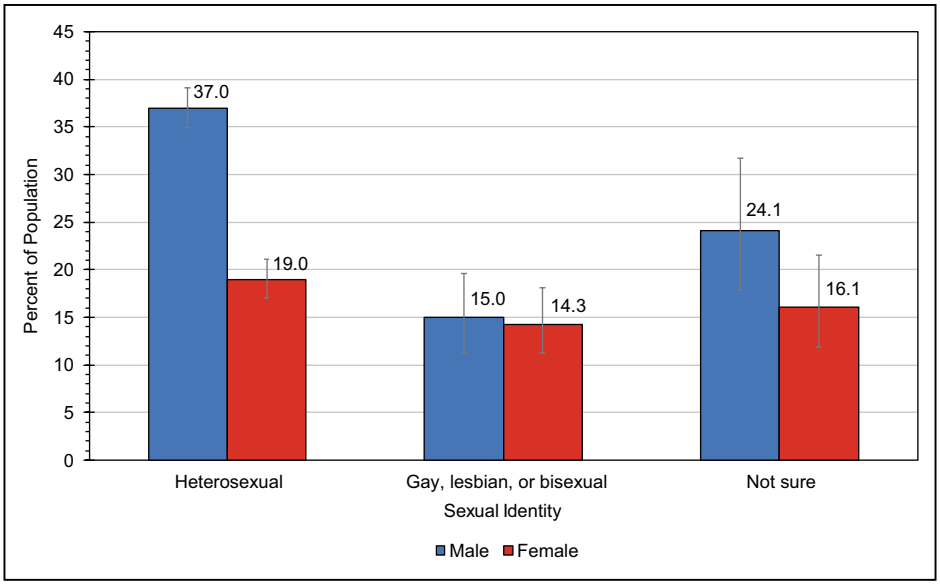

Chart 4-4. Prevalence of US students in grades 9 to 12 who were active at least 60 min/d on all 7 days by sexual identity and sex, 2017.
Error bars represent 95% confidence intervals.
This time included physical activity that increased heart rate and breathing some of the time during the 7 days before the survey.
Source: Data derived from Kann et al[5] using Youth Risk Behavior Surveillance System, 2017.[130]

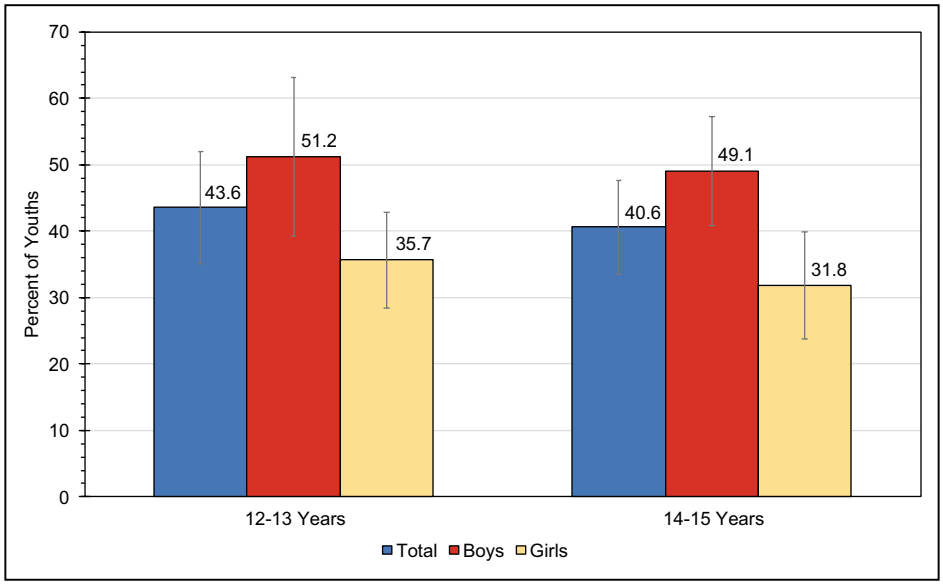

Chart 4-5. Prevalence of US children 12 to 15 years of age who had adequate levels of cardiorespiratory fitness by sex and age, 2012.
Error bars represent 95% confidence intervals.
Source: Data derived from Gahche et al[18] using National Health and Nutrition Examination Survey, National Youth Fitness Survey, 2012.[131]

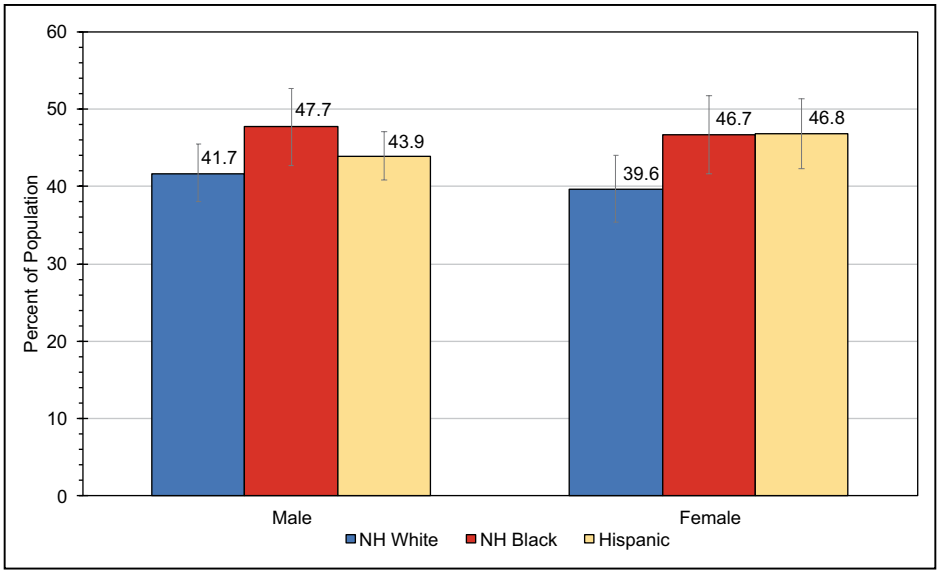

Chart 4-6. Percentage of US students in grades 9 to 12 who played video or computer games or used a computer* for ≥3 hours on an average school day by race/ethnicity and sex, 2017.
Error bars represent 95% confidence intervals.
NH indicates non-Hispanic.
*For something other than schoolwork.
Source: Data derived from Kann et al[5] using Youth Risk Behavior Surveillance System, 2017.[130]

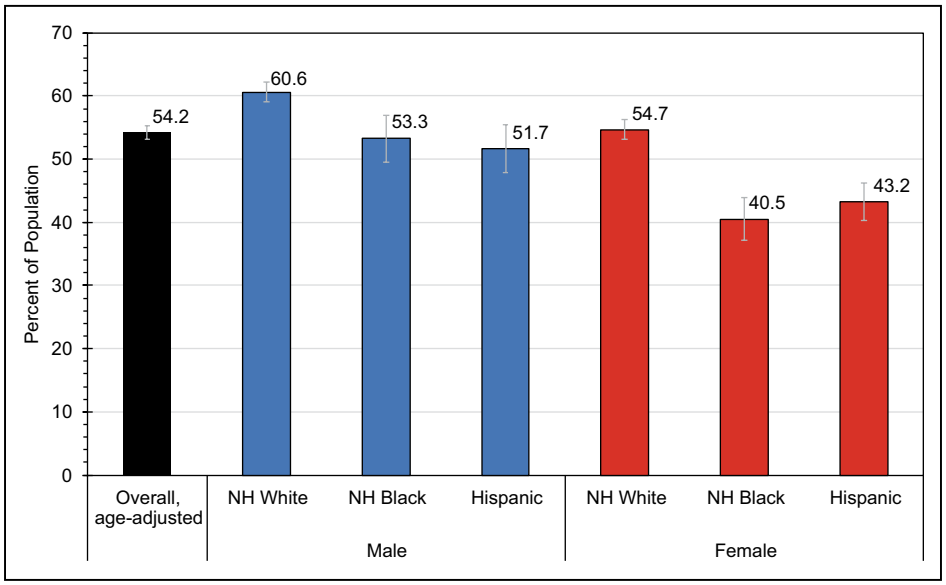

Chart 4-7. Prevalence of meeting the aerobic guidelines among US adults ≥18 years of age by race/ethnicity and sex, 2018.
Error bars represent 95% confidence intervals.
Percentages are age adjusted. The aerobic guidelines of the 2018 Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time physical activity for ≥150 min/wk, vigorous activity for ≥75 min/wk, or an equivalent combination.
NH indicates non-Hispanic.
Source: American Heart Association unpublished tabulation of National Health Interview Survey, 2018.[24]

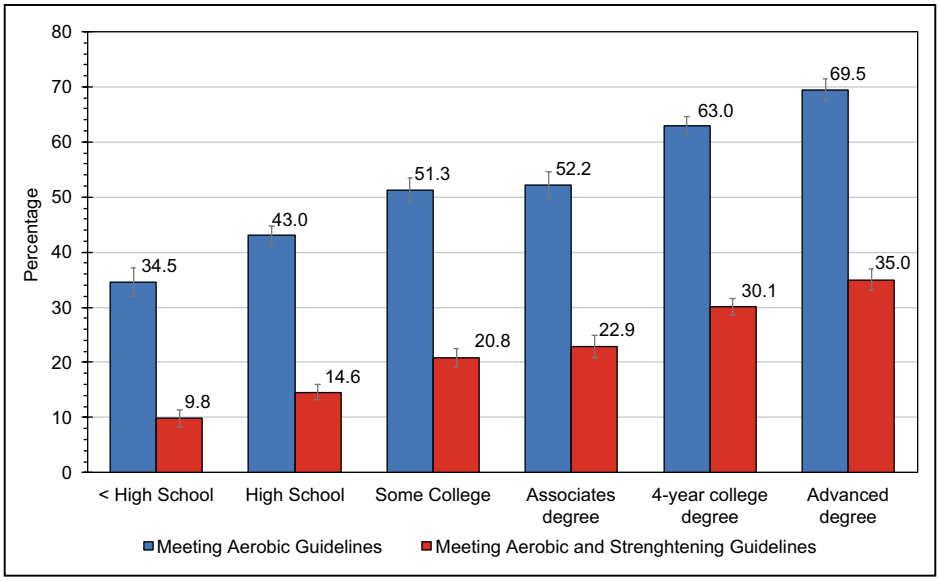

Chart 4-8. Prevalence of meeting the aerobic guidelines among US adults ≥25 years of age by educational attainment, 2018.
Error bars represent 95% confidence intervals.
Data are age adjusted to the year 2000 standard population for adults ≥18 years of age. The 2018 Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time physical activity for≥150 min/wk, vigorous activity for ≥75 min/wk, or an equivalent combination (eg, aerobic guideline). The 2018 Physical Activity Guidelines for Americans also recommend engaging in muscle-strengthening activities ≥2 d/wk (eg, muscle-strengthening guideline).
Source: Data derived from Healthy People 2020[8] using National Health Interview Survey, 2018.[24]

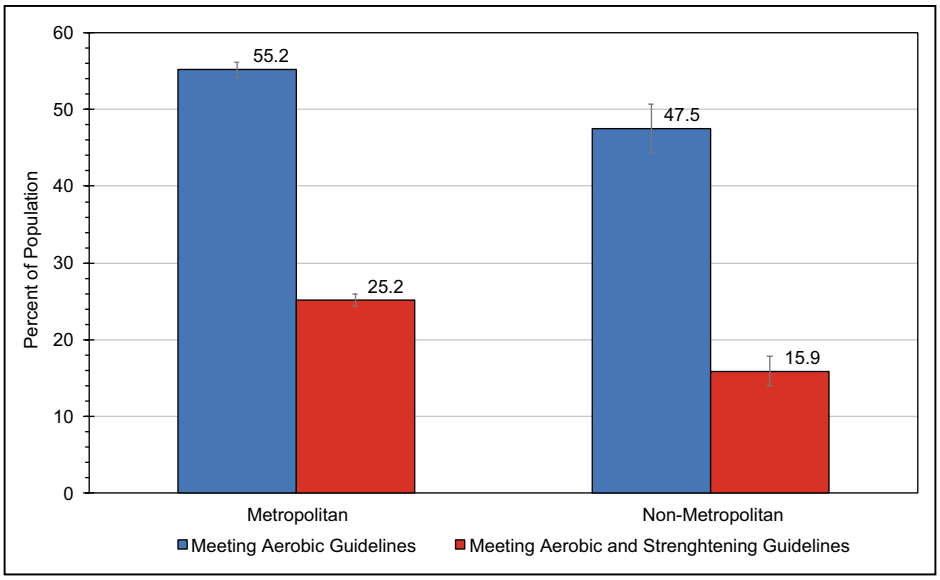

Chart 4-9. Prevalence of meeting the aerobic guidelines among US adults ≥18 years of age by location of residence, 2018.
Error bars represent 95% confidence intervals.
Data are age adjusted to the year 2000 standard population for adults ≥18 years of age. The 2018 Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time physical activity for ≥150 min/wk, vigorous activity for ≥75 min/wk, or an equivalent combination (eg, aerobic guideline). The 2018 Physical Activity Guidelines for Americans also recommend engaging in muscle-strengthening activities ≥2 d/wk (eg, muscle-strengthening guideline).
Source: Data derived from Healthy People 2020[8] using National Health Interview Survey, 2018.[24]

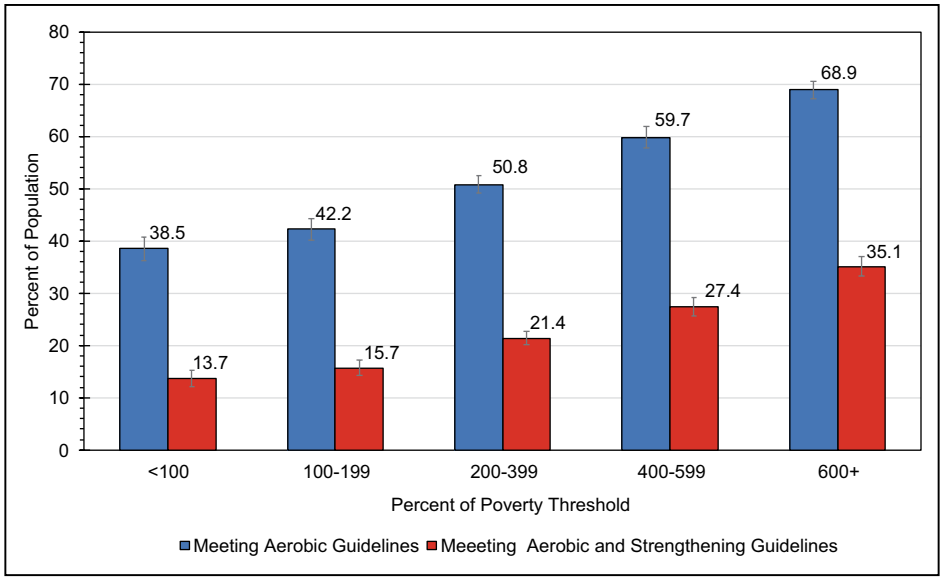

Chart 4-10. Prevalence of meeting the aerobic and muscle-strengthening guidelines among US adults ≥18 years of age by family income (percent of poverty threshold), 2018.

Error bars represent 95% confidence intervals.

Data are age adjusted to the year 2000 standard population for adults ≥18 years of age. The 2018 Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time physical activity for≥150 min/wk, vigorous activity for ≥75 min/wk, or an equivalent combination (eg, aerobic guideline). The 2018 Physical Activity Guidelines for Americans also recommend engaging in muscle-strengthening activities ≥2 d/wk (eg, muscle-strengthening guideline). Poverty status is based on family income and family size using the US Census Bureau poverty thresholds.

Source: Data derived from Healthy People 2020[8] using National Health Interview Survey, 2018.[24]

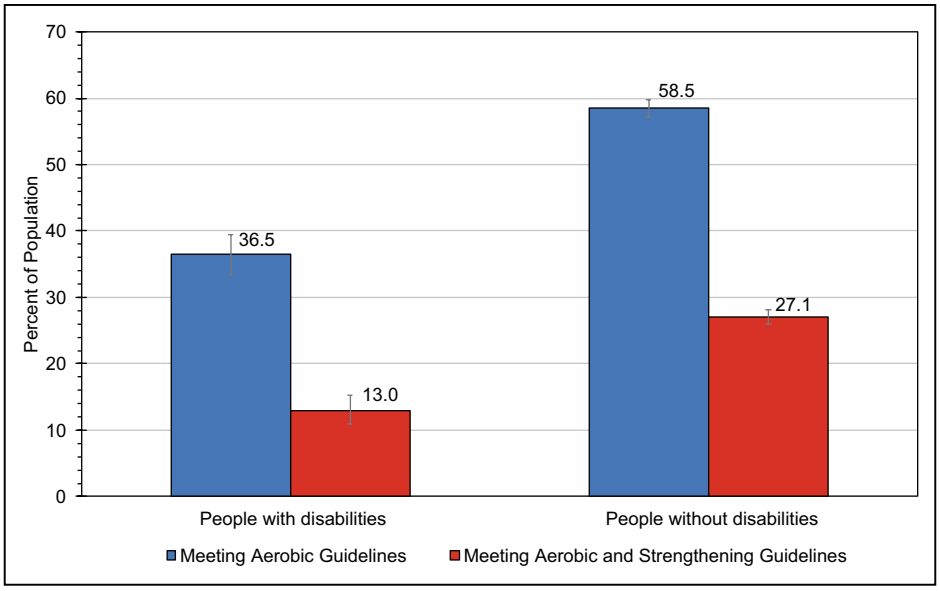

Chart 4-11. Prevalence of meeting both the aerobic and muscle-strengthening guidelines among US adults ≥18 years of age by disability status, 2017.

Error bars represent 95% confidence intervals.

Percentages are age adjusted. The 2018 Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time physical activity for≥150 min/wk, vigorous activity for ≥75 min/wk, or an equivalent combination (eg, aerobic guideline). The 2018 Physical Activity Guidelines for Americans also recommend engaging in muscle-strengthening activities ≥2 d/wk (eg, muscle-strengthening guideline).

Source: Data derived from Healthy People 2020[8] using National Health Interview Survey, 2017.[24]

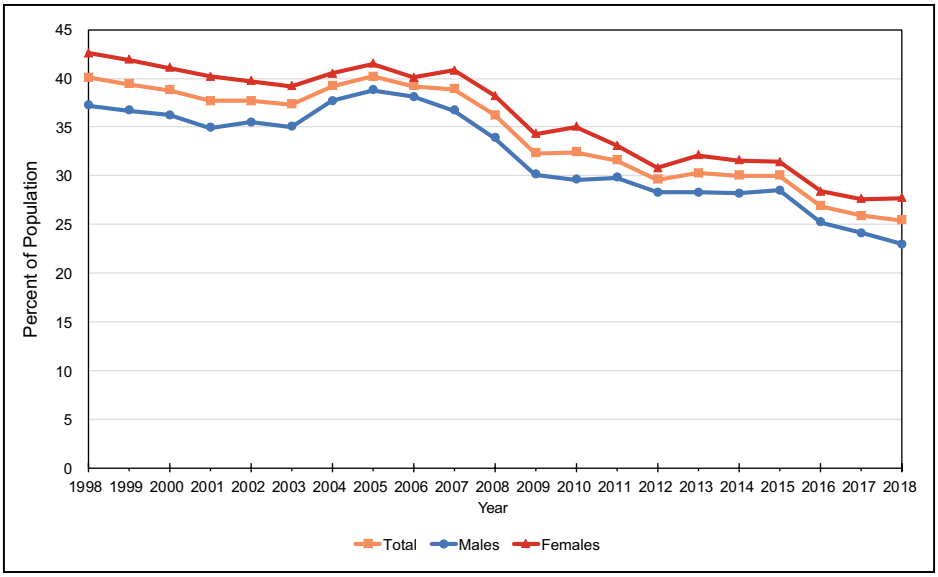

Chart 4-12. Trends in the prevalence of physical inactivity among US adults ≥18 years of age, overall and by sex, 1998 to 2018.
Data are age adjusted to the year 2000 standard population for adults ≥18 years of age. Physical inactivity is defined as reporting no engagement in leisure-time physical activity in bouts lasting ≥10 minutes.
Source: Data derived from Healthy People 2020[8] using National Health Interview Survey, 1998 to 2018.[24]

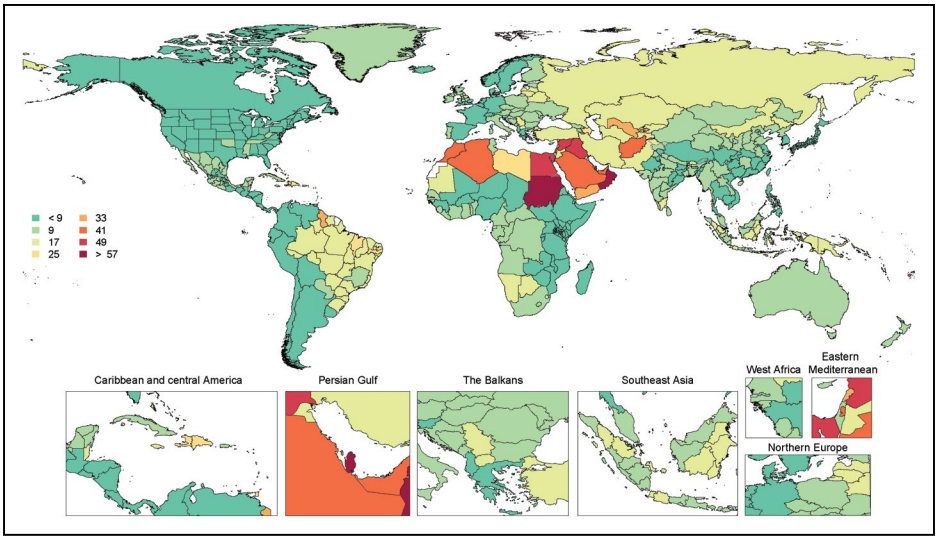

Chart 4-13. Age-standardized global mortality rates attributable to low physical activity per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[129] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[132]

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5. NUTRITION

See Tables 5-1 through 5-3 and Charts 5-1 through 5-6

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This chapter 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 CVH.

Abbreviations Used in Chapter 5

AF	atrial fibrillation
AHA	American Heart Association
AHEI	Alternate Healthy Eating Index
AHS-2	Adventist Health Study-2
AMI	acute myocardial infarction
apoB	apolipoprotein B
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CER	cost-effectiveness ratio
CHD	coronary heart disease
CI	confidence interval
CRP	C-reactive protein
CSA	community-supported agriculture
CVD	cardiovascular disease
CVD PREDICT	Cardiovascular Disease Policy Model for Risk, Events, Detection, Interventions, Costs, and Trends
CVH	cardiovascular health
DALY	disability-adjusted life-year
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
DHA	docosahexaenoic acid
DII	Dietary Inflammatory Index

(*Continued*)

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Abbreviations Used in Chapter 5 Continued

dp-ucMPG	plasma dephosphorylated-uncarboxylated matrix Gla-protein
EPA	eicosapentaenoic acid
EPIC	European Prospective Investigation Into Cancer and Nutrition
EVITA	Effect of vitamin D on mortality in heart failure
FDA	US Food and Drug Administration
GBD	Global Burden of Disease Study
GRS	genetic risk score
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HBP	high blood pressure
HD	heart disease
HDL-C	high-density lipoprotein cholesterol
HEI	Healthy Eating Index
HF	heart failure
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
IHD	ischemic heart disease
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
LVEF	left ventricular ejection fraction
MDCS	Malmö Diet and Cancer Study
MetS	metabolic syndrome
MHO	metabolically healthy obesity
MI	myocardial infarction
MUFA	monounsaturated fatty acid
MVMM	multivitamin/mineral
NA	not available
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NSHDS	Northern Sweden Health and Disease Study
OR	odds ratio
PREDIMED	Prevención con Dieta Mediterránea
PREMIER	Efficacy and Safety of Adalimumab and Methotrexate (MTX) Versus MTX Monotherapy in Subjects With Early Rheumatoid Arthritis
PUFA	polyunsaturated fatty acid
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
SCD	sudden cardiac death
SD	standard deviation
SES	socioeconomic status
SFA	saturated fatty acid
SNP	single-nucleotide polymorphism
SSB	sugar-sweetened beverage
SUN	Seguimiento Universidad de Navarra
TC	total cholesterol
TOHP	Trials of Hypertension Prevention
UI	uncertainty interval
VITAL	Vitamin D and Omega-3 Trial
VITAL-HF	Vitamin D and Omega-3 Trial–Heart Failure
WHI	Women's Health Initiative

Prevalence and Trends in the AHA Healthy Diet Metrics

(See Table 5-1 and 5-2 and Charts 5-1 and 5-2)

In 2010, the AHA released an Impact Goal that included 2 objectives: "By 2020, to improve the cardiovascular health of all Americans by 20%, while reducing deaths from CVDs and stroke by 20%."[1] This includes following a healthy diet pattern characterized by 5 primary and 3 secondary metrics (Table 5-1) that should be consumed within a context that is appropriate in energy balance and consistent with a DASH-type eating plan.[2]

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.[3] 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 0–1).

With the use of the alternative scoring system, the mean AHA healthy diet score improved between 2003 to 2004 and 2015 to 2016 in the United States for adults. In adults, the prevalence of a poor diet improved from 56.0% to 47.8% for the primary score and 43.7% to 36.4% for the secondary score (Table 5-2). Changes in score were attributable largely to increased consumption of whole grains and nuts, seeds, and legumes and decreased consumption of SSBs. No significant changes were observed for consumption of total fruits and vegetables, fish and shellfish, sodium, processed meat, and saturated fat.

Similar changes in AHA healthy diet scores between 2003 to 2004 and 2015 to 2016 were seen in minority groups and those with lower income or education, although significant disparities persisted (Charts 5-1 and 5-2). The proportion with a poor diet decreased from 64.7% to 58.3% for NH Black individuals, from 66.0% to 57.5% for Mexican American individuals, and from 54.0% to 45.9% for NH White individuals (Chart 5-1). The proportion with a poor diet (<40% adherence) decreased from 50.7% to 38.8% in adults with income-to-poverty ratio ≥3.0 but only from 67.7% to 59.7% in adults with income-to-poverty ratio <1.3 (Chart 5-2).

Dietary Habits in the United States: Current Intakes of Foods and Nutrients

Adults

(See Table 5-3 and Charts 5-3 and 5-4)

The average dietary consumption by US adults of selected foods and nutrients related to cardiometabolic health based on data from 2015 to 2016 NHANES is detailed below by sex and race/ethnicity (Table 5-3):

- Consumption of whole grains was low with sex and racial variations and ranged from 0.6 (Mexican American males) to 1.1 (NH White males) servings per day. For each of these groups, <10% of adults met guidelines of ≥3 servings per day.
- Whole fruit consumption similarly showed a sex and racial difference and ranged from 1.0 (NH Black males) to 1.6 (Mexican American females) servings per day. For each of those groups, <10% of adults met guidelines of ≥2 cups/d. When 100% fruit juices were included, the number of servings increased, and the proportions of adults consuming ≥2 cups/d increased.
- Nonstarchy vegetable consumption ranged from 1.6 (NH Black males) to 2.4 (NH White females) servings per day. The proportion of adults meeting guidelines of ≥2.5 cups/d was <10%.
- Consumption of fish and shellfish ranged from 1.0 (NH White individuals) to 1.8 (NH Black females) servings per week. The proportions of adults meeting guidelines of ≥2 servings per week were ≈17% of NH White adults, ≈23% of NH Black adults, and ≈18% of Mexican American adults.
- Weekly consumption of nuts and seeds was ≈6 servings among NH White adults and ≈3 servings among NH Black adults and Mexican American adults. Approximately 1 in 3 White adults, 1 in 6 NH Black adults, and 1 in 5 Mexican American adults met guidelines of ≥4 servings per week.
- Consumption of processed meats was lowest among Mexican American females (1.0 servings per week) and highest among NH White males (≈2.5 servings per week). Between 57% (NH White males) and 80% (Mexican American females) of adults consumed ≤2 servings per week.
- Consumption of SSBs was lowest among NH White females (5.8 servings per week) and highest among NH Black individuals and Mexican American males (≈10 servings per week). The proportions of adults meeting guidelines of <36 oz per week was ≈63% for NH White adults, 42% for Mexican American adults, and 37% for NH Black adults.
- Consumption of sweets and bakery desserts ranged from 4.7 servings per week among Mexican American females to 3.3 servings per week among NH Black males. The majority of NH White, NH Black, and Mexican American adults consumed <2.5 servings per week.
- The proportion of total energy intake from added sugars ranged from 10.8% for Mexican American males to 22.1% for NH Black females. Between 12% of NH Black females and 38.1% of Mexican American males consumed ≤6.5% of total energy intake from added sugars.

- Consumption of EPA and DHA ranged from 0.075 to 0.103 g/d in each sex and racial or ethnic subgroup. Fewer than 9% of US adults met the guideline of ≥0.250 g/d.
- One-quarter to two-fifths of adults consumed <10% of total calories from saturated fat, and approximately one-half to two-thirds consumed <300 mg dietary cholesterol per day.
- The ratio of (PUFAs+MUFAs)/SFAs ranged from 1.8 in NH White males and Mexican American males to 2.6 in NH Black females. The proportion with a ratio ≥2.5 ranged from 40% in NH Black females to 12.6% in NH White males.
- Only ≈8% of NH White adults, ≈5% of Black adults, and ≈12% of 3Mexican American adults consumed ≥28 g of dietary fiber per day.
- Fewer than 10% of adults consumed <2.3 g sodium per day. Estimated mean sodium intake 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. Sodium added to food outside the home accounts for more than two-thirds of total sodium intake in the United States (Chart 5-4).[4] Top sources of sodium intake vary by race/ethnicity, with the largest contributor being yeast breads for NH White adults, sandwiches for NH Black adults, burritos and tacos for Hispanic adults, and soups for NH Asian adults.[5]

Children and Teenagers

According to NHANES 2015 to 2016 data, the average dietary consumption by US children and teenagers of selected foods and nutrients related to cardiometabolic health is detailed below[6]:

- Whole grain consumption was low with an estimated average intake of 0.95 serving per day (95% CI, 0.88–1.03) among US youth 2 to 19 years of age. Youth with higher parental education had higher intake.
- Whole fruit consumption was low with an estimated average intake of 0.68 serving per day (95% CI, 0.58–0.77). The consumption pattern decreased with age. NH Asian youth and other races, including multiracial youth, had the highest intake of whole fruit, followed by NH White youth, other Hispanic youth, Mexican American youth, and NH Black youth. The average intake of 100% fruit juice was 0.46 serving per day (95% CI, 0.39–0.53). The consumption pattern also decreased with age. NH White youth had the lowest intake of fruit juice, followed by NH Asian youth and other races, including multiracial youth, Mexican American youth, other Hispanic youth, and NH Black youth.
- Nonstarchy vegetable consumption was low with an estimated average intake of 0.57 serving per day (95% CI, 0.53–0.62). The consumption pattern increased with age.
- Consumption of fish and shellfish was very low with an estimated average intake of 0.06 serving per day (95% CI, 0.04–0.07). The consumption pattern increased with age. Hispanic youth had the highest intake of fish and shellfish, followed by NH Asian youth and other races, including multiracial youth, NH Black youth, Mexican American youth, and NH White youth.
- Consumption of nuts and seeds was low with an estimated average intake of 0.40 serving per day (95% CI, 0.33–0.47). NH White youth had the highest intake of nuts and seeds, followed by NH Asian youth and other races, including multiracial youth, other Hispanic youth, NH Black youth, and Mexican American youth. The consumption pattern of nuts and seeds increased with attainment of parental education and parental income.
- Consumption of unprocessed red meats was 0.31 serving per day (95% CI, 0.27–0.34) on average with higher intake among youth with attainment of parental education less than high school and high school graduate, and lower among youth with parental education of some college or above and college graduate or above.
- Consumption of processed meats was 0.27 serving per day (95% CI, 0.24–0.29) on average with higher intake among males and lower intake among females. NH White youth have the highest intake of processed meat, followed by NH Black youth, Mexican American youth, NH Asian youth, and other races, including multiracial youth and other Hispanic youth.
- Consumption of SSBs was 1.0 serving per day (95% CI, 0.89–1.11) on average among US youth. The consumption pattern of SSBs increased with age. NH Black youth have the highest intake of SSBs, followed by Mexican American youth, NH White youth, other Hispanic youth, NH Asian youth, and other races, including multiracial youth.
- Consumption of sweets and bakery desserts contributed to an average of 6.07% of calories (95% CI, 5.55%–6.60%) among US youth, with no significant heterogeneity across age, sex, race/ethnicity, parental education, and household income.
- Consumption of EPA and DHA was low with an estimated average intake of 0.04 g/d (95% CI, 0.03–0.05). The consumption pattern of EPA and DHA increased with age. NH Asian youth and other races, including multiracial youth, have the highest intake of EPA and DHA, followed by other Hispanic youth, Mexican American youth, NH White youth, and NH Black youth.
- Consumption of SFAs was ≈12.1% of calories (95% CI, 11.8%–12.4%) among US youth.

Consumption of dietary cholesterol was 254 mg/d (95% CI, 244–264) with NH White youth having the lowest intake (238 mg/d [95% CI, 226–250]) and Mexican American youth having the highest intake (292 [95% CI, 275–309]).
- Consumption of dietary fiber was 15.6 g/d (95% CI, 15.1–16.0) on average among US youth, with no significant heterogeneity across age, sex, race/ethnicity, parental education, and household income.
- Consumption of sodium was 3.33 g/d (95% CI, 3.28–3.37) on average among US youth. The consumption pattern increased with age. NH Asian youth and other races, including multiracial youth, have the highest intake of sodium, followed by NH Black youth, Mexican American youth, and NH White youth.

Secular Trends

In addition to individual foods and nutrients, overall dietary patterns can be a useful tool for assessing diet quality.[7] 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.[8] 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. Different dietary patterns have been defined such as HEI-2010, AHEI, Mediterranean, DASH-type, Western, prudent, and vegetarian patterns.

Between 1999 and 2010, the average AHEI-2010 score of US adults improved from 39.9 to 46.8.[9] 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 2016, the mean HEI-2015 score in US children and adolescents 2 to 19 years of age improved from 44.6 (95% CI, 43.5-45.8) to 49.6 (95% CI, 48.5–50.8) (11.2% improvement). The mean AHA primary diet score increased from 14.8 (95% CI, 14.1-15.4) to 18.8 (95% CI, 18.1–19.6) (27.0% improvement) and the mean AHA secondary score from 29.2 (95% CI, 28.1-30.4) to 33.0 (95% CI, 32.0–33.9) (13.0% improvement). On the basis of the AHA primary score, the estimated proportion of US children with poor dietary quality significantly decreased from 76.8% (95% CI, 72.9%–80.2%) to 56.1% (95% CI, 51.4%–60.7%); the estimated proportion with intermediate quality significantly increased from 23.2% (95% CI, 19.8%–26.9%) to 43.7% (95% CI, 39.1%–48.3%). The estimated proportion with an ideal diet significantly improved but remained low (from 0.07% to 0.25%). On the basis of the AHA secondary score, the estimated proportion of US children with poor dietary quality significantly decreased from 61.0% (95% CI, 56.5%–65.2%) to 49.1% (95% CI, 45.0%–53.3%); the estimated proportion with intermediate quality significantly increased from 39.0% (95% CI, 34.7%–43.4%) to 50.4% (95% CI, 46.3%–54.4%). The estimated proportion with an ideal diet significantly improved from 0.04% to 0.50%. The overall dietary quality improvement among US youth was attributable mainly to the increased consumption fruits/vegetables (especially whole fruits) and whole grains, with additional increases in total dairy, total protein foods, seafood, and plant proteins and decreased consumption of SSBs and added sugar. Persistent dietary variations were identified across multiple sociodemographic groups. The mean HEI-2015 score in 2015 to 2016 was 55.0 (95% CI, 53.7–56.4) for youth 2 to 5 years of age, 49.2 (95% CI, 47.9–50.6) for youth 6 to 11 years of age, and 47.4 (95% CI, 46.0–48.8) for youth 12 to 19 years of age, with similar persistent variations across levels of sociodemographic characteristics.

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 with 2003 to 2008 and 2011 to 2012 NHANES data in 2- to 4-year-old children from low-income households.[10] 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.

In a study using data from the Food and Agriculture Organization Food Balance Sheets from 1961 to 1965, 2000 to 2003, and 2004 to 2011 in 41 countries, a Mediterranean adequacy index was calculated from available energy intake for food groups consistent or inconsistent with the Mediterranean dietary pattern.[11] Adherence to the Mediterranean dietary pattern decreased from 1961 to 1965 to 2000 to 2003, with stabilization overall from 2004 to 2011.

Trends in Dietary Supplement Intake (See Chart 5-5)

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.[12] From 1999 to

2000 to 2011 to 2012, use of multivitamins/multiminerals decreased from 37% to 31%, use of omega-3 fatty acids increased from 1.4% to 11%, and use of vitamin D supplements remained stable (34% to 38%; Chart 5-5). Fifty-two percent of US adults reported using any supplement, including multivitamins/multiminerals (31%), vitamin D (38%), and omega-3 fatty acids (11%).[13] Trends in any supplement use over time were increasing in older adults, stable among middle-aged adults, and decreasing in younger adults.

Social Determinants

- 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.[14–16]
- 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.[17]
- 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.[18] 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 Black people, Mexican American people, and lowest-income households.[19]

Genetics/Family History

- Genetic factors may contribute to food preferences and modulate the association between dietary components and adverse CVH outcomes.[20–22] However, there is a paucity of gene-diet interaction studies with independent replication to support personalizing dietary recommendations according to genotype.
- In a randomized trial of 609 overweight-obese, nondiabetic participants that compared the effects of healthy low-fat and healthy low-carbohydrate weight loss diets, 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.[23]
- The interactions between a GRS composed of 97 BMI-associated variants and 3 diet-quality scores were examined in a pooled analysis of 30 904 participants from the Nurses' Health Study, the Health Professional Follow-Up Study, and the Women's Genome Health Study. Higher diet quality was found to attenuate the association between GRS and BMI (*P* for interaction terms <0.005 for AHEI-2010 score, Alternative Mediterranean Diet score, and DASH diet score).[24] A 10-unit increase in the GRS was associated with a 0.84-unit (95% CI, 0.72–0.96) increase in BMI for those in the highest tertile of AHEI score compared with a 1.14-unit (95% CI, 0.99–1.29) increase in BMI in those in the lowest tertile of AHEI score.

Impact on US Mortality

- Nationally representative data from 37 233 US adults were analyzed to examine the association between low-carbohydrate and low-fat diets and mortality. Neither low-carbohydrate nor low-fat diets were associated with total mortality; however, diet quality and sources of macronutrients appeared to play a role in that healthy low-carbohydrate (HR, 0.91 [95% CI, 0.87–0.95]; *P*<0.001) and low-fat (HR, 0.89 [95% CI, 0.85–0.93]; *P*<0.001) diets were associated with lower mortality and unhealthy low-carbohydrate (HR, 1.07 [95% CI, 1.02–1.11]; *P*=0.01) and low-fat (HR, 1.06 [95% CI, 1.01–1.12]; *P*=0.04) diets were linked to higher mortality.[25]
- NHANES III (1988–1994) data from 3733 overweight/obese (BMI ≥25 kg/m^2) adults (20–90 years of age) were analyzed to assess the relationship between the DII and mortality. Results show that the DII scores of metabolically unhealthy obese/overweight individuals were associated with increased mortality risk ($HR_{\text{tertile 3 versus tertile 1}}$, 1.44 [95% CI, 1.11–1.86]; P_{trend}=0.008; $HR_{\text{1SD increase}}$, 1.08 [95% CI, 0.99–1.18]) and, more specifically, CVD-related mortality ($HR_{\text{T3 versus T1}}$, 3.29 [95% CI, 2.01–5.37]; P_{trend}< 0.001; $HR_{\text{1SD increase}}$ 1.40 [95% CI, 1.18–1.66]). These associations were not observed among MHO adults, and no cancer mortality risk was observed for either metabolically unhealthy obese/overweight or MHO individuals. The SUN (n=18 566) and PREDIMED (n=6790) Spanish cohort studies similarly analyzed the DII in relation to mortality. Significant associations were found in differences between the highest and lowest quartiles of the DII and mortality in both the SUN (HR, 1.85 [95% CI, 1.15–2.98]; P_{trend}=0.004)[26] and PREDIMED (HR, 1.42 [95% CI,

1.00–2.02]; P_{trend}=0.009) studies. A subsequent meta-analysis of 12 studies examined the association between the DII and mortality and found the DII to be significantly associated with a 23% increase in mortality (95% CI, 16%–32%) in the highest versus lowest quartiles of the DII.[26,27]

- NHANES 1999 to 2010 data from 20 256 US adults (mean, 47.5 years of age) were analyzed to evaluate the relationship between dietary uricemia score and dietary atherogenic score (which were derived in regression models on 37 micronutrients and macronutrients predicting levels of serum uric acid and apoB, respectively) and all-cause and cause-specific mortality. Individuals in the highest dietary uricemia score quartile were at greater risk for all-cause (HR, 1.17 [95% CI, 1.07–2.30]), cancer (HR, 1.06 [95% CI, 1.01–1.14]), and CVD (HR, 1.36 [95% CI, 1.21–1.59]) mortality. Similar patterns were noted in the dietary atherogenic score, with those in the highest quartiles (versus those in the lowest) experiencing increased risk for all-cause (25%), cancer (11%), and CVD (40%) mortality.[28]
- A number of studies examined the relationship between sugar intake and all- and cause-specific mortality. A 6-year cohort study of 13 440 US adults (mean, 63.6 years of age) found that higher consumption (each additional 12 oz serving per day) of sugary beverages (HR, 1.11 [95% CI, 1.03–1.19]) and 100% fruit juices (HR, 1.24 [95% CI, 1.09–1.42]) was associated with higher all-cause (but not CHD-specific) mortality. In 2 Swedish studies (MDCS; n=24 272 and NSHDS; n=24 475), higher sugar consumption (>20% energy intake) was linked to higher mortality risk (30%), and low sugar consumption (<5% energy intake) was also associated with higher mortality risk (23%) in the MCDS study.[29,30]
- A systematic review of 18 cohort studies (n=251 497) examined the relationship between glycemic index and glycemic load with risk of all-cause mortality and CVD and found no associations between glycemic index or glycemic load and CVD or all-cause mortality. However, a positive association was found with all-cause mortality[29] among females with the highest (versus lowest) glycemic index (RR, 1.17 [95% CI, 1.02–1.35]).[29–31]
- In an assessment of the relationship between dairy intake and mortality, data from 3 large prospective cohort studies with 217 755 US adults showed a dose-response relationship in which 2 daily servings of dairy were associated with the lowest CVD mortality, and higher intake was linked to higher mortality, especially cancer mortality. Compared with other subtypes of dairy (eg, skim/low-fat milk, cheese, yogurt, ice cream/sherbet), whole milk (and additional 0.5 serving per day) was associated with higher risks of cancer mortality (HR, 1.11 [95% CI, 1.06–1.17]), CVD mortality (HR, 1.09 [95% CI, 1.03–1.15), and total mortality (HR, 1.11 [95% CI, 1.09–1.14). A similar large cohort study with 45 009 Italians found no dose-response relationship between dairy (eg, milk, cheese, yogurt, butter) consumption and mortality, and no differences were present between full-fat and reduced-fat milk. However, there was a significant reduction of 25% in risk of all-cause mortality among those consuming 160 to 200 g/d (HR, 0.75 [95% CI, 0.61–0.91]) milk versus nonconsumers. Another European study examined the relationship between dietary protein and protein sources and mortality among 2641 Finnish males. Higher meat intake (HR, 1.23 [95% CI, 1.04–1.47])) and higher ratio of animal to plant protein (HR, 1.23 [95% CI, 1.02–1.49]) were associated with higher mortality. This relationship was more pronounced among those with a history of CVD, cancer, and type 2 diabetes. No relationships were noted between other protein sources (eg, fish, eggs, dairy, plant protein) and mortality.[32–34]
- The association between nut and peanut butter consumption and mortality has also been assessed. In a large prospective cohort study of 566 398 US adults (50–71 years of age at baseline) with a median follow-up of 15.5 years, nut consumption was inversely related to mortality (HR, 0.78 [95% CI, 0.76–0.81]; $P \leq 0.001$) and was associated with reductions in cancer, CVD, infectious, respiratory, and liver and renal disease mortality (but not Alzheimer- or diabetes-related mortality). No significant relationships were found between peanut butter and cause-specific or all-cause mortality (HR, 1.00 [95% CI, 0.98–1.04]; P=0.001).[35]
- Moderate egg consumption and all-cause and cause-specific[36] mortality were investigated in a large cohort of 40 621 adults (29–69 years of age) in the EPIC-Spain prospective cohort study across 18 years. Mean egg consumption was 22 g/d (SD, 15.8 g/d) in females and 30.9 g/d (SD, 23.1 g/d) in males, and no association was found between the highest and lowest quartiles of egg consumption and all-cause mortality (HR, 1.01 [95% CI, 0.91–1.11]; P=0.96), or cancer and CVD mortality. However, egg consumption appears to be linked to deaths resulting from other causes (HR, 0.76 [95% CI, 0.63–0.93]; P=0.003), specifically nervous system–related deaths (HR, 0.59 [95% CI, 0.35–1.00]; P=0.036).[36]
- The association between dietary choline and overall- and cause-specific mortality was examined in a large, nationally representative study of 20 325 US adults (mean, 47.4 years of age). It was found that higher choline consumption is associated with worse lipid profiles, poorer glycemic control, and lower CRP levels (all comparisons P<0.001).

Those with highest compared with lowest consumption had increased risk of mortality (23%), stroke (30%), and CVD (33%) (all comparisons $P<0.001$). A subsequently performed meta-analysis confirmed these results and found choline to be linked to higher mortality risk (RR, 1.12 [95% CI, 1.08–1.17]; $I^2=2.9$) and CVD mortality risk (RR, 1.28 [95% CI, 1.17–1.39]; $I^2=9.6$).[37]

CVH Impact of Diet

Dietary Patterns

- The observational findings for benefits of the Mediterranean diet have been confirmed in a large primary prevention trial in Spain among patients with CVD risk factors.[38] The PREDIMED trial demonstrated an ≈30% reduction in the risk of stroke, MI, and death attributable to cardiovascular causes in those patients randomized to unrestricted-calorie Mediterranean-style diets supplemented with extra-virgin olive oil or mixed nuts,[38] without changes in body weight.[39] In a subgroup analysis of 3541 patients without diabetes in the PREDIMED trial, HRs for incident diabetes were 0.60 (95% CI, 0.43–0.85) for the Mediterranean diet with olive oil group and 0.82 (95% CI, 0.61–1.10) for the Mediterranean diet with nuts group compared with the control group.
- In a randomized crossover trial of 118 overweight omnivores at low-moderate CVD risk, a reduced-calorie lacto-ovo-vegetarian diet was compared with a reduced-calorie Mediterranean diet by providing face-to-face, individual counseling sessions. Both diets were equally successful in reducing body weight and fat mass. LDL-C, uric acid, and vitamin B_{12} were lower during the vegetarian diet, whereas triglycerides were lower during the Mediterranean diet, without substantial differences between oxidative stress markers and inflammatory cytokines.[40]
- In a systematic review and meta-analysis of 29 observational studies, the RR for the highest versus the lowest category of the Mediterranean diet was 0.81 (95% CI, 0.74–0.88) for CVD, 0.70 (95% CI, 0.62–0.80) for CHD/AMI, 0.73 (95% CI, 0.59–0.91) for unspecified stroke (ischemic/hemorrhagic), 0.82 (95% CI, 0.73–0.92) for ischemic stroke, and 1.01 (95% CI, 0.74–1.37) for hemorrhagic stroke.[41]
- In a meta-analysis of 20 prospective cohort studies, the RR for each 4-point increment of the Mediterranean diet score was 0.84 (95% CI, 0.81–0.88) for unspecified stroke, 0.86 (95% CI, 0.81–0.91) for ischemic stroke, and 0.83 (95% CI, 0.74–0.93) for hemorrhagic stroke.[42]
- In another systematic review, a meta-analysis of 3 RCTs showed a beneficial effect of the Mediterranean diet on total CVD incidence (RR, 0.62 [95% CI, 0.50–0.78]) and total MI incidence (RR, 0.65 [95% CI, 0.49–0.88]).[43]
- Another meta-analysis of 38 prospective cohort studies showed that the RR for the highest versus the lowest categories of Mediterranean diet adherence was 0.79 (95% CI, 0.77–0.82) for total CVD mortality, 0.73 (95% CI, 0.62–0.86) for CHD incidence, 0.83 (95% CI, 0.75–0.92) for CHD mortality, 0.80 (95% CI, 0.71–0.90) for stroke incidence, 0.87 (95% CI, 0.80–0.96) for stroke mortality, and 0.73 (95% CI, 0.61–0.88) for MI incidence.[43]
- 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 to 139, 140 to 149, and ≥150 mm Hg, respectively.[44] 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.[45] In an umbrella review of systematic reviews, a meta-analysis of 33 controlled trials showed that the DASH diet was associated with decreased SBP (mean difference, –5.2 mm Hg [95% CI, –7.0 to –3.4]), DBP (–2.60 mm Hg [95% CI, –3.50 to –1.70]), TC (–0.20 mmol/L [95% CI, –0.31 to –0.10]), LDL-C (–0.10 mmol/L [95% CI, –0.20 to –0.01]), HbA_{1c} (–0.53% [95% CI, –0.62 to –0.43]), fasting blood insulin (–0.15 μU/mL [95% CI, –0.22 to –0.08]), and body weight (–1.42 kg [95% CI, –2.03 to –0.82]).[46] A meta-analysis of 15 prospective cohort studies showed that the DASH diet was associated with decreased incident CVD (RR, 0.80 [95% CI, 0.76–0.85]), CHD (0.79 [95% CI, 0.71–0.88]), stroke (0.81 [95% CI, 0.72–0.92]), and diabetes (0.82 [95% CI, 0.74–0.92]).[46] In another systematic review and meta-analysis of 7 prospective cohort studies, the RR for each 4-point increment of DASH diet score was 0.95 (95% CI, 0.94–0.97) for CAD.[47]
- Compared with a higher-carbohydrate DASH diet, a DASH-type diet with higher protein lowered BP by 1.4 mm Hg, LDL-C by 3.3 mg/dL, and triglycerides by 16 mg/dL but also lowered HDL-C 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-C 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]
- A secondary analysis of the AHS-2 among NH White participants showed that vegetarian dietary patterns (vegans, lacto-ovo-vegetarians, and pesco-vegetarians) at baseline were associated with lower prevalence of hypertension at 1

to 3 years of follow-up compared with the non-vegetarians: prevalence ratio was 0.46 (95% CI, 0.25–0.83) for vegans, 0.57 (95% CI, 0.45–0.73) for lacto-ovo-vegetarians, and 0.62 (95% CI, 0.42–0.91) for pesco-vegetarians. This association remained after adjustment for BMI among the lacto-ovo-vegetarians.[50]

- In a systematic review and meta-analysis of 9 prospective cohort studies, higher adherence to a plant-based dietary pattern was significantly associated with lower risk of type 2 diabetes (RR, 0.77; 95% CI, 0.71–0.84).[51]
- In a RCT of 48 835 postmenopausal females, a low-fat dietary pattern (lower fat and higher carbohydrate, vegetables, and fruit) intervention led to significant reductions in breast cancer followed by death (HR, 0.84 [95% CI, 0.74–0.96]) and in diabetes requiring insulin (HR, 0.87 [95% CI, 0.77–0.98]) over a median follow-up of 19.6 years compared with usual diet.[52]
- In a prospective cohort study of 105 159 adults followed up for a median of 5.2 years, for a 10% increment in the percentage of ultraprocessed foods in the diet, the HR was 1.12 (95% CI, 1.05–1.20) for overall CVD, 1.13 (95% CI, 1.02–1.24) for CHD, and 1.11 (95% CI, 1.01–1.21) for cerebrovascular disease.[53]

Fats and Carbohydrates

- In meta-analyses of RCTs comparing higher and lower fiber intake, higher fiber intake lowered body weight (–0.37 kg [95% CI, –0.63 to –0.11 kg]), TC (–0.15 mmol/L [95% CI, –0.22 to –0.07 mmol/L]), and SBP (–1.27 mm Hg [95% CI, –2.50 to –0.04 mm Hg]) and tended to lower HbA_{1c} (–0.54% [95% CI, –1.28% to 0.20%]).[54] In similar meta-analyses of RCTs for whole grains and glycemic index, higher whole grain intake only significantly reduced body weight (–0.62 kg [95% CI, –1.19 to –0.05 kg]), whereas no consistent health effects were found for glycemic index. In meta-analyses of observational studies, higher total dietary fiber intake was associated with a lower risk of incident CHD (RR, 0.76 [95% CI, 0.69–0.83]), CHD mortality (RR, 0.69 [95% CI, 0.60–0.81]), and incident stroke (RR, 0.78 [95% CI, 0.69–0.88]).[54] Higher whole grain intake was associated with a lower risk of incident CHD (RR, 0.80 [95% CI, 0.70–0.91]), CHD mortality (RR, 0.66 [95% CI, 0.56–0.77]), and stroke death (RR, 0.74 [95% CI, 0.58–0.94]). Evidence for associations between glycemic index, glycemic load, and source of dietary fiber and CVD outcomes was less robust.
- In a randomized trial of 609 nondiabetic participants with a BMI of 28 to 40 kg/m^2 that compared the effects of healthy low-fat and healthy low-carbohydrate weight loss diets, weight loss at 12 months did not differ between groups.[23]
- In a meta-analysis of RCTs, consumption of 1% of calories from *trans* fat in place of SFAs, MUFAs, or PUFAs increased the ratio of TC to HDL-C by 0.031, 0.054, and 0.67; increased apoB levels by 3, 10, and 11 mg/L; decreased apolipoprotein A-1 levels by 7, 5, and 3 mg/L; and increased Lp(a) levels by 3.8, 1.4, and 1.1 mg/L, respectively.[55]
- 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.[56] 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.
- Gut microbiota is associated with the risk of obesity, type 2 diabetes, and many other cardiometabolic diseases. In a 6-month randomized controlled feeding trial of 217 healthy young adults with BMI <28 kg/m^2, the high-fat diet (fat 40% energy) had overall unfavorable effects on gut microbiota: increased *Alistipes* (P=0.04) and *Bacteroides* (P<0.001) and decreased *Faecalibacterium* (P=0.04). The low-fat diet (fat, 20% energy) appeared to have beneficial effects on gut microbiota: increased α-diversity assessed by the Shannon index (P=0.03) and increased abundance of *Blautia* (P=0.007) and *Faecalibacterium* (P=0.04).[57]
- 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.[58] In a matched case-control study of 2428 postmenopausal females nested in the WHI Observational Study, higher plasma phospholipid long-chain SFAs (OR, 1.18 [95% CI, 1.09–1.28]) and lower PUFA n-3 (OR, 0.93 [95% CI, 0.88–0.99]) were associated with increased CHD risk. Replacing 1 mol% PUFA n-6 or *trans* fatty acid with an equivalent amount of PUFA n-3 was associated with 10% lower CHD risk (OR, 0.90 [95% CI, 0.84–0.96]).[59]
- In a study using NHANES 2007 to 2014 data (n=18 434 participants), ORs for newly diagnosed hypertension comparing the highest and lowest tertiles were 0.60 (95% CI, 0.50–0.73) for dietary n-3 fatty acids, 0.52 (95% CI, 0.43–0.62) for dietary n-6 fatty acids, and 0.95 (95% CI, 0.79–1.14) for n-6:n-3 ratio.[60]

- In a prospective study of 3042 CVD-free adults followed up for a mean of 8.4 years, exclusive olive oil use was inversely associated with the risk of developing CVD (RR, 0.07 [95% CI, 0.01–0.66]) compared with no olive oil consumption.[61] In the same study, adults with ≥50 mg/dL Lp(a) had 2 times higher CVD risk than those with <50 mg/dL Lp(a) (HR, 2.18 [95% CI, 1.11–4.28]), driven mainly by the Lp(a) effect in males.[62]

Foods and Beverages

- In a systematic review and dose-response meta-analysis of 123 prospective studies, the risk of CHD, stroke, and HF was inversely associated with consumption of whole grain, vegetables and fruits, nuts, and fish.[63] In contrast, the risk of these conditions was positively associated with consumption of egg, red meat, processed meat, and SSBs.
- 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.[64] In a prospective cohort of 5775 participants, the HR for the highest versus the lowest quartile of SSB consumption was 1.21 (95% CI, 1.02–1.45) for hypertension.[65]
- In a meta-analysis of 16 prospective cohort studies, each daily serving of fruits or vegetables was associated with a 4% lower risk of cardiovascular mortality (RR, 0.96 [95% CI, 0.92–0.99]).[66]
- 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]).[67]
- 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]).[68] In another meta-analysis of 8 cohort or case-control studies, whole grain or cereal fiber intake was inversely associated with type 2 diabetes (RR, 0.68 [95% CI, 0.64–0.73]).[69]
- In a meta-analysis of 14 prospective cohort studies, every 20-g/d higher intake of fish was associated with 4% reduced risk of CVD mortality (RR, 0.96 [95% CI, 0.94–0.98]).[70] The association was stronger in Asian cohorts than Western cohorts. 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]).[71]
- 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 was associated with a higher incidence of CHD (RR, 1.42 [95% CI, 1.07–1.89]).[72] In an RCT (n=113 healthy adults), LDL-C and apoB were significantly higher with red and white meat than with nonmeat consumption for 4 weeks, regardless of SFA content. Regardless of protein source, high SFA content (≈14% total energy) significantly increased LDL-C, apoB, and large LDL particles compared with low SFA content (≈7% total energy).[73]
- In a study of 169 310 female nurses and 41 526 male health professionals, 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 never or almost never consuming nuts. Results were largely consistent for peanuts, tree nuts, and walnuts.[74] 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, apoB by 3.7 mg/dL, and triglycerides by 2.2 mg/dL. No heterogeneity by nut type was observed.[75] In another 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]).[76]
- 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.[77]
- In a crossover RCT (n= 25 normocholesterolemic and 27 moderately hypercholesterolemic participants), 8-week consumption of moderate amounts of a soluble green/roasted (35:65) coffee blend significantly reduced TC, LDL-C, very-low-density lipoprotein cholesterol, triglycerides, SBP, DBP, heart rate, and body weight among moderately hypercholesterolemic participants. The beneficial influence on SBP, DBP, heart rate, and body weight was also observed in healthy participants.[78]
- In a cross-sectional study of 12 285 adults, for males, consumption of >30 g alcohol per day was significantly associated with a higher risk of MetS (OR, 1.73 [95% CI, 1.25–2.39]), HBP (OR, 2.76 [95% CI, 1.64–4.65]), elevated blood glucose (OR, 1.70 [95% CI, 1.24–2.32]), and abdominal obesity (OR, 1.77 [95% CI, 1.07–2.92])

compared with nondrinking.[79] In males, drinkers at all levels had a lower risk of coronary disease than nondrinkers, whereas alcohol consumption was not associated with the risk of hypertension or stroke.[80] In females, consumption of 10.1 to 15.0 g alcohol per day was associated only with a higher risk of elevated blood glucose (OR, 1.65 [95% CI, 1.14–2.38]) compared with nondrinking.[79] Compared with nondrinkers, consumption of 0.1 to 10.0 g alcohol per day was associated with a lower risk of coronary disease and stroke, and consumption of 0.1 to 15.0 g/d was associated with a lower risk of hypertension in females.[80]

Sodium, Potassium, Phosphorus, and Magnesium

- In a meta-regression analysis of 133 RCTs, a 100-mmol/d (2300-mg/d) reduction in sodium was associated with a 7.7–mm Hg (95% CI, −10.4 to −5.0) lower SBP and a 3.0–mm Hg (95% CI, −4.6 to −1.4) lower DBP among people with >131/78 mm Hg SBP/DBP. The association was weak in people with ≤131/78 mm Hg SBP/DBP: A 100-mmol/day reduction in sodium was associated with a 1.46–mm Hg (95% CI, −2.7 to −0.20) lower SBP and a 0.07–mm Hg (95% CI, −1.5 to 1.4) lower DBP.[81] The effects of sodium reduction on BP appear to be stronger in individuals who are older, hypertensive, and Black.[82,83]
- In a systematic review and nonlinear dose-response meta-analysis of 14 prospective cohort studies and 1 case-control study, a 1-g/d increment in sodium intake was associated with a 6% increase in stroke risk (RR, 1.06 [95% CI, 1.02–1.10]), and a 1-unit increment in dietary sodium-to-potassium ratio (millimoles per millimole) was associated with a 22% increase in stroke risk (RR, 1.22 [95% CI, 1.04–1.41]).[84]
- 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.[85–91] 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) or imprecise estimation of sodium intake through a single dietary recall or a single urine excretion.[89]
- 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.[90]
- 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).[90]
- In a longer-term (median, 24 years) post hoc analysis of the TOHP (median of five 24-hour urine measurements), every 1-unit 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).[91]
- In a secondary analysis of the PREMIER trial, changes in phosphorus intake were not significantly associated with changes in BP. Phosphorus type (plant, animal, or added) significantly modified this association, with only added phosphorus associated with increases in SBP (mean coefficient, 1.24 mm Hg/100 mg [95% CI, 0.36–2.12]) and DBP (0.83 mm Hg/100 mg [95% CI, 0.22–1.44]). An increase in urinary phosphorus excretion was significantly associated with an increase in DBP (0.14 mm Hg/100 mg [95% CI, 0.01–0.28]).[92]
- In a systematic review and meta-analysis of 18 prospective cohort studies, the highest magnesium intake category was associated with an 11% decrease in total stroke risk (RR, 0.89 [95% CI, 0.83–0.94]) and a 12% decrease in ischemic stroke risk (RR, 0.88 [95% CI, 0.81–0.95]) compared with the lowest magnesium intake category. After further adjustment for calcium intake, the inverse association remained for total stroke (RR, 0.89 [95% CI, 0.80–0.99]).[93]

Dietary Supplements

- In an RCT of 15 480 adults with diabetes and no history of ASCVD, 1 g n-3 fatty acids had no effect on first serious vascular event (RR, 0.97 [95% CI, 0.87–1.08]) or a composite outcome of first serious vascular event or revascularization (RR, 1.00 [95% CI, 0.91–1.09]) or mortality (RR, 0.95 [95% CI, 0.86–1.05]) compared with placebo (1 g olive oil).[94]
- 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).[95]
- A meta-analysis of 77 917 participants in 10 RCTs with ≥500 participants treated for ≥1 year found that fish oil supplementation (EPA dose range,

226–1800 mg/d; DHA 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]).[96] However, an updated meta-analysis of 124 477 participants (that included additional data from 3 large RCTs) found that marine omega-3 supplementation significantly lowered the risk of MI (RR, 0.92 [95% CI, 0.86–0.99]; *P*=0.020), CHD death (RR, 0.92 [95% CI, 0.86–0.98]; *P*=0.014), total CHD (RR, 0.95 [95% CI, 0.91–0.99]; *P*=0.008), CVD death (RR, 0.93 [95% CI, 0.88–0.99]; *P*=0.013), and total CVD (RR, 0.97 [95% CI, 0.94–0.99]; *P*=0.015). In addition, significant linear dose-response risk reductions were found for total CVD and major vascular events.[97]

- An observational study of 197 761 US veterans assessed omega-3 fatty acid supplement use and fish intake years on ischemic stroke over 3.2 years (2.2–4.3 years) and incident nonfatal CAD over 3.6 (2.4–4.7 years). It was found that omega-3 fatty acid supplement use was independently associated with a decreased risk of ischemic stroke (HR, 0.88 [95% CI, 0.81–0.95]) but not with nonfatal CAD. Fish intake was not independently associated with either outcome.[98]
- In an RCT of 25 871 adults (males ≥50 years of age and females ≥55 years of age), the effects of daily supplementation of 2000 IU vitamin D and 1 g marine n-3 fatty acids on the prevention of cancer and CVD were examined.[99] Vitamin D had no effect on major cardiovascular events (HR, 0.97 [95% CI, 0.85–1.12]), cancer (HR, 0.96 [95% CI, 0.88–1.06]), or any secondary outcomes. Marine n-3 fatty acid supplementation had no effect on major cardiovascular events (HR, 0.92 [95% CI, 0.80–1.06]), invasive cancer (HR, 1.03 [95% CI, 0.93–1.13]), or any secondary outcomes.
- A secondary RCT data analysis study conducted across 3 years with 161 patients with advanced HF assessed the effects of daily vitamin D supplementation of 4000 IU on lipid parameters (TC, HDL-C, LDL-C, TC/HDL-C ratio, LDL-C/HDL-C ratio, and triglycerides) and vascular calcification parameters (fetuin-A and dp-ucMPG). Long-term vitamin D supplementation did not improve lipid profiles and did not affect vascular calcification markers in these patients. In addition, no sex-specific vitamin D effects were found.[100] A similar study, a post hoc analysis of the EVITA trial, assessing daily vitamin D_3 supplementation of 4000 IU also found no improvement in cardiac function among patients with advanced HF. However, subgroup analyses among those ≥50 years of age indicated improvements of 2.73% in LVEF (95% CI, 0.14%–5.31%) at the 12-month follow-up and 2.60% (95% CI, –2.47% to 7.67%) improvement at the 36-month follow-up.[101]
- A Cochrane review of 1 RCT with 1355 females (with previous preeclampsia) from various hospital sites in Argentina, South Africa, and Zimbabwe who began calcium supplementation before conception (500 mg daily until 20 weeks' gestation) found that calcium made little to no difference in developing serious health problems during pregnancy, including preeclampsia[102] (RR, 0.80 [95% CI, 0.61–1.06]; *P*=0.121, low-quality evidence), severe maternal morbidity and mortality (RR, 0.93 [95% CI, 0.68–1.26]; low-quality evidence), pregnancy loss or stillbirth at any age (RR, 0.83 [95% CI, 0.61–1,14]; low-quality evidence), or a cesarean section (RR, 1.11 [95% CI, 0.96–1,28; low-quality evidence). Calcium was found to slightly reduce the risk of a composite outcome of preeclampsia or pregnancy loss or stillbirth at any age (RR, 0.82 [95% CI, 0.66–1.00; low-quality evidence). Results should be interpreted with caution, particularly because ≈25% of the sample was lost to follow-up.[103]
- The VITAL-HF, an ancillary study of the VITAL RCT, examined whether vitamin D_3 (2000 IU/d) or marine omega-3 fatty acids (n-3) (1 g/d, including EPA 460 mg+ DHA 380 mg) were associated with first HF-related hospitalization or recurrent hospitalization for HF among 25 871 adults with HF between 2011 and 2017. No significant relationships were found between either vitamin D or n-3 fatty acid supplementation and first HF hospitalization. However, marine n-3 supplementation (326 events) significantly reduced recurrent HF hospitalization compared with placebo (379 events) (HR, 0.86 [95% CI, 0.74–0.998]; *P*=0.048).[104]
- A secondary analysis of the WHI examining the efficacy of calcium and vitamin D supplementation on AF prevention found that calcium and vitamin D had no reduction in incidence of AF compared with placebo (HR, 1.02 [95% CI, 0.92–1.13]). Although a relationship between baseline CVD risk factors and vitamin D deficiency was present, no significant association was found between baseline 25-hydroxyvitamin D serum levels and incident AF (HR, 0.92 in lowest versus highest subgroup [95% CI, 0.66–1.28]). Similarly, using data from the WHI RCT, another study examined whether calcium and vitamin D supplementation (1000 mg elemental calcium carbonate and 400 IU vitamin D_3/d) moderated the effects of premenopausal hormone therapy on CVD events among 27 347 females. Females

reporting prior hysterectomy (n=16 608) were randomized to the conjugated equine estrogens (0.625 mg/d)+medroxyprogesterone (2.5 mg/d) trial, and those without prior hysterectomy (n=10,739) were randomized to the conjugated equine estrogen trial (0.625 mg/d). In the conjugated equine estrogen trial, receiving calcium and vitamin D was associated with lowered stroke risk (HR, 0.49 [95% CI, 0.25–0.97]). In both trials, in females with a low intake of vitamin D, a significant synergist effect of calcium and vitamin D and hormone therapy on LDL-C was observed (P=0.03).[105]

- Meta-analyses of RCTs examining the effects of multivitamins, vitamin D, calcium, vitamin C, B-complex, antioxidants, and vitamin B_3 (niacin) have demonstrated no salutary cardiovascular benefits.[106]
- An umbrella review of 10 systematic reviews and meta-analyses examined the relationship between vitamin C supplementation and CVD biomarkers (ie, cardiovascular arterial stiffness, BP, lipid profile, endothelial function, and glycemic control) and found weak evidence for salutary effects from vitamin C supplementation on CVD biomarkers. However, subgroup analyses revealed that specific groups of participants (ie, those who were older or with higher BMI, elevated CVD risk, and lower intake of vitamin C) may benefit from vitamin C supplementation.[107]
- A 2-sample mendelian randomization study including 7781 individuals of European descent examined the relationship between vitamin E and risk of CAD and found higher vitamin E to be associated with a higher risk of CAD and MI. Specifically, each 1-mg/L increase in vitamin E was significantly associated with CAD (OR, 1.05 [95% CI, 1.03–1.06]), MI (OR, 1.04 [95% CI 1.03–1.05]), elevated TC (SD, 0.043 [95% CI, 0.038–0.04]), LDL-C (SD, 0.021 [95% CI, 0.016–0.027]), triglycerides (SD, 0.026 [95% CI, 0.021–0.031]), and lower levels of HDL-C (SD, −0.019 [95% CI, −0.024 to −0.014]).[108]
- Meta-analyses of folic acid RCTs suggested reductions in stroke risk (RR, 0.80 [95% CI, 0.69–0.93]) and CVD (RR, 0.83 [95% CI, 0.73–0.93]), although the benefit was driven mainly by the China Stroke Primary Prevention Trial, a large RCT of 20 702 adults with hypertension and no history of stroke or MI.[109]

Cost

The US Department of Agriculture reported that the Consumer Price Index for all food increased by 1.9% in 2019.[110] Prices for foods eaten at home increased by 0.9% in 2019, whereas prices for foods eaten away from home increased by 3.1%.[110] Using data from Euromonitor International, the US Department of Agriculture calculated the share of consumer expenditures attributed to food in multiple countries in 2018. The proportion of consumer expenditures spent on food ranged from 6.4% in the United States to 9.1% in Canada, 23.4% in Mexico, and 59.0% in Nigeria.[111]

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.[112]
- 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 that fruits and vegetables were served (3.9 d/wk versus 0.7 d/wk) and decreasing the number of days that SSBs (0.1 d/wk versus 1.8 d/wk) and sugary foods (0.3 d/wk versus 2.7 d/wk) were served.[113] 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.

Healthy Diet and Health Care Cost Savings

- A study evaluated the health care costs associated with following the Healthy US-Style eating pattern (measured by the HEI) and the Healthy Mediterranean-Style (measured by the Mediterranean diet score) and found that a 20% increase in compliance with the HEI was estimated to result in annual cost savings of $31.5 billion (range, $23.9 to $38.9 billion). Half of the cost savings were attributed to the reduction in costs associated with CVD, whereas the other half were attributed to cancer and type 2 diabetes cost reductions. Similarly, a 20% increase in conformance with the Mediterranean diet score resulted in annual cost savings of $16.7 billion (range, $6.7 to $25.4 billion). The biggest contributors to these costs savings were HD ($5.4 billion), type 2 diabetes ($4.6 billion), Alzheimer disease ($2.6 billion), stroke ($1.0 billion), and, to a lesser degree, site-specific cancer (<$1 billion).[114]
- Based on combined data from NHANES (2013–2016) and a community-based randomized trial

of cash and subsidized CSA intervention, a microsimulation model was developed to assess the cost-effectiveness of improving dietary quality (as measured by the HEI) on CVD and type 2 diabetes in low-income US adults. The implementation of the model in the short term (10-year time horizon) and long term (life-course time horizon) demonstrated that both a cash transfer ($300) and subsidized CSA ($300/y subsidy) lowered total discounted DALYs accumulated over the life course attributable to CVD and diabetes complications from 24 797 per 10 000 people (95% CI, 24 584–25 001) at baseline to 23 463 per 10 000 (95% CI, 23 241–23 666) under the cash intervention and 22 304 per 10 000 (95% CI, 22 084–22 510) under the CSA intervention. Both interventions demonstrated ICERs <$100 000 per prevented DALY, with the cash transfer being more effective in the short term and the CSA being equally cost-effective in the long-term, highlighting cost savings to society of –$191 100 per DALY averted (95% CI, –191 767 to –188 919) for the cash intervention and –$93 182 per DALY averted (95% CI, –93 707 to –92 503) for the CSA intervention.[115]

Cost-Effectiveness of Sodium Reduction and SSB Tax

- 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 using the UK experience (government-supported industry agreements, government monitoring of industry compliance, public health campaign).[116] 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 (equivalent to country-specific purchasing power of US $1) per DALY saved over 10 years. Globally, the estimated average CER was $204 (international dollars) per DALY (95% CI, 149–322) saved. The estimated CER was highly favorable in high-, middle-, and low-income countries. A US study examined cost-effectiveness of implementing voluntary sodium target reformulation among people ever working in the food system and those in the processed food industry and found benefits in both. Achieving FDA reformulations across 10 years could lead to 20-year health gains in those who had ever worked in the food system of 180 000 QALYs (95% UI, 150 000–209 000) and health care–related savings of $5.2 billion (95% UI, 3.5–8.3 billion) with an ICER of $62 000 (95% UI, 1000–171 000) per each gained QALY. Those working in the processed food industry could see similar improvements of 32 000 gained QALYs (95% UI, 27 000–37 000), health cost savings of $1 billion (95% UI, 0.7–1.6 billion), and an ICER of $486 000 (95% UI, 148 000–1 094 000) for each gained QALY. The long-term reformulation would cost the industry $16.6 billion (95% UI, 12–31 billion). This highlights that potential health benefits and cost-savings are greater than the costs associated with sodium reformulation.[117]
- A policy review of worldwide consumption of SSBs found that SSB consumption has increased significantly, which is problematic given the mounting evidence illustrating the association between high SSB daily intake and heightened risk of obesity and CVD. This review also presents evidence in support of an SSB tax because its effectiveness in lowering SSB consumption in several countries to date.[118] In the United States, a validated microsimulation model (CVD PREDICT) was used to assess cost-effectiveness, CVD reductions, and QALYs gained as a result of imposing a penny-per-ounce tax on SSBs. Cost savings were identified for the US government ($106.56 billion) and private sector ($15.60 billion). A 100% price pass-through led to reductions of 4494 (2.06%) of lifetime MI events (95% UI, 2640–6599) and 1540 (1.42%) total IHD deaths (95% UI, 995–2118) versus no tax and to a gain of 0.020 lifetime QALYs. The lifetime cost to the beverage industry is $0.92 billion (or $49.72 billion if electing to absorb half the proposed SSB tax).[119] Similar evidence was found in the Philippines, where a 13%/L SSB tax was associated with fewer deaths resulting from diabetes (–5913), IHD (–10 339), and stroke (–7950) across 20 years and also averting 13 890 cases of catastrophic expenditure. In addition, health care savings of $627 million and annual revenue increases of $813 million were projected over 20 years.[120]

Global Trends in Key Dietary Factors

Analysis of SSB sales data suggests that the regions in the world with the highest SSB consumption are North America, Latin America, Australasia, and Western Europe.[121] A number of countries and US cities have implemented SSB taxes. 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 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).[122] In Berkeley, CA, a 1–cent per ounce SSB excise tax was implemented in January 2015.[123] According to store-level data, posttax year 1 SSB sales declined by 9.6% compared with SSB sales predicted from pretax trends. In 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.[124] 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.

In a systematic review of population-level sodium initiatives, reduction in mean sodium intake occurred in 5 of 10 initiatives.[125] Successful population-level sodium initiatives tended to use multiple strategies and included structural activities such as food product reformulation. For example, 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,[126] 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.

Global Burden (See Chart 5-6)

- The GBD 2019 Study [127] used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 369 diseases and injuries and 87 risk factors in 204 countries and territories. The age-standardized mortality attributable to dietary risks is highest in Central Asia (Chart 5-6).
- An updated report from the GBD 2019 Study estimated the impact of 15 dietary risk factors on mortality and DALYs worldwide using a comparative risk assessment approach.[127] In 2019, an estimated 7.9 million deaths (95% UI, 6.5–9.8 million; 14% of all deaths) and 188 million DALYs (95% UI, 156–225 million; 7% of all DALYs) were attributable to dietary risks. The leading dietary risk factors were high sodium intake (1.9 million [95% UI, 0.5–4.2 million] deaths), low whole grain intake (1.8 million [95% UI, 0.9–2.3 million] deaths), and low legume intake (1.1 million [95% UI, 0.3–1.8 million] deaths). Countries with low-middle Socio-Demographic Index and middle Socio-Demographic Index had the highest age-standardized rates of diet-related deaths (119 [95% UI, 96–147] and 116 [95% UI, 92–147] deaths per 100 000 population), whereas countries with high Socio-Demographic Index had the lowest age-standardized rates of diet-related deaths (56 [95% UI, 47–69] deaths per 100 000 population). Age-standardized diet-related death rates decreased between 1990 to 2019 from 154 (95% UI, 128–186) to 101 (95% UI, 82–124) deaths per 100 000 population, although the proportion of deaths attributable to dietary risks was largely stable.

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 (percent 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)–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)–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 fruit and vegetables per day; no more than 1500 mg/d 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 score of zero was identified as approximately the 90th percentile distribution of US population intake.

†Selected by the AHA on the basis of evidence for likely causal effects on cardiovascular events, diabetes, 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.[3] 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: Data derived from AHA's My Life Check–Life's Simple 7,[2] Lloyd-Jones et al,[3] and Rehm et al.[128]

Table 5-2. Trends in Key Dietary Components Among US Adults, NHANES 2003 to 2004 to NHANES 2015 to 2016

AHA Score	Survey-weighted mean/percentages (95% CI)*							
	2003–2004	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	*P* for Trend
Primary	19.0 (18.1–20.0)	19.9 (19.2–20.6)	19.5 (18.7–20.3)	20.9 (20.5–21.4)	21.2 (20.4–21.9)	21.0 (20.3–21.7)	20.8 (19.9–21.6)	<0.001
Fruits and vegetables	5.0 (4.7–5.3)	5.0 (4.8–5.3)	4.9 (4.7–5.2)	5.1 (4.9–5.3)	5.1 (4.9–5.3)	4.9 (4.7–5.0)	4.8 (4.5–5.0)	0.18
Whole grains	2.1 (1.9–2.3)	2.4 (2.3–2.6)	2.4 (2.2–2.6)	2.8 (2.7–2.9)	3.1 (2.9–3.3)	3.0 (2.8–3.1)	3.0 (2.8–3.2)	<0.001
Fish and shellfish	2.5 (2.2–2.8)	2.6 (2.4–2.8)	2.5 (2.2–2.7)	2.8 (2.4–3.1)	2.5 (2.2–2.8)	2.5 (2.2–2.9)	2.3 (1.9–2.6)	0.23
SSBs	5.6 (5.2–6.0)	6.3 (6.0–6.6)	6.2 (5.9–6.5)	6.6 (6.4–6.8)	6.7 (6.4–7.0)	6.9 (6.5–7.3)	7.1 (6.8–7.3)	<0.001
Sodium	3.8 (3.6–3.9)	3.5 (3.4–3.6)	3.5 (3.4–3.6)	3.6 (3.5–3.8)	3.8 (3.7–3.9)	3.8 (3.6–3.9)	3.7 (3.5–3.8)	0.17
Secondary	34.6 (33.4–35.8)	35.6 (34.5–36.6)	35.5 (34.2–36.7)	37.3 (36.6–38.0)	38.0 (36.9–39.2)	37.5 (36.6–38.3)	37.1 (35.8–38.3)	<0.001
Nuts, seeds and legumes	4.1 (3.9–4.4)	4.4 (4.1–4.7)	4.3 (3.9–4.7)	4.4 (4.2–4.6)	4.8 (4.6–5.0)	4.7 (4.4–5.0)	5.0 (4.6–5.4)	<0.001
Processed meat	6.6 (6.4–6.8)	6.5 (6.1–6.8)	6.7 (6.5–6.9)	6.6 (6.4–6.9)	6.7 (6.4–6.9)	6.7 (6.5–7.0)	6.7 (6.5–7.0)	0.09
Saturated fat	4.9 (4.7–5.1)	4.8 (4.7–5.0)	5.0 (4.8–5.2)	5.3 (5.1–5.5)	5.4 (5.2–5.6)	5.0 (4.8–5.2)	4.5 (4.3–4.8)	0.48
Diet quality by primary and secondary scores, %								
Primary score								
Poor	56.0 (51.6–60.2)	52.4 (48.3–56.5)	53.9 (49.9–57.9)	47.8 (45.3–50.3)	45.8 (41.8–49.9)	46.6 (42.7–50.7)	47.8 (43.1–52.6)	<0.001
Intermediate	43.4 (39.2–47.6)	46.9 (43.0–50.8)	45.3 (41.5–49.1)	50.7 (48.0–53.3)	52.7 (48.8–56.6)	51.8 (47.7–55.9)	50.8 (46.2–55.4)	0.001
Ideal	0.7 (0.5–1.0)	0.7 (0.4–1.3)	0.8 (0.5–1.6)	1.5 (1.0–2.2)	1.5 (0.9–2.4)	1.6 (1.0–2.5)	1.4 (1.0–2.1)	0.001
Secondary score								
Poor	43.7 (39.6–47.8)	41.7 (38.1–45.4)	41.3 (37.1–45.7)	36.1 (34.0–38.3)	33.9 (31.2–36.7)	35.8 (33.3–38.3)	36.4 (32.6–40.4)	<0.001
Intermediate	55.2 (51.2–59.2)	56.8 (53.1–60.4)	57.5 (53.1–61.7)	61.6 (59.3–63.8)	64.1 (61.6–66.5)	62.0 (59.5–64.4)	62.0 (58.1–65.7)	<0.001
Ideal	1.1 (0.7–1.7)	1.5 (1.0–2.2)	1.3 (0.9–1.8)	2.3 (1.5–3.3)	2.0 (1.4–2.9)	2.3 (1.8–2.9)	1.6 (1.0–2.5)	0.02

AHA indicates American Heart Association; NHANES, National Health and Nutrition Examination Survey; and SSBs, sugar-sweetened beverages.

*All dietary variables were adjusted for energy to 2000 kcal/d using the residual method before the analysis. Each AHA consumption target was evaluated with the use of a continuous scoring system. Intake of each dietary component was scored from 0 to 10 (beneficial components) and from 10 to 0 (harmful components). For beneficial dietary components, individuals with zero intake received the lowest score (0). For harmful dietary components, the lowest score (0) was assigned to a higher level approximately equivalent to the 80th to 90th percentile of intake among US adults and rounded to a practical value (eg, 4500 mg/d sodium, one 50-g serving/d of processed meat, two 8-oz servings/d of SSBs, and 15% energy of saturated fat). Intermediate dietary intake was scored linearly between 0 and 10. For example, an adult consuming 3000 mg/d sodium would receive 5 sodium points (ie, their sodium consumption was halfway between 1500 mg/d and the maximum value of 4500 mg/d).

Source: Unpublished analyses courtesy of Dr Junxiu Liu, Tufts University, using NHANES, 2003 to 2016.[129]

Table 5-3. Population Mean Consumption* of Food Groups and Nutrients of Interest by Sex and Race/Ethnicity Among US Adults ≥20 Years of Age, NHANES 2015 to 2016

	NH White males		NH Black males		Mexican American males		NH White females		NH Black females		Mexican American females	
	Average consumption	% Meeting guidelines	Average consumption	% Meeting guidelines	Average consumption	% Meeting guidelines	Average consumption	% Meeting guidelines	Average consumption	% Meeting guidelines	Average consumption	% Meeting guidelines
Foods												
Whole grains, servings/d	1.1±0.7	7.5	0.7±1.5	5.5	0.6±1.1	3.0	0.9±0.6	4.7	0.8±1.4	4.0	0.7±1.1	3.2
Whole fruit, servings/d	1.4±1.2	10.0	1.0±2.0	4.3	1.4±2.1	9.5	1.5±1.1	9.9	1.1±2	6.8	1.6±2.3	8.7
Total fruit, servings/d	1.8±1.4	13.7	1.7±2.6	8.9	2±2.7	16.5	1.9±1.2	12.0	1.9±2.5	14.6	2.2±2.9	18.6
Nonstarchy vegetables, servings/d	2.2±1.2	6.4	1.6±1.9	2.2	2±1.8	3.2	2.4±1.3	9.1	1.8±1.8	3.2	2.3±2	6.0
Starchy vegetables,† servings/d	0.9±0.7	NA	1.0±1.5	NA	0.5±1	NA	0.9±0.7	NA	0.9±1.2	NA	0.8±1.2	NA
Legumes, servings/wk	1.5±2.1	29.9	1.0±3.4	15.2	3.4±6.4	46.4	1.2±1.6	25.3	1.1±3.2	21.2	2.9±5.7	45.6
Fish and shellfish, servings/wk	1.0±1.8	16.0	1.4±3.9	21.1	1.2±4.1	18.2	1.0±1.5	18.6	1.8±4.1	24.5	1.2±4	17.3
Nuts and seeds, servings/wk	5.8±6.5	37.3	2.8±9.5	13.4	2.5±7.5	20.5	6.2±6.1	36.8	3.4±8.3	20.5	3±8.9	17.5
Unprocessed red meats, servings/wk	3.5±2.7	NA	3.4±5.7	NA	3.9±5.1	NA	2.4±1.9	NA	2.4±3.6	NA	3.1±4.5	NA
Processed meat, servings/wk	2.5±1.9	56.7	2.1±3.2	62.0	1.8±3.1	67.2	1.8±1.5	65.7	1.4±2.4	70.9	1±1.8	79.8
SSBs, servings/wk	8.3±8.7	57.6	10.3±12.5	32.9	10±12.4	39.2	5.8±6.6	67.7	9.7±13.5	41.2	8±12.6	45.3
Sweets and bakery desserts, servings/wk	3.7±3.6	57.8	3.3±6.8	62.2	4.2±7.6	61.7	4.2±4.1	56.2	3.7±7.2	59.1	4.7±8.5	52.2
Refined grain, servings/d	4.8±1.4	9.4	5.2±3.1	7.5	7.0±3.2	0.82	4.8±1.4	9.8	4.9±2.6	7.1	6.7±3.5	3.0
Nutrients												
Total calories, kcal/d	2418±522	NA	2211±1086	NA	2485±1140	NA	1742±344	NA	1762±824	NA	1852±803	NA
EPA/DHA, mg/d	0.079±0.103	9.0	0.101±0.247	10.6	0.075±0.159	6.9	0.084±0.111	8.8	0.103±0.251	8.2	0.090±0.241	7.9
α-Linoleic acid, g/d	1.65±0.55	42.4	1.69±1.12	43.8	1.56±0.73	41.6	1.95±0.71	87.9	1.86±1.02	86.7	1.72±0.88	87.1
n-6 PUFAs, % energy	7.4±2.9	NA	8.8±6.8	NA	7.3±5.8	NA	11.6±5.1	NA	11.9±14.8	NA	10.1±6.7	NA
Saturated fat, % energy	12±2	26.0	11±4	36.2	11.4±3.6	30.7	12±2.1	26.8	10.9±3.9	37.3	11.2±3.7	37.5
Ratio of (PUFAs+MUFAs)/SFAs	1.8±0.6	12.6	2.2±1.6	25.1	1.8±1.3	13.6	2.3±0.8	29.7	2.6±2.2	40.0	2.3±1.4	31.3
Dietary cholesterol, mg/d	280±107	66.2	313±216	54.6	331±213	54.9	307±115	61.9	315±199	55.6	342±244	54.3
Carbohydrate, % energy	45.3±6.2	NA	46.3±12.2	NA	47.3±10.6	NA	46.2±5.8	NA	48.7±11.3	NA	49.3±10.5	NA
Dietary fiber, g/d	16.4±4.8	6.7	14.1±8.3	4.8	18.2±9.7	9.7	17.8±4.7	10.0	15±8.1	4.7	20.2±10	14.8
Sodium, g/d	3.4±0.58	7.7	3.5±1.11	4.7	3.4±1.06	7.4	3.5±0.54	5.6	3.4±0.91	7.0	3.4±0.98	4.4
Added sugar, % energy	11.1±9.5	36.9	13.8±17.5	23.0	10.8±13.2	38.1	16.7±9.6	20.0	22.1±33.6	11.8	15.3±16.5	22.6

Values for average consumption are mean±SD. Data are from NHANES 2015 to 2016, derived from two 24-hour dietary recalls per person, with population SD adjusted for within-person vs between-person variation. All values are energy adjusted by individual regressions or percent energy, and for comparability, means and proportions are reported for a 2000-kcal/d diet. To obtain actual mean consumption levels, the group means for each food or nutrient can be multiplied by the group-specific total calories (kilocalories per day) divided by 2000 kcal/d. The calculations for foods use the US Department of Agriculture Food Patterns Equivalent Database on composition of various mixed dishes, which incorporates partial amounts of various foods (eg, vegetables, nuts, processed meats) in mixed dishes; in addition, the characterization of whole grains is now derived from the US Department of Agriculture database instead of the ratio of total carbohydrate to fiber.

DHA indicates docosahexaenoic acid; EPA, eicosapentaenoic acid; MUFA, monounsaturated fatty acid; NA, not available; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; and SSBs, sugar-sweetened beverages.

*All intakes and guidelines adjusted to a 2000-kcal/d diet. Servings are defined as follows: whole grains, 1-oz equivalents; fruits and vegetables, 1/2-cup equivalents; legumes, 1/2 cup; fish/shellfish, 3.5 oz or 100 g; nuts and seeds, 1 oz; unprocessed red or processed meat, 3.5 oz or 100 g; SSBs, 8 fl oz; and sweets and bakery desserts, 50 g. Guidelines defined as follows: whole grains, 3 or more 1-oz equivalent (eg, 21 g whole wheat bread, 82 g cooked brown rice, 31 g Cheerios) servings/d; fruits, ≥2 cups/d; nonstarchy vegetables, ≥2.5 cups/d; legumes, ≥1.5 cups/wk; fish or shellfish, 2 or more 100-g (3.5-oz) servings/wk; nuts and seeds, 4 or more 1-oz servings/wk; processed meats (bacon, hot dogs, sausage, processed deli meats), 2 or fewer 100-g (3.5-oz) servings/wk (one-fourth of discretionary calories); SSBs (defined as ≥50 cal/8 oz, excluding 100% fruit juices), ≤36 oz/wk (≈1/4 of discretionary calories); sweets and bakery desserts, 2.5 or fewer 50-g servings/wk (≈1/4 of discretionary calories); EPA/DHA, ≥0.250 g/d[72]; α-linoleic acid, ≥1.6/1.1 g/d (males/females); saturated fat, <10% energy; dietary cholesterol, <300 mg/d; dietary fiber, ≥28 g/d; sodium, <2.3 g/d; ratio of (PUFAs+MUFAs)/SFAs ≥2.5; and added sugars ≤6.5% total energy intake. No dietary targets are listed for starchy vegetables and unprocessed red meats because of their positive association with long-term weight gain and their positive or uncertain relation with diabetes and cardiovascular disease.

†Including white potatoes (chips, fries, mashed, baked, roasted, mixed dishes), corn, plantains, green peas, etc. Sweet potatoes, pumpkin, and squash are considered red-orange vegetables by the US Department of Agriculture and are included in nonstarchy vegetables.

Source: Unpublished analyses courtesy of Dr Junxiu Liu, Tufts University, using NHANES, 2015 to 2016.[129]

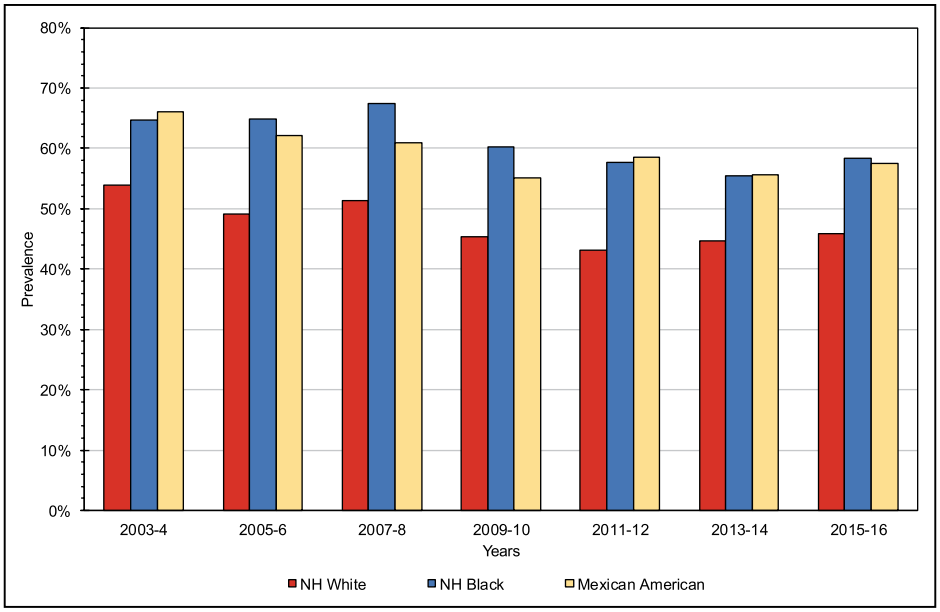


Chart 5-1. Trends in prevalence of poor AHA healthy diet score by race/ethnicity, United States, 2003 to 2016.
Components of AHA healthy diet score are defined in Table 5-1. Poor diet was defined as <40% adherence on the basis of the primary AHA continuous diet score. AHA indicates American Heart Association; and NH, non-Hispanic.
Source: Unpublished analyses courtesy of Dr Junxiu Liu, Tufts University, using National Health and Nutrition Examination Survey data, 2003 to 2016.[129]

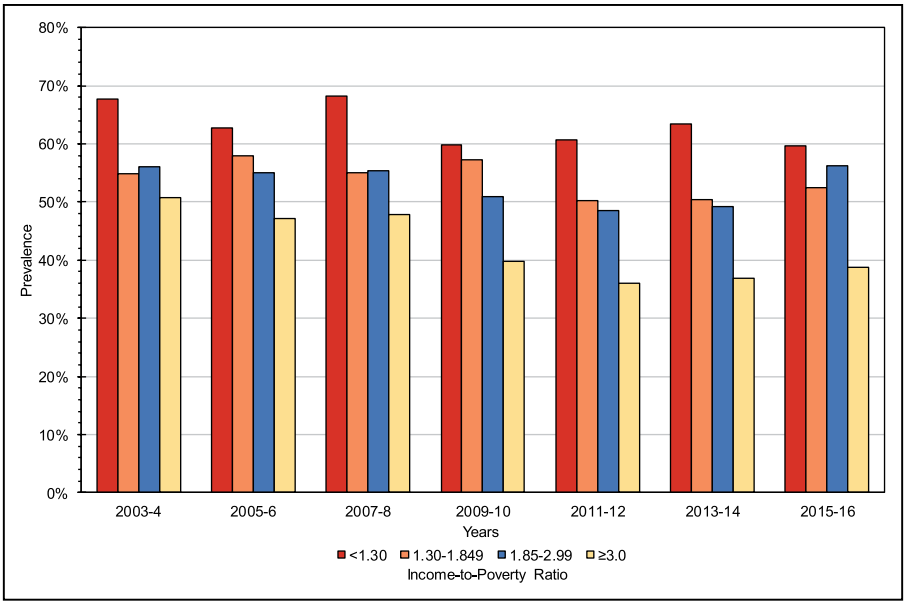


Chart 5-2. Trends in prevalence of poor AHA healthy diet score in the United States by ratio of family income to poverty level, 2003 to 2016.
Components of AHA healthy diet score are defined in Table 5-1. Poor diet was defined as <40% adherence, on the basis of the primary AHA continuous diet score. AHA indicates American Heart Association.
Source: Unpublished analyses courtesy of Dr Junxiu Liu, Tufts University, using National Health and Nutrition Examination Survey data, 2003 to 2016.[129]

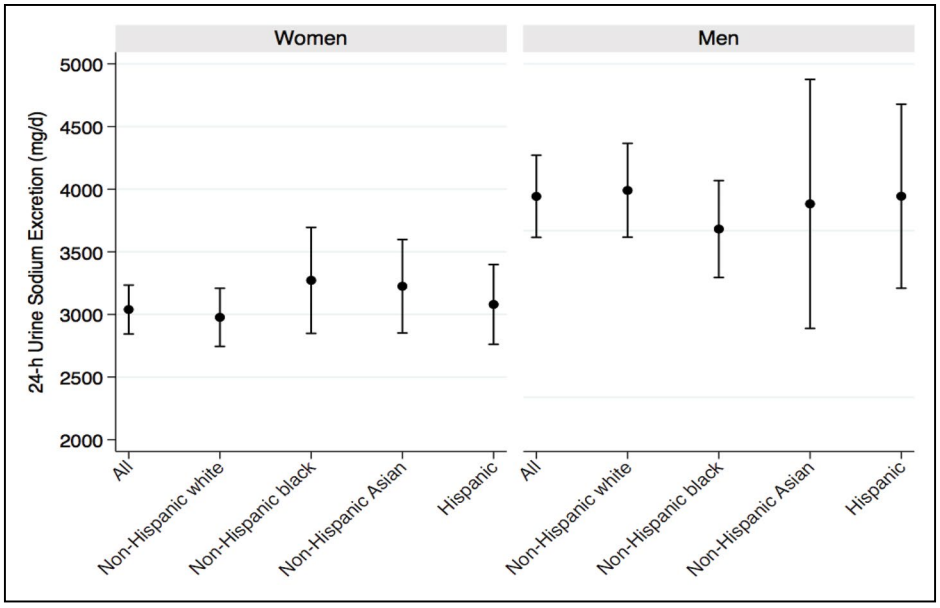
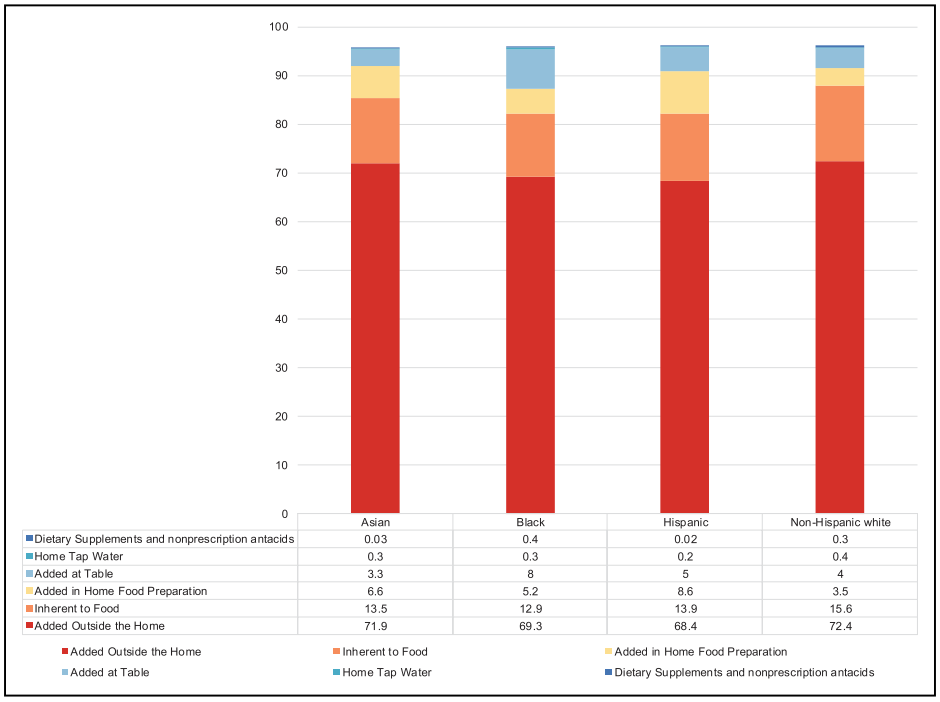


Chart 5-3. Estimated mean sodium intake by 24-hour urinary excretion, United States, 2013 to 2014.
Estimates based on nationally representative sample of 827 nonpregnant, noninstitutionalized US adults 20 to 69 years of age who completed a 24-hour urine collection in NHANES 2013 to 2014.
NHANES indicates National Health and Nutrition Examination Survey.
Source: Data derived from Cogswell et al[130] using NHANES 2013 to 2014.[129]



	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 adults in 3 geographic regions in the United States, 2013 to 2014.
Sources of sodium intake were 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; and Minneapolis–St. Paul, MN) with equal numbers of males and females from 4 racial/ethnic groups (Asian, Black, Hispanic, non-Hispanic White individuals).
Source: Reprinted from Harnack et al.[4] Copyright © 2017, American Heart Association, Inc.

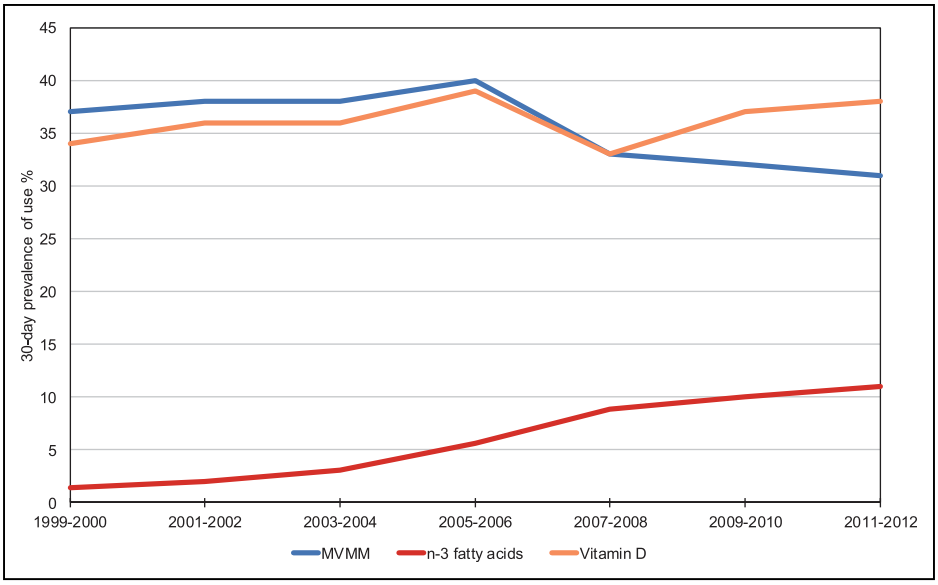


Chart 5-5. Trends in use of MVMM, vitamin D, and n-3 fatty acid supplements among adults in the United States (NHANES, 1999–2012).
MVMM indicates multivitamin/mineral; and NHANES, National Health and Nutrition Examination Survey.
Source: Data derived from Kantor et al.[13]

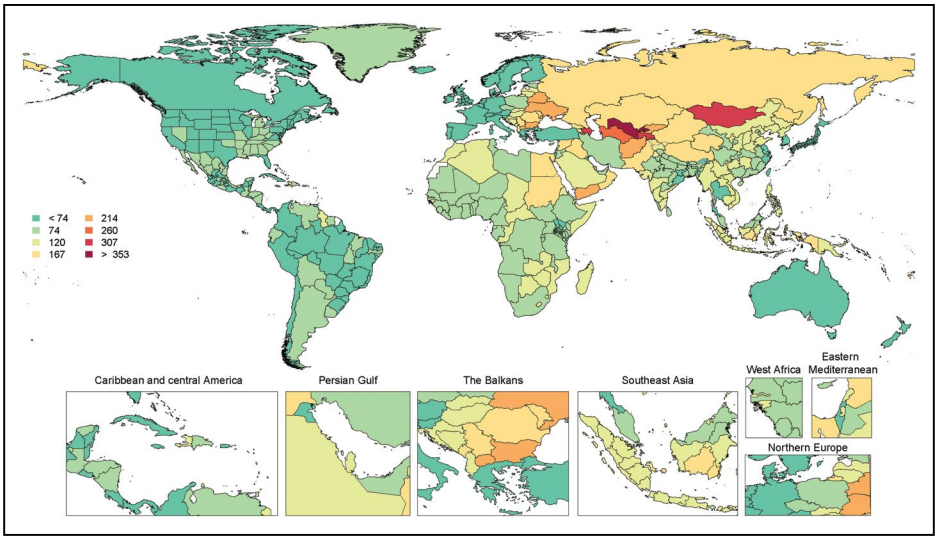


Chart 5-6. Age-standardized global mortality rates attributable to dietary risks per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[127] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[131]

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6. OVERWEIGHT AND OBESITY

See Table 6-1 and Charts 6-1 through 6-8

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Overweight and obesity are major risk factors for CVD, including CHD, stroke, AF, VTE, and congestive HF.[1–3] According to NHANES 2015 to 2018, the age-adjusted prevalence of obesity was 40.6%, with 39.9% of males and 41.1% of females having obesity. The prevalence of obesity among youth over the same time period was 19.0% (Table 6-1).The AHA has identified BMI <85th percentile in youth (2–19 years of age) and <25 kg/m^2 in adults (≥20 years of age) as 1 of the 7 components of ideal CVH.[4] In 2015 to 2018, 63.4% of US youth and 26.4% of US adults met these criteria (Chapter 2, Cardiovascular Health, Chart 2-1).

Abbreviations Used in Chapter 6

AF	atrial fibrillation
AHA	American Heart Association
APPROACH	Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease
BMI	body mass index
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
CI	confidence interval
CVD	cardiovascular disease
CVH	cardiovascular health
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
GBD	Global Burden of Disease Study
GWAS	genome-wide association study

(*Continued*)

Abbreviations Used in Chapter 6 Continued

HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HR	hazard ratio
IMT	intima-media thickness
IRR	incidence rate ratio
LDL-C	low-density lipoprotein cholesterol
Look AHEAD	Look: Action for Health in Diabetes
MACE	major adverse cardiovascular event
MESA	Multi-Ethnic Study of Atherosclerosis
MetS	metabolic syndrome
MHO	metabolically healthy obesity
MI	myocardial infarction
NCHS	National Center for Health Statistics
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHDS	National Hospital Discharge Survey
NHLBI	National Heart, Lung, and Blood Institute
OR	odds ratio
PCI	percutaneous coronary intervention
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	relative risk
SBP	systolic blood pressure
SCD	sudden cardiac death
SE	standard error
SES	socioeconomic status
SNP	single-nucleotide polymorphism
SPRINT	Systolic Blood Pressure Intervention Trial
UI	uncertainty interval
VTE	venous thromboembolism
WC	waist circumference
WHI	Women's Health Initiative
YRBSS	Youth Risk Behavior Surveillance System

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Classification of Overweight and Obesity

- For adults, NHLBI weight categories are as follows: overweight (BMI, 25.0–29.9 kg/m^2) and obese class I (BMI, 30.0–35.0 kg/m^2), class II (BMI, 35.0–39.9 kg/m^2), and class III (BMI, ≥40.0 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 Black people and underestimate risk in Asian people.[5] For this reason, lower BMI cutoffs have been recommended to identify increased health risks for Asian and South Asian populations.[6]
- For youth, sex-specific BMI-for-age 2000 CDC growth charts for the United States are used,[7] and overweight is defined as 85th to <95th percentile and obesity as ≥95th percentile. A 2013 AHA

scientific statement recommended that the definition of severe obesity for children ≥2 years of age 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.[8] 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.[8]

- Current obesity guidelines define WC ≥40 in (102 cm) for males and ≥35 in (88 cm) for females as being associated with increased cardiovascular risk[9]; however, lower cutoffs have been recommended for various racial/ethnic groups, for example, ≥90 cm for Asian males and ≥80 cm for Asian females.[5,10] WC measurement is recommended for those with BMI of 25 to 34.9 kg/m^2 to provide additional information on CVD risk.[11]

Prevalence

Youth

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

- According to 2015 to 2018 data from NHANES, the overall prevalence of obesity (≥95th percentile) among youth 2 to 19 years of age was 19.0% (Table 6-1). A similar prevalence was found with the use of NHANES data from 2015 to 2016, with increasing prevalence in older age groups (Chart 6-1).[12,13]
- According to 2015 to 2018 data from NHANES, the prevalence of obesity was lower for NH Asian boys and girls than in other racial and ethnic groups (Table 6-1).[13]
- The prevalence of childhood obesity varies by SES.
  - — According to 2011 to 2014 NHANES data, for children 2 to 19 years of age, the prevalence of obesity by percentage of poverty level was 18.9% (95% CI, 17.3%–20.6%) for ≤130%, 19.9% (95% CI, 16.8%–23.3%) for 131% to 350%, and 10.9% (95% CI, 8.0%–1.4%) for >350% of the federal poverty level.[14]
  - — In addition, obesity prevalence among children 2 to 19 years of age was higher for those whose parents had a high school diploma or less education (21.6% [95% CI, 20.0%–23.3%]) than for adolescents whose parents had a bachelor's degree or higher (9.6% [95% CI, 7.3%–12.5%]).[14]
- According to NHANES 1999 to 2014, the prevalence of obesity among adolescents 12 to 19 years of age was 21.6% (95% CI, 18.5%–24.7%) in the South region, 20.8% (95% CI, 17.6%–24.0%) in the Midwest region, 18.2% (95% CI, 13.1%–23.4%) in the Northeast region, and 15.8% (95% CI, 12.6%–19.1%) in the West region.[15]
- According to self-reported height and weight data from the YRBSS 2015, 13.9% (95% CI, 12.5%–15.5%) of US high school students had obesity and 16.0% (95% CI, 15.2%–16.9%) were overweight. The percentages of obesity were higher in boys (16.8% [95% CI, 14.8%–19.0%]) than girls (10.8% [95% CI, 9.3%–12.5%]) and in Black students (16.8% [95% CI, 14.2%–19.6%]) and Hispanic students (16.4% [95% CI, 14.8%–18.2%]) than in White students (12.4% [95% CI, 10.5%–14.6%]).[16] Obesity rates varied by states: The highest rates of obesity in girls were observed in Kentucky and Mississippi (16.2%) and in boys in West Virginia (23.4%); the lowest rates in girls were observed in Nevada (6.3%), whereas for boys, the lowest rates were seen in Montana (13.0%).

Adults

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

- According to NHANES 2015 to 2018, among US adults ≥20 years of age, the age-adjusted prevalence of obesity was 39.9% in males and 41.1% in females (Table 6-1). The prevalence of extreme obesity was 6.2% in males and 10.5% in females.
- In both males and females, the prevalence of obesity was lowest in NH Asian adults. Among males, the prevalence of obesity was highest among Hispanic males. Among females, the prevalence of obesity was highest among NH Black and Hispanic females (Table 6-1).
- The age-adjusted prevalence of obesity was 44.8% (95% CI, 41.1%–48.5%) among middle-aged (40–59 years of age) adults, 42.8% (95% CI, 37.9%–47.7%) among older (≥60 years of age) adults, and 40.0% (95% CI, 34.9%–45.1%) among younger (20–39 years of age) adults. No significant differences by age groups or between males and females were observed (Chart 6-2).[17]
- In the United States, the prevalence of obesity as estimated from self-reported height and weight in the BRFSS (2018) was 30.9% and varies by region and state.[18,19] Self-reported estimates usually underestimate BMI and obesity. In 2018, by state, the prevalence of obesity was highest in the South (33.6%) and Midwest (33.1%) and lower in the Northeast (28.0%) and West (26.9%) (Charts 6-3 through 6-6). The highest prevalence of obesity was 39.5% in West Virginia and Mississippi, and the lowest was 23.0% in Colorado (Charts 6-3 through 6-6).

Secular Trends

Youth

- According to NHANES data, overall prevalence of obesity and severe obesity in youth (2–19 years of age) did not increase significantly between 2007 to 2008 and 2015 to 2016. Among children 2 to

5 years of age, a quadratic trend was seen, with obesity decreasing from 10.1% (95% CI, (7.7%–12.9%) in 2007 to 2008 to 8.4% (95% CI, 5.8%–11.7%) in 2011 to 2012 and increasing to 13.9% (95% CI, 11.6%–16.5%) in 2015 to 2016.[20]

- According to NCHS/CDC surveys and NHANES, the prevalence of obesity among children and adolescents increased substantially from 1963 to 1965 through 2009 to 2010, but this increase has slowed.[21]
- Specifically, according to NHANES data, from 1988 to 1994, 2005 to 2006, and 2011 to 2014, the percentage of children 12 to 19 years of age with obesity increased from 10.5% (95% CI, 8.8%–12.5%) to 17.8% (95% CI, 14.0%–22.0%) to 20.6% (95% CI, 16.2%–25.6%), respectively.[21,22]
- Among infants and children from birth to >2 years of age, 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.[23]
- 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%.[16]

Adults (See Chart 6-7)

- From 1999 to 2000 through 2017 to 2018, the age-standardized prevalence of obesity and severe obesity increased significantly from 30.5% (95% CI, 27.6%–33.4%) to 42.4% (95% CI, 38.9%–45.9%) and from 4.7% (95% CI, 3.5%–5.9%) to 9.2% (95% CI, 7.4%–11.0%), respectively (Chart 6-7).[17] In the United States, the prevalence of obesity among adults, estimated from NHANES data, increased from 1999 to 2000 through 2013 to 2014 from 30.5% (95% CI, 27.7%–33.3%) to 37.7% (95% CI, 35.8%–39.7%); 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% [95% CI, 33.0%–38.3%] to 41.1% [95% CI, 38.5%–43.7%] and from 7.5% [95% CI, 6.2%–9.1%] to 10.0% [95% CI, 8.3%–12.0%], respectively) but not males (from 33.4% [95% CI, 29.3%–37.7%] to 35.1% [95% CI, 33.1%–37.3%] and from 4.2% [95% CI, 3.3%–5.3%] to 5.5% [95% CI, 4.3%–6.9%], respectively).[24]
- From NHANES 1999 to 2002 to NHANES 2007 to 2010, the prevalence of total and undiagnosed diabetes, 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).[25]
- 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 from the increase in BMI.[26]

Family History and Genetics

- Overweight and obesity have considerable genetic components, with heritability estimates ranging from ≈30% to 75%.[27,28] However, only ≈1.5% of interindividual variation of BMI is explained by commonly occurring SNPs, which suggests a role for DNA methylation variants to explain the genetic contributions to obesity.[29]
- Monogenic or mendelian causes of obesity include mutations with strong effects in genes that control appetite and energy balance (eg, *LEP, MC4R*) and obesity that occurs in the context of genetic syndromes (eg, Prader-Willi syndrome).[30]
- 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[31,32] and replicated in many studies with diverse populations and age groups since then.[33–37] The mechanisms underlying the association remain incompletely elucidated but could be related to mitochondrial thermogenesis[6] or food intake.[38]
- Other GWASs have reported numerous additional loci,[39] 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. Variants associated with lean mass also have been reported.[40,41] Fine mapping of loci, including efforts focused on GWASs in African ancestry, in addition to mechanistic studies, is required to define functionality of obesity-associated loci.[42]
- 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.[43]

- Genetic variants also are associated with weight loss response to dietary intervention.[44]
- 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.[45]

Prevention

- In a 2016 meta-analysis based on studies conducted from 1958 to 2010, 70% of adults with obesity did not have obesity in childhood or adolescence.[46]
- 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.[47] Obesity reduction policies and programs implemented by country are also available online.[48]

Awareness, Treatment, and Control

- 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.[49]
- Notification of a child's unhealthy weight by health care practitioners increased from 22% in 1999 to 34% in 2014.[50]
- The randomized Look AHEAD trial showed that among adults who were overweight, had obesity, and had type 2 diabetes, an intensive lifestyle intervention produced a greater percentage of weight loss at 4 years than diabetes support education.[51,52] After 8 years of intervention, the percentage of weight loss ≥5% and ≥10% was greater in the intensive lifestyle intervention group than in the diabetes support education group (50.3% and 26.9% for the intensive lifestyle group versus 35.7% and 17.2% for the diabetes support education group).[52]
- A comprehensive review and meta-analysis of 34 RCTs suggested that dietary weight loss interventions reduce all-cause mortality (RR, 0.82 [95% CI, 0.71–0.95]), but the benefit on lowering cardiovascular mortality was less clear.[53]
- Benefits reported for bariatric surgery include substantial weight loss; remission of diabetes, hypertension, and dyslipidemia; reduced incidence of mortality; reduction in microvascular disease; and fewer CVD events.[54] Long-term follow-up of the Longitudinal Assessment of Bariatric Surgery-2 study, a multicenter observational cohort study of 1300 participants who underwent bariatric surgery, demonstrated that most participants maintained the majority of their weight loss. However, at 7 years after surgery, lower prevalence rates of diabetes and hypertension were achieved only among those who underwent Roux-en-Y gastric bypass, not among those who underwent laparoscopic gastric banding.[55]
- A study of the 12-year follow-up of 1156 individuals with severe obesity, including 418 who underwent gastric bypass, demonstrated sustained weight loss and both remission and prevention of incident type 2 diabetes, hypertension, and dyslipidemia.[56] An RCT demonstrated that weight loss from laparoscopic sleeve gastrectomy was similar to that achieved by traditional (Roux-en-Y) gastric bypass surgery, although the latter achieved greater improvement in lipid levels.[57,58]
- In a retrospective cohort study of individuals with a median follow-up of 3.9 years, the 385 patients in the bariatric surgery group had a cumulative incidence of MACEs of 30.8% (95% CI, 27.6%–30.0%) compared with 47.7% (95% CI, 46.1%–49.2%) among 3243 matched patients who did not undergo bariatric surgery.[59]
- A study of 161 adolescents and 396 adults who underwent Roux-en-Y gastric bypass found similar differences in percent weight change between adolescents and adults. Adolescents were more likely than adults to have remission of type 2 diabetes (risk ratio, 1.27 [95% CI, 1.03–1.57]) and hypertension (risk ratio, 1.51 [95% CI, 1.21–1.88]).[60]

Mortality

- Childhood BMI in the highest quartile was 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]).[61]
- A 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 the lowest mortality observed at BMI of 22 to 23 kg/m^2 among healthy never smokers.[62]
- In 10 large population cohorts in the United States, individual-level data from adults 20 to 79 years of age with 3.2 million person-years of follow-up (1964–2015) demonstrated that 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.[2]

- In the APPROACH registry of individuals after CABG and PCI, overweight and class I obesity (BMI, 20–24.9 kg/m^2) were associated with lower mortality, whereas BMI ≥40 kg/m^2 was associated with elevated mortality.[63] According to data from the National Adult Cardiac Surgery registry from 2002 to 2013, there was lower mortality in individuals with overweight and class I and II obesity (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 in those with underweight (OR, 1.51 [95% CI, 1.41–1.62]), with these results persisting after adjustment for residual confounding and reverse causation.[64]
- 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.[65]

Complications

Youth

- 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 at >30 years of age.[46]
- Children and adolescents who are overweight and have obesity are at increased risk for future adverse health effects, including the following[66]:
  - Increased prevalence of traditional cardiovascular risk factors such as hypertension, hyperlipidemia, and diabetes. Among 8579 youths in NHANES, higher BMI was associated with higher SBP and DBP, lower HDL-C, and high triglycerides and HbA_{1c} levels.[67,68]
  - 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 diabetes (RR, 5.4 [95% CI, 3.4–8.5]), hypertension (RR, 2.7 [95% CI, 2.2–3.3]), dyslipidemia (high LDL-C: RR, 1.8 [95% CI, 1.4–2.3]; low HDL-C: RR, 2.1 [95% CI, 1.8–2.5]), high triglycerides (RR, 3.0 [95% CI, 2.4–3.8]), and carotid atherosclerosis (RR, 1.7 [95% CI, 1.4–2.2]), whereas those who achieved normal weight by adulthood had risks comparable to those of individuals who never had obesity.[69]
- A systematic review and meta-analysis of 37 studies showed that high childhood BMI was associated with an increased incidence of adult diabetes (OR, 1.70 [95% CI, 1.30–2.22]) and CHD (OR, 1.20 [95% CI, 1.10–1.31]) but not stroke; however, the accuracy of childhood BMI predicting any adult morbidity was low. Only 31% of future diabetes and 22% of future hypertension and CHD occurred in those who as youth ≥12 years of age had been classified as overweight or who had obesity.[70]
- Another study examining longitudinal data from 2.3 million adolescents (16–19 years of age) demonstrated increased cardiovascular mortality in adulthood among 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.[71]

Adults

- Obesity is associated with increased lifetime risk of CVD and increased prevalence of type 2 diabetes, hypertension, dyslipidemia, VTE, AF, and dementia.[2,3]
- Analyses of continuous BMI show that the risk of type 2 diabetes increases with increasing BMI.[72]
- In the SPRINT trial, there was a J-shaped associated between BMI and all-cause mortality and risk of stroke.[73] An increased risk of stroke was also seen in a comparison of participants with obesity and normal-weight participants in the Copenhagen City Heart Study (HR, 1.4 [95% CI, 1.2–1.6]) and the Copenhagen General Population Study (HR, 1.1 [95% CI, 1.0–1.2]).[74]
- Cardiovascular risks are even higher with class III obesity than with class I or class II obesity.[75] Among 156 775 postmenopausal females in the WHI, for severe obesity versus normal BMI, HRs for mortality were 1.97 (95% CI, 1.77–2.20) in White females, 1.55 (95% CI, 1.20–2.00) in Black females, and 2.59 (95% CI, 1.55–4.31) in Hispanic

females; for CHD, HRs were 2.05 (95% CI, 1.80–2.35), 2.24 (95% CI, 1.57–3.19), and 2.95 (95% CI, 1.60–5.41), respectively; and for congestive HF, HRs were 5.01 (95% CI, 4.33–5.80), 3.60 (95% CI, 2.30–5.62), and 6.05 (95% CI, 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.[75]

- 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.[76] In a 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.[77]
- A meta-analysis of 10 case-referent studies and 4 prospective cohort studies 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.[78]
- A meta-analysis of 25 studies with 2 405 381 participants found a summary RR for risk of atrial fibrillation of 1.28 (95% CI, 1.20–1.38) for each 5-unit increase in BMI.[79]
- Obesity in females is associated with increased risk of adverse pregnancy outcomes, (eg, preeclampsia, gestational hypertension, gestational diabetes).
  - The risk of preeclampsia was higher in females who were overweight (OR, 1.73 [95% CI, 1.59–1.87]) or obese (OR, 3.15 [95% CI, 2.96–3.35]) in a systematic review of 23 studies including 1.4 million females.[80]
  - The risk of gestational hypertension was higher among females with obesity (OR, 2.91 [95% CI, 2.76–3.07]) than among females with a normal prepregnancy BMI.[81]
  - The risk of gestational diabetes was 2.14 (95% CI, 1.82–2.53), 3.56 (95% CI, 3.05–4.21), and 8.56 (95% CI, 5.07–16.04) among overweight, obese, and severely obese females, respectively, compared with females with normal prepregnancy BMI.[82]
- A BMI paradox is often reported, with higher-BMI patients demonstrating favorable outcomes among adults with prevalent congestive HF, hypertension, peripheral vascular disease, and CAD; similar findings have been seen for percent body fat. However, studies suggest that the obesity paradox might be explained by lead-time bias because it is not present before the development of CVD.[2,83]
- In a study of 2625 participants with new-onset diabetes 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.[84]
- A meta-analysis including 10 studies with 1 381 445 participants found that compared with normal-weight individuals, participants with overweight or obesity were at an increased risk of SCD (RR, 1.21 [95% CI, 1.08–1.35] and 1.52 [95% CI, 1.31–1.77], respectively).[85]
- 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 MetS criteria, sometimes excluding WC.
  - Using strict criteria of 0 MetS components and no previous CVD diagnosis, a 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.[86]
  - MHO appears to be unstable over time, with 1 study showing that 44.5% of individuals with MHO transitioned to metabolically unhealthy obesity over 8 years of follow-up.[87]
  - 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).[88] Among older adults in MESA, approximately half of the participants with MHO developed MetS 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.[89]
  - CVD risk is higher in individuals with MHO than in metabolically healthy normal-weight individuals.[3,90] For example, a meta-analysis of 22 prospective studies suggested that CVD risk was higher in participants with MHO than metabolically healthy normal-weight participants (RR, 1.45 [95% CI, 1.20–1.70]); however, the risk in individuals with MHO 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]).[3]

— 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.[91,92]

Health Care Use and Cost

Obesity costs the health care system, health care payers, and individuals with obesity.

- In the United States, the estimated annual medical cost of obesity in 2008 was $147 billion.[93] It is estimated that $9.7 billion in health care costs in 2016 was attributable to morbid obesity.[94]
- In 2006, the annual medical costs for individuals with obesity were $1429 higher than for normal-weight individuals.[93] Another study estimated that mean annual per capita health care expenses associated with obesity were $1160 for males and $1525 for females.[95]
- According to NHANES I data linked to Medicare and mortality records, individuals 45 years of age 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.[96]
- 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.[97]
- 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.[93]
- According to 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).[98]
- A 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.[99]
- 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.[100]
- A 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.[101] 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.[102] Other large studies failed to demonstrate a cost benefit for bariatric surgery versus matched patients.[103–105]
- The cost-effectiveness of bariatric surgery among individuals with diabetes is unclear, with 2 studies showing cost savings[106,107] but another study demonstrating no improvement compared with intensive lifestyle and medical interventions.[108]

Global Burden (See Chart 6-8)

- The GBD 2019 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 369 diseases and injuries and 87 risk factors in 204 countries and territories.[109]
  — Age-standardized mortality rates attributable to high BMI are generally lower in high-income Asia Pacific, Western Europe, East Asia, Australasia, and South Asia (Chart 6-8).
- 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.[110] 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 diabetes are highly prevalent and underdiagnosed.[111] As of 2013, around the world, obesity rates are higher for females than males and in developed countries than developing countries. Higher obesity rates for females than for males occur for those ≥45 years of age in developed countries but for those ≥25 years of age in developing countries.[112]

- Between 1980 and 2013, the prevalence of overweight and obesity rose by 27.5% for adults.[112] 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.[113]
- 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, both of which were associated with incident hypertension.[114]
- 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.[115]

Table 6-1. Prevalence of Overweight, Obesity, and Severe Obesity in Youth and Adults, United States, 2015 to 2018

	Prevalence of overweight and obesity,* age 2-19 y		Prevalence of obesity,* age 2-19 y		Prevalence of overweight and obesity,* age ≥20 y		Prevalence of obesity,* age ≥20 y		Prevalence of extreme obesity,* age ≥20 y	
	n†	%	n†	%	n†	%	n†	%	n†	%
Total	25888119	35.4	13808070	19.0	170089860	71.3	96449063	40.6	19521332	8.4
Male	13098420	35.0	7339896	20.0	85334941	74.8	45444679	39.9	6939345	6.2
Female	12789699	35.8	6468175	18.0	84754919	68.1	51004384	41.1	12581987	10.5
NH White										
Male	5905581	30.9	3040242	16.2	53986824	73.9	29600892	40.7	4413505	6.3
Female	5700018	31.7	2591516	14.2	51939540	65.4	30581668	38.7	7592720	10.2
NH Black										
Male	1570898	31.5	954234	19.1	8395621	69.9	4583941	38.2	912855	7.5
Female	2181564	45.2	1312326	27.1	11688513	78.4	8201670	55.2	2435459	16.3
Hispanic										
Male	4217447	45.9	2522750	28.6	15360673	84.8	8056325	44.0	1069379	5.7
Female	3831492	43.8	2055875	23.4	14346806	77.8	8591006	46.2	2007719	10.8
NH Asian										
Male	465874	26.4	218315	11.3	3586711	55.9	893904	13.5	99259	1.4
Female	334922	18.8	126797	7.4	3234798	42.9	1203128	15.9	64898	0.9

NH indicates non-Hispanic.

*Overweight and obesity in adults is defined as body mass index (BMI) ≥25 kg/m^2. Obesity in adults is defined as BMI ≥30 kg/m^2. Extreme obesity is defined as BMI ≥40 kg/m^2. Prevalence estimates for adults were age adjusted with the direct method to standardize estimates to the projected 2000 US census population with age categories of 20 to 39, 40 to 59, and ≥60 years. In children, overweight and obesity are based on BMI-for-age values ≥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.[116] Prevalence estimates for youth are unadjusted.

†Population counts applied to the average of the 2013 and 2015 Census Bureau population estimates.

Source: Unpublished tabulation using National Health and Nutrition Examination Survey, 2015 to 2018.[13]

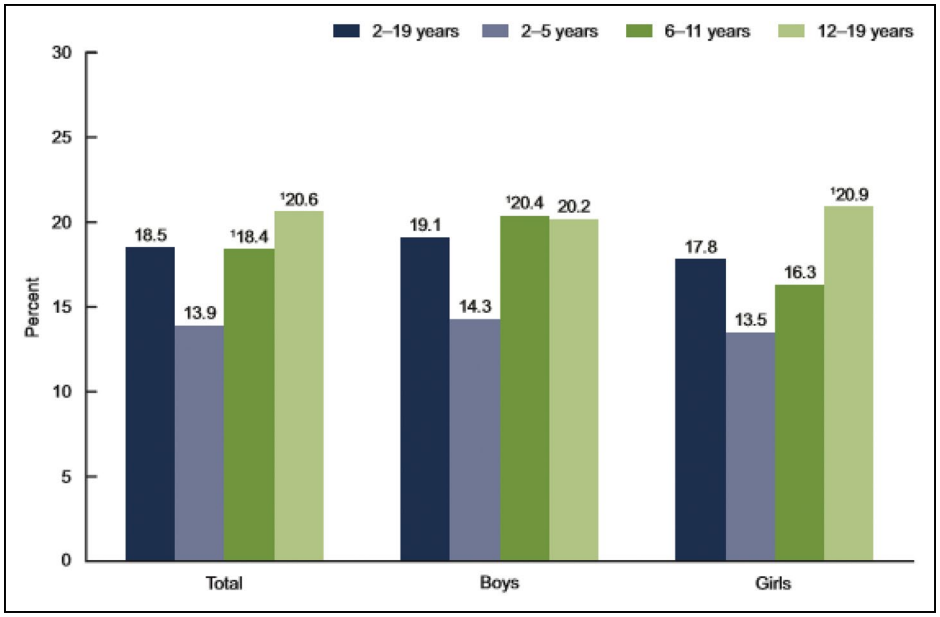

Chart 6-1. Prevalence of obesity among US youth 2 to 19 years of age by sex and age, 2015 to 2016.
[1]Significantly different from those 2 to 5 years of age.
Source: Reprinted from Hales et al[12] using National Health and Nutrition Examination Survey, 2015 to 2016.

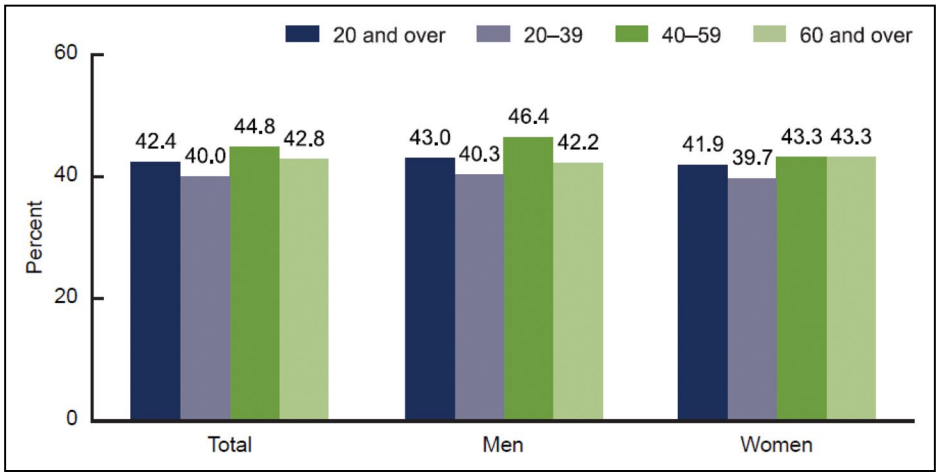

Chart 6-2. Prevalence of obesity among US adults ≥20 years of age by sex and age, 2017 to 2018.
Estimates were age adjusted by the direct method to the 2000 US census population using the age groups 20 to 39, 40 to 59, and ≥60 years.
Source: Reprinted from Hales et al[17] using data from National Health and Nutrition Examination Survey, 2017 to 2018.

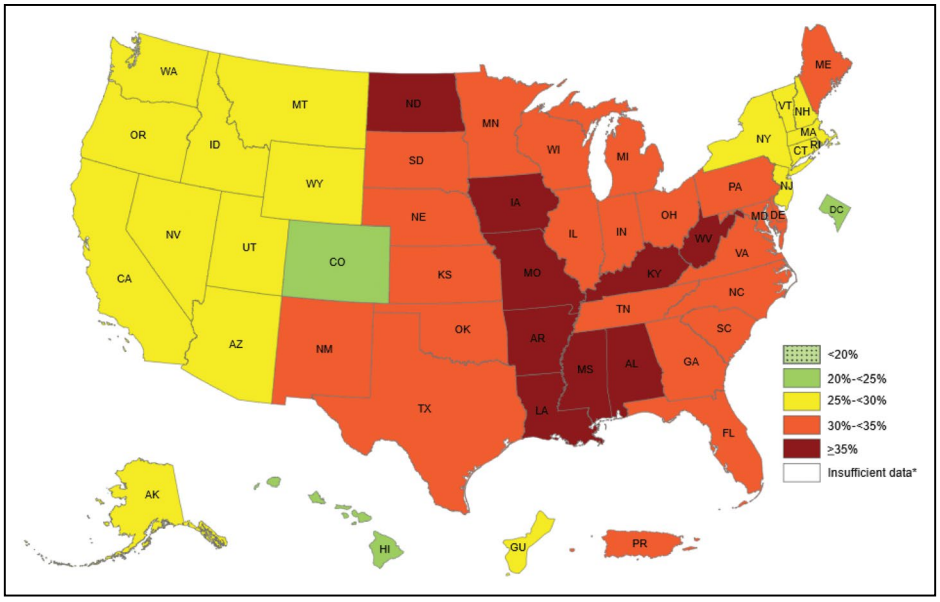

Chart 6-3. Prevalence of self-reported obesity among adults by US state and territory, 2018.
Prevalence estimates reflect BRFSS methodological changes that started in 2011. These estimates should not be compared with prevalence estimates before 2011. BRFSS indicates Behavioral Risk Factor Surveillance System.
*Sample size <50 or the relative SE (dividing the SE by the prevalence) ≥30%.
Source: Reprinted from Centers for Disease Control and Prevention, Obesity Prevalence Map using BRFSS, 2015 to 2017.[117]

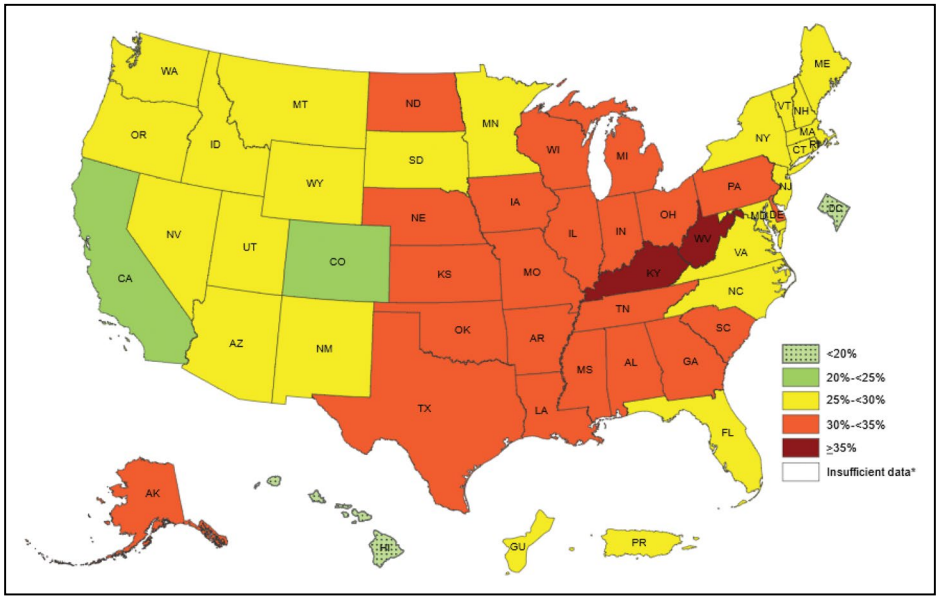

Chart 6-4. Prevalence of self-reported obesity among non-Hispanic White adults by US state and territory, 2016 to 2018.
*Sample size <50 or the relative SE (dividing the SE by the prevalence) ≥30%.
Source: Reprinted from Centers for Disease Control and Prevention, Obesity Prevalence Map using Behavioral Risk Factor Surveillance System, 2015 to 2017.[117]

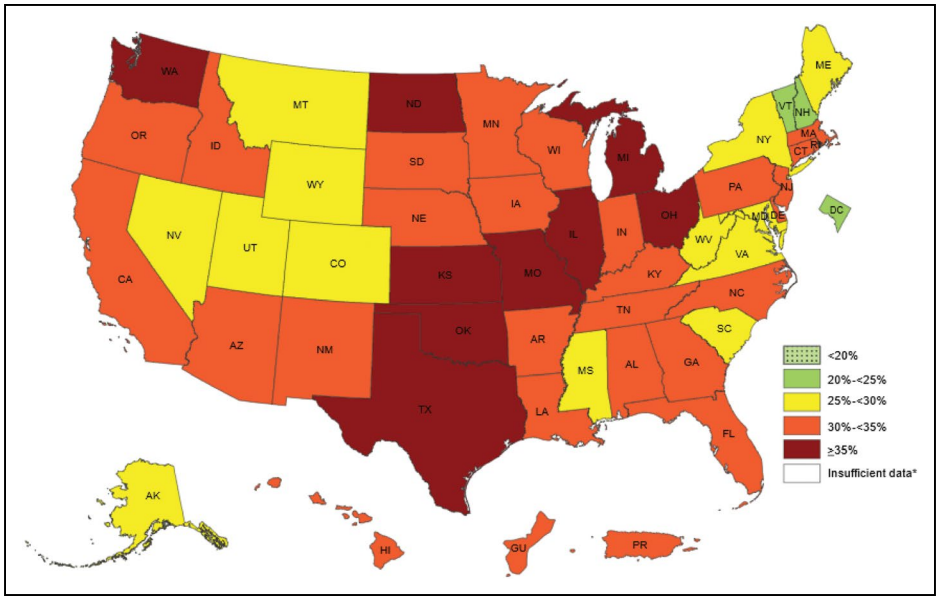

Chart 6-5. Prevalence of self-reported obesity among Hispanic adults by US state and territory, 2016 to 2018.
*Sample size <50 or the relative SE (dividing the SE by the prevalence) ≥30%.
Source: Reprinted from Centers for Disease Control and Prevention, Obesity Prevalence Map using Behavioral Risk Factor Surveillance System, 2015 to 2017.[117]

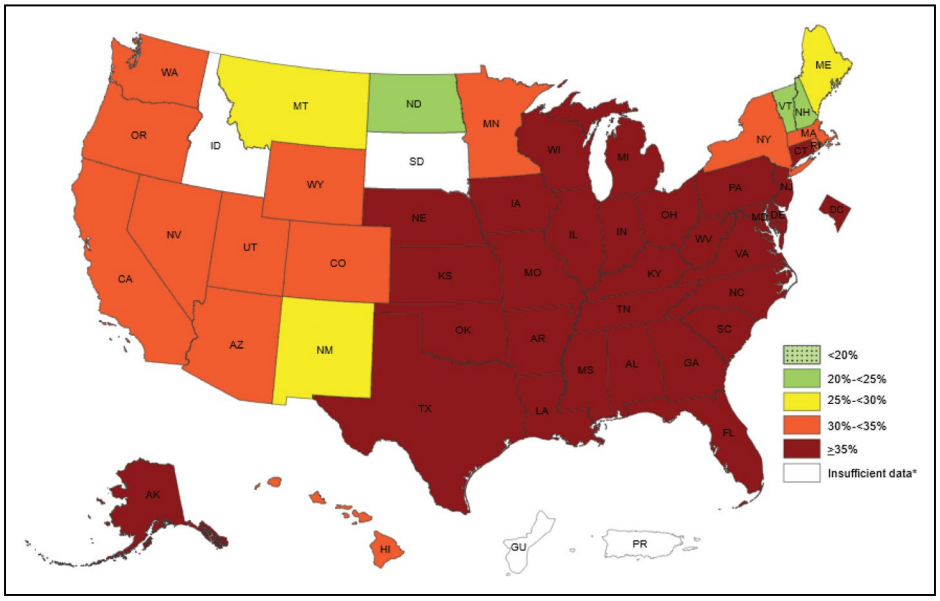

Chart 6-6. Prevalence of self-reported obesity among non-Hispanic Black adults by US state and territory, 2016 to 2018.
*Sample size <50 or the relative SE (dividing the SE by the prevalence) ≥30%.
Source: Reprinted from Centers for Disease Control and Prevention, Obesity Prevalence Map using Behavioral Risk Factor Surveillance System, 2015 to 2017.[117]

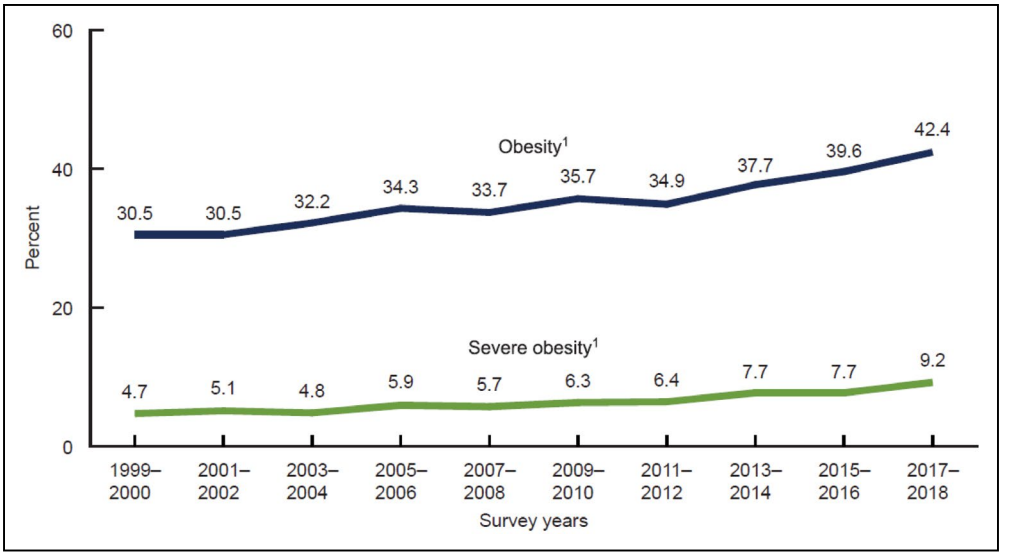

Chart 6-7. Trends in age-adjusted obesity prevalence among US adults ≥20 years of age, 1999 to 2000 through 2017 to 2018.
Estimates were age adjusted by the direct method to the 2000 US census population using the age groups 20 to 39, 40 to 59, and ≥60 years.
[1]Significant linear trend.
Source: Reprinted from Hales et al[7] using National Health and Nutrition Examination Survey, 1999 to 2018.

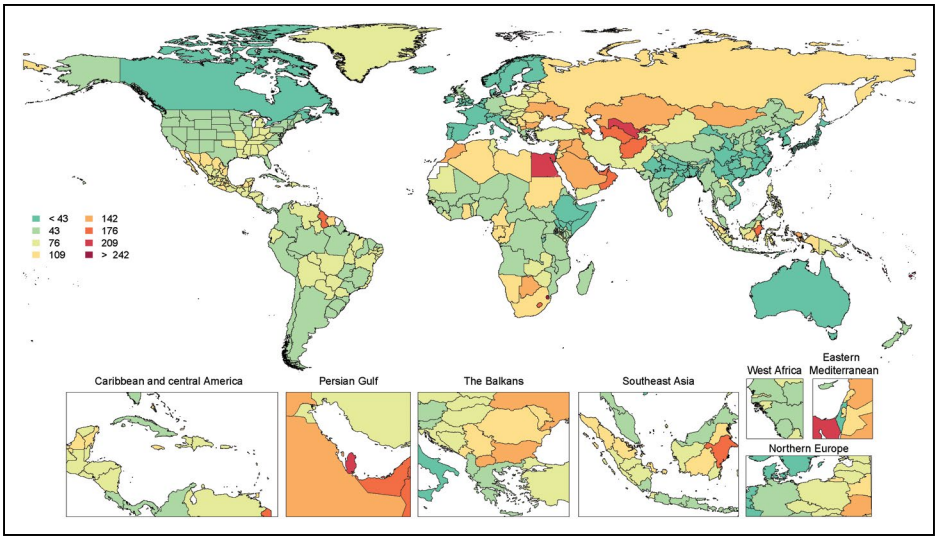

Chart 6-8. Age-standardized mortality rates attributable to high body mass index per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[109] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[118]

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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 atherosclerosis and CVD and is 1 of 7 metrics the AHA has used to define CVH in children and adults. The American Heart Association, American College of Cardiology, and several other societies released the Cholesterol Clinical Practice Guideline in 2018.[1] There is substantial interest in lowering average cholesterol levels in the overall population in the United States and in identifying individuals likely to benefit most from targeted cholesterol-lowering interventions.

Abbreviations Used in Chapter 7

ACC	American College of Cardiology
AHA	American Heart Association
apoB	apolipoprotein B
ASCVD	atherosclerotic cardiovascular disease
ATP III	Adult Treatment Panel III
BMI	body mass index
BRFSS	Behavioral Risk Factor Surveillance System
CAC	coronary artery calcification
CAD	coronary artery disease
CASCADE FH	Cascade Screening for Awareness and Detection of FH
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
CVH	cardiovascular health
ED	emergency department
FH	familial hypercholesterolemia
GBD	Global Burden of Disease Study
GWAS	genome-wide association study
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
IMT	intima-media thickness
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
NCDR	National Cardiovascular Data Registry

(*Continued*)

Abbreviations Used in Chapter 7 Continued

NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
OR	odds ratio
PALM	Patient and Provider Assessment of Lipid Management Registry
PCSK9	proprotein convertase subtilisin/kexin type 9
PESA	Progression of Early Subclinical Atherosclerosis
PINNACLE	Practice Innovation and Clinical Excellence
QALY	quality-adjusted life-year
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SE	standard error
TC	total cholesterol
UI	uncertainty interval

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Prevalence of High TC

Youth

(See Chart 7-1)

- Among children 6 to 11 years of age, the mean TC level in 2015 to 2018 was 157.3 mg/dL. For males, it was 157.4 mg/dL; for females, it was 157.1 mg/dL. The racial/ethnic breakdown in NHANES 2015 to 2018[2] was as follows (unpublished NHLBI tabulation using NHANES[2]):
  - For NH White children, 156.1 mg/dL for males and 157.8 mg/dL for females
  - For NH Black children, 157.1 mg/dL for males and 156.3 mg/dL for females
  - For Hispanic children, 157.6 mg/dL for males and 154.8 mg/dL for females
  - For NH Asian children, 167.5 mg/dL for males and 159.0 mg/dL for females
- Among adolescents 12 to 19 years of age,[2] the mean TC level in 2015 to 2018 was 155.1 mg/dL; for males, it was 152.7 mg/dL; for females, it was 157.5 mg/dL. The racial/ethnic breakdown was as follows (unpublished NHLBI tabulation using NHANES[2]):
  - For NH White adolescents, 151.2 mg/dL for males and 158.0 mg/dL for females
  - For NH Black adolescents, 155.8 mg/dL for males and 157.1 mg/dL for females
  - For Hispanic adolescents, 152.3 mg/dL for males and 153.8 mg/dL for females
  - For NH Asian adolescents, 155.2 mg/dL for males and 165.0 mg/dL for females
- Among youth 6 to 19 years of age, the prevalence of adverse TC levels (TC ≥200 mg/dL) in 2009 to

2016 was 7.1% (95% CI, 6.4%–7.8%; Chart 7-1A). Conversely, ideal levels of lipids (as opposed to adverse or borderline levels) may be a particularly relevant target for youth. Among youth 6 to 19 years of age, the prevalence of ideal TC levels (TC <170 mg/dL) in 2015 to 2016 was 71.4% (95% CI, 69.0%–73.8%; Chart 7-1B).[3] The remainder of youth had borderline levels (TC 170–199 mg/dL).

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

- Among adults ≥20 years of age, the mean TC level in 2015 to 2018 was 190.6 mg/dL. For males, it was 187.7 mg/dL; for females, it was 193.0 mg/dL. Across 3 NHANES time periods (1999–2002, 2007–2010, and 2015–2018), NH Black adults had the lowest serum TC compared to NH White adults and Mexican American adults (Chart 7-2). The racial/ethnic breakdown by sex in 2015 to 2018 was as follows (unpublished NHLBI tabulation using NHANES[2]):
  - For NH White adults, 187.2 mg/dL for males and 194.6 mg/dL for females
  - For NH Black adults, 184.0 mg/dL for males and 186.5 mg/dL for females
  - For Hispanic adults, 190.6 mg/dL for males and 189.3 mg/dL for females
  - For NH Asian adults, 190.8 mg/dL for males and 192.3 mg/dL for females
- The prevalences of TC levels ≥200 mg/dL and ≥240 mg/dL among US adults ≥20 years of age in 2015 to 2018 (unpublished NHLBI tabulation using NHANES 2) are shown overall and by sex and race/ethnicity in Table 7-1 and Charts 7-3 and 7-4. In 2015 to 2018, the percentages of adults with high TC (≥240 or ≥200 mg/dL) were lower for NH Black adults than for NH White and Asian and Hispanic adults, and females had higher prevalences of high TC than males.
- The Healthy People 2010 guideline of an age-adjusted population mean TC level of ≤200 mg/dL has been achieved in adults, in males, in females, and in all race/ethnicity subgroups.[2,4] The Healthy People 2020 target is a mean population TC level of 177.9 mg/dL for adults, which had not been achieved among the population of US adults or in any race/ethnicity subgroup as of 2015 to 2018 NHANES (Chart 7-2).[5] Conversely, the Healthy People 2020 target of ≤13.5% for the proportion of adults with high TC ≥240 mg/dL has been achieved as of the combined period 2015 to 2018 for adults overall and all race-sex subgroups (Table 7-1), although some race-sex subgroups show variability around this threshold between 2015 to 2016 and 2017 to 2018 (Chart 7-4).[6]

Prevalence of Abnormal Levels of Lipid Subfractions

LDL Cholesterol

Youth
(See Chart 7-1)

- Limited data are available on LDL-C for children 6 to 11 years of age.
- Among adolescents 12 to 19 years of age, the mean LDL-C level in 2013 to 2016 was 86.7 mg/dL (males, 85.6 mg/dL; females, 87.8 mg/dL). The racial/ethnic breakdown was as follows (unpublished NHLBI tabulation using NHANES[2]):
  - For NH White adolescents, 86.7 mg/dL for males and 87.9 mg/dL for females
  - For NH Black adolescents, 81.7 mg/dL for males and 88.4 mg/dL for females
  - For Hispanic adolescents, 85.0 mg/dL for males and 84.2 mg/dL for females
  - For NH Asian adolescents, 81.7 mg/dL for males and 103.3 mg/dL for females; however, these values are based on data from small sample sizes (50 NH Asian males and 53 NH Asian females)
- High levels of LDL-C (≥130 mg/dL) occurred in 5.9% of male adolescents and 5.2% of female adolescents during 2013 to 2016 (unpublished NHLBI tabulation using NHANES[2]).
- Conversely, ideal levels of LDL-C (<110 mg/dL) were present in 84.1% (95% CI, 79.8%–88.4%) of all adolescents in 2013 to 2014 (Chart 7-1B).[3]

Adults

- In 2013 to 2016 (unpublished NHLBI tabulation using NHANES[2]), the mean level of LDL-C for American adults ≥20 years of age was 112.1 mg/dL. The racial/ethnic breakdown was as follows:
  - Among NH White adults, 112.3 mg/dL for males and 112.3 mg/dL for females
  - Among NH Black adults, 111.0 mg/dL for males and 108.1 mg/dL for females
  - Among Hispanic adults, 117.5 mg/dL for males and 109.3 mg/dL for females
  - Among NH Asian adults, 113.8 mg/dL for males and 108.2 mg/dL for females
- In 2013 to 2016, the age-adjusted prevalence of high LDL-C (≥130 mg/dL) was 28.9% (unpublished NHLBI tabulation using NHANES[2] [Table 7-1]).

HDL Cholesterol

Youth
(See Chart 7-1)

- Among children 6 to 11 years of age, the mean HDL-C level in 2015 to 2018 was 56.3 mg/dL. For males, it was 57.6 mg/dL, and for females, it was 54.9 mg/dL. The racial/ethnic breakdown was as follows (unpublished NHLBI tabulation using NHANES[2]):

- For NH White children, 57.3 mg/dL for males and 55.1 mg/dL for females
- For NH Black children, 60.6 mg/dL for males and 58.2 mg/dL for females
- For Hispanic children, 55.9 mg/dL for males and 52.5 mg/dL for females
- For NH Asian children, 60.7 mg/dL for males and 56.0 mg/dL for females

- Among children 6 to 11 years of age, low levels of HDL-C (<40 mg/dL) occurred in 5.9% of males and 9.0% of females in 2015 to 2018 (unpublished NHLBI tabulation using NHANES[2]).
- Among adolescents 12 to 19 years of age, the mean HDL-C level was 52.4 mg/dL. For males, it was 50.2 mg/dL, and for females, it was 54.8 mg/dL. The racial/ethnic breakdown was as follows (NHANES 2015–2018,[2] unpublished NHLBI tabulation):
  - For NH White adolescents, 50.2 mg/dL for males and 55.0 mg/dL for females
  - For NH Black adolescents, 54.8 mg/dL for males and 57.4 mg/dL for females
  - For Hispanic adolescents, 49.1 mg/dL for males and 52.9 mg/dL for females
  - For NH Asian adolescents, 51.9 mg/dL for males and 54.6 mg/dL for females
- Low levels of HDL-C (<40 mg/dL) occurred in 18.4% of male adolescents and 7.4% of female adolescents in 2015 to 2018 (unpublished NHLBI tabulation using NHANES[2]).
- Conversely, ideal levels of HDL-C (>45 mg/dL) were present in 75.4% (95% CI, 72.1% –78.7%) of all youth 6 to 19 years of age in 2015 to 2016 (Chart 7-1B).[3]

Adults

- In 2015 to 2018 (unpublished NHLBI tabulation using NHANES[2]), the mean level of HDL-C for American adults ≥20 years of age was 54.4 mg/dL. The racial/ethnic breakdown was as follows:
  - Among NH White adults, 49.0 mg/dL for males and 60.9 mg/dL for females
  - Among NH Black adults, 53.4 mg/dL for males and 60.8 mg/dL for females
  - Among Hispanic adults, 45.3 mg/dL for males and 55.0 mg/dL for females
  - Among NH Asian adults, 47.4 mg/dL for males and 60.5 mg/dL for females
- Age-adjusted prevalence rates of low HDL-C (<40 mg/dL) for 2015 to 2018 are shown overall and by sex and race/ethnicity in Table 7-1. Prevalence rates were higher among males than females and were highest among Hispanic adults.

Triglycerides

Youth

(See Chart 7-1)

- Limited data are available on triglycerides for children 6 to 11 years of age.
- Among adolescents 12 to 19 years of age, the geometric mean triglyceride level in 2013 to 2016 was 61.8 mg/dL. For males, it was 62.2 mg/dL, and for females, it was 61.3 mg/dL. The racial/ethnic breakdown was as follows (unpublished NHLBI tabulation using NHANES[2]):
  - Among NH White adolescents, 63.8 mg/dL for males and 61.6 mg/dL for females
  - Among NH Black adolescents, 45.6 mg/dL for males and 48.4 mg/dL for females
  - Among Hispanic adolescents, 70.2 mg/dL for males and 68.4 mg/dL for females
  - Among NH Asian adolescents, 59.0 mg/dL for males and 74.0 mg/dL for females
- High levels of triglycerides (≥130 mg/dL) occurred in 11.9% of male adolescents and 7.6% of female adolescents during 2013 to 2016 (unpublished NHLBI tabulation using NHANES 2013–2016[2]).
- Conversely, ideal levels of triglycerides (<90 mg/dL) were present in 76.7% (95% CI, 70.8%–82.5%) of all adolescents in 2013 to 2014 (Chart 7-1B).[3]

Adults

- Among American adults ≥20 years of age, the geometric mean triglyceride level in 2013 to 2016 was 95.6 mg/dL (unpublished NHLBI tabulation using NHANES[2]). The geometric mean triglyceride levels were 103.0 mg/dL for males and 89.1 mg/dL for females. The racial/ethnic breakdown was as follows:
  - Among NH White adults, 103.4 mg/dL for males and 92.1 mg/dL for females
  - Among NH Black adults, 82.2 mg/dL for males and 66.7 mg/dL for females
  - Among Hispanic adults, 113.5 mg/dL for males and 99.7 mg/dL for females
  - Among NH Asian adults, 109.9 mg/dL for males and 84.6 mg/dL for females
- In 2013 to 2016, 22.2% of adults had high triglyceride levels (≥150 mg/dL; unpublished NHLBI tabulation using NHANES[2]).

Secular Trends in TC and Lipid Subfractions

Youth

(See Chart 7-1)

- Between 1999 and 2016, there were favorable trends in mean levels of TC, HDL-C, and non–HDL-C among youth 6 to 19 years of age. There were also favorable trends in levels of LDL-C, triglycerides, and apoB among adolescents 12 to 19 years of age over a similar period (data not available for younger children). The proportion of youths 6 to 19 years of age with all ideal levels of TC, HDL-C, and non–HDL-C increased significantly from 42.1% (95% CI, 39.6%–44.7%) in 2007 to 2008 to 51.4% (95% CI,

48.5%–54.2%) in 2015 to 2016, and the proportion with at least 1 adverse level decreased from 23.1% (95% CI, 21.5%–24.7%) in 2007 to 2010 to 19.2% (95% CI, 17.6%–20.8%) in 2013 to 2016 (Chart 7-1). The proportion of adolescents 12 to 19 years of age with all ideal levels of TC, HDL-C, non–HDL-C, LDL-C, triglycerides, and apoB did not change significantly, from 39.6% (95% CI, 33.7%–45.4%) in 2007 to 2008 to 46.8% (95% CI, 40.9%–52.6%) in 2013 to 2014, and the proportion with at least 1 adverse level remained stable from 2007 to 2010 to 2011 to 2014 at 25.2% (25.2% in 2011–2014 [95% CI, 22.2%–28.2%]; Chart 7-1).[3]

Adults (≥20 Years of Age)

- The prevalence of high TC (≥240 mg/dL) has decreased over time, from 18.3% of adults in 1999 to 2000 to 10.5% in 2017 to 2018.[7]
  - From 1999 to 2018, mean serum TC for adults ≥20 years of age decreased across all subgroups of race/ethnicity (Chart 7-2).
  - Declines in mean TC levels were also observed among adults receiving lipid-lowering medication, from 206 mg/dL in 2005 to 2006 to 187 mg/dL in 2015 to 2016.[8]
  - Between 2001 to 2004 and 2013 to 2016, declines in TC levels were greater among males (mean TC, 201 and 188 mg/dL, respectively) than females (mean TC, 203 and 194 mg/dL, respectively).[9]
- Mean levels of LDL-C decreased from 126.2 mg/dL during 1999 to 2000 to 112.8 mg/dL during 2015 to 2016. The age-adjusted prevalence of high LDL-C (≥130 mg/dL) decreased from 42.9% during 1999 to 2000 to 29.4% during 2015 to 2016 (unpublished NHLBI tabulation using NHANES[2]).
- The prevalence of low HDL-C (<40 mg/dL) declined from 22.2% in 2007 to 2008 to 16.0% in 2017 to 2018.[7]
- Mean HDL-C levels were stable between 2001 to 2004 and 2013 to 2016 among both males (from 47 to 48 mg/dL) and females (from 58 to 60 mg/dL), with no significant differences by sex in changes over time (*P* for interaction by sex=0.872).[9]
- Geometric mean levels of triglycerides declined from 123 mg/dL in 1999 to 2000 to 97 mg/dL in 2013 to 2014.[10]
- Among males, age-adjusted levels of apoB declined from 98 mg/dL in 2005 to 2006 to 93 mg/dL in 2011 to 2012 and did not change subsequently through 2015 to 2016; among females, age-adjusted mean apoB declined from 94 mg/dL in 2005 to 2006 to 91 mg/dL in 2015 to 2016.[11]

Family History and Genetics

- There are several known monogenic or mendelian causes of high blood cholesterol and lipids, the most common of which is FH, which affects up to ≈1 in 200 individuals.[12]
- High cholesterol is heritable even in families who do not harbor one of these monogenic forms of disease.
  - GWASs in 100 000s of individuals of diverse ancestry, in addition to use of electronic health record–based samples, and whole-exome sequencing (which offers more comprehensive coverage of the coding regions of the genome) have brought the current number of known lipid loci to >200.[13–17]
  - The loci associated with blood lipid levels are often associated with cardiovascular and metabolic traits, including CAD, type 2 diabetes, hypertension, waist-hip ratio, and BMI,[18] and mendelian randomization studies confirm causal associations between LDL-C, triglycerides, non-HDL-C, and CAD and coronary events but do not support a causal role for apolipoprotein A1 or HDL-C.[19–23]

Familial Hypercholesterolemia

- FH is a monogenic disorder that has been associated with mutations in *LDLR*, *APOB*, *LDLRAP1*, and *PCSK9*, which affect uptake and clearance of LDL-C.[24,25]
- According to data from NHANES during 1999 to 2014, the estimated US prevalence of definite/probable FH using the Dutch Lipid Clinic criteria was 0.47% (SE, 0.03%), and the estimated prevalence of severe dyslipidemia (LDL-C ≥190 mg/dL) was 6.6% (SE, 0.2%) among adults.[26] According to data from NHANES 1999 to 2012, the estimated US prevalence of LDL-C ≥190 mg/dL was 0.42% (95% CI, 0.15%–0.70%) among adolescents.[12]
- According to a meta-analysis of data from 11 million individuals worldwide, the pooled estimate of heterozygous FH prevalence was 0.32% (95% CI, 0.26%–0.39%), or 1 in 313 individuals worldwide. The prevalence of homozygous FH was estimated as 1 in 400 000.[27]
- 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.[28] However, individuals with LDL-C ≥190 mg/dL and a confirmed FH mutation representing lifelong elevation of LDL-C levels have substantially higher odds for CAD than those with LDL-C ≥190 mg/dL without pathogenic mutations.[24]
  - Compared with individuals with LDL-C <130 mg/dL and no mutation, those with both LDL-C ≥190 mg/dL and an FH mutation had a 22-fold increased risk for CAD (OR, 22.3 [95% CI, 10.7–53.2]).

— Compared with individuals with LDL-C <130 mg/dL and no mutation, individuals with LDL-C ≥190 mg/dL and no FH mutation had a 6-fold higher risk for CAD (OR, 6.0 [95% CI, 5.2–6.9]).

- In a Norwegian registry–based cohort, adults with genetic FH also had a significantly higher incidence of severe aortic stenosis requiring replacement at a mean of 65 years of age (standardized incidence ratio, 7.7 [95% CI, 5.2–11.5] during 18 300 person-years of follow-up) compared with the total Norwegian population (24 incident cases compared with 3.1 expected cases).[29]
- In a 20-year follow-up study, early initiation of statin treatment among 214 children with FH was associated with a decrease in LDL-C by 32%, slowed progression of subclinical atherosclerosis (carotid IMT change 0.0056 mm/y, not significantly different from unaffected siblings), and lower cumulative incidence by 39 years of age of cardiovascular events compared with affected parents (0% versus 7% and 1% versus 26% of fatal and nonfatal cardiovascular events, respectively).[30]
- On the basis of NHANES 1999 to 2014 data, despite a high frequency of cholesterol screening and awareness (>80%), statin use was low in adults with definite/probable FH (52.3% [SE, 8.2%]) and with severe dyslipidemia (37.6% [SE, 1.2%]).[26] Among adults with diagnosed FH in the CASCADE FH Registry, 25% achieved LDL-C <100 mg/dL and 41% achieved LDL-C reduction ≥50%; factors associated with ≥50% reduction from untreated LDL-C levels were high-intensity statin use (OR, 7.33 [95% CI, 1.86–28.86]; used in 42%) and use of >1 medication to lower LDL-C (OR, 1.80 [95% CI, 1.34–2.41]; used in 45%).[31]
- Cascade screening, which recommends cholesterol testing for all first-degree relatives of patients with FH, can be an effective strategy to identify affected family members who would benefit from therapeutic intervention.[32] A systematic review of 10 studies of cascade testing for FH identified that the average yield was 44.8% and the mean new cases per index case was 1.65.[33]
- In a study of 1.2 million volunteer blood donors, FH screening identified 1 of 339 individuals who met criteria for FH, suggesting that leveraging blood donation to identify and guide early detection, treatment, and cascade screening may provide an innovative method for population-based FH screening.[34]

Familial Combined Hyperlipidemia

- Familial combined hyperlipidemia is a complex oligogenic disorder that affects 1% to 3% of the general population, which makes it the most prevalent primary dyslipidemia. In individuals with premature CAD, the prevalence is up to 10% to 14%. Familial combined hyperlipidemia has a heterogeneous clinical presentation within families and within individuals, including fluctuating elevations in LDL-C or triglycerides, as well as elevated apoB levels. Environmental interactions are important in familial combined hyperlipidemia, and metabolic comorbidities are common. Probably because of its complex nature, familial combined hyperlipidemia remains underdiagnosed.[35]

Screening

- Nearly 70% of adults (67% of males and 72% of females) reported that they had been screened for cholesterol (defined as reporting that they had their cholesterol checked with the past 5 years) according to data from NHANES 2011 to 2012, which were unchanged since 2009 to 2010.[36]
  — Among NH White adults, 71.8% were screened (70.6% of males and 72.9% of females).
  — Among NH Black adults, 71.9% were screened (66.8% of males and 75.9% of females).
  — Among NH Asian adults, 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).
- According to BRFSS 2017, the state with the highest age-adjusted percentage of adults who had their blood cholesterol checked in the past 5 years was New Jersey (90.0%), whereas the state with the lowest percentage was Alaska (74.7%).[37]
- In the United States, universal cholesterol screening is recommended for all children between 9 and 11 years of age and again between 17 and 21 years of age, and reverse-cascade screening of family members is recommended for children found to have moderate to severe hypercholesterolemia.[1,38]
  — Despite published guidelines, in a 2013 to 2014 survey of 614 practicing pediatricians in the United States, only 30.3% and 42.4% of pediatricians reported that they usually/most/all of the time screened healthy 9- to 11-year-olds and 17- to 21-year-olds, respectively.[39]
  — It has been estimated that in the United States the numbers of children 10 years of age needed to universally screen to identify 1 case of severe hyperlipidemia (LDL-C ≥190 mg/dL or LDL-C ≥160 mg/dL plus family history) or any hyperlipidemia (LDL-C ≥130 mg/dL) were 111 and 12, respectively. These numbers were 49 and 7, respectively, for a targeted screening program based on parental dyslipidemia or early CVD in a first-degree relative. The incremental costs of detection per case for universal

(versus targeted) screening were $32 170 for severe and $1980 for any hyperlipidemia, and the universal (versus targeted) strategy would annually detect ≈8000 more children with severe hyperlipidemia and 126 000 more children with any hyperlipidemia.[40]

Awareness

- Among US adults who were considered eligible for lipid-lowering therapy on the basis of the 2013 ACC/AHA guidelines, the proportion who reported being told that they had high cholesterol (awareness of high cholesterol) increased from 63.6% (95% CI, 59.0%–68.2%) to 69.4% (95% CI, 65.0%–73.9%) between 2005 to 2006 and 2015 to 2016.[8]
- Among US adults with a history of clinical ASCVD, the proportion who were aware of high cholesterol levels increased from 51.5% to 67.7% between 2005 to 2006 and 2015 to 2016 (*P* for linear trend=0.07).[8]
- According to NHANES 2005 to 2014 data, awareness among young adults 18 to 39 years of age with high (≥240 mg/dL) or borderline high (200–239 mg/dL) TC was 56.9% (SE, 2.4%) and 22.5% (SE, 1.4%), respectively.[41] Independent predictors of awareness included older age (OR, 2.35 [95% CI, 1.53–3.61] for 30–39 versus 18–29 years of age), having insurance (OR, 2.14 [95% CI, 1.25–3.65]), and private clinic or doctor's office as usual source of care (OR, 2.09 [95% CI, 1.24–3.53] versus no usual source).

Treatment

- Among US adults eligible for statins on the basis of the 2018 Cholesterol Clinical Practice Guideline,[1] self-reported statin use was estimated with NHANES data from 2011 to 2014 as follows[42]:
  - For adults ≥21 years of age with ASCVD, self-reported statin use was 64.6% overall (in 2013–2014), was lower among females (58.5%) than males (68.9%), and differed by race and ethnicity (67.7% among NH White, 56.1% among NH Black, 56.7% among NH Asian, and 43.9% among Hispanic adults).
  - For adults ≥21 years of age with LDL-C ≥190 mg/dL, self-reported statin use was 65.5% overall (in 2013–2014), was higher among females (65.3%) than males (55.3%), and differed by race and ethnicity (65.2% among NH White, 65.9% among NH Black, 56.4% among NH Asian, and 54.1% among Hispanic adults).
  - For adults 40 to 75 years of age with diabetes, self-reported statin use was 46.2% overall (in 2013–2014), was lower among females (42.3%) than males (49.1%), and differed by race and ethnicity (47.3% among NH White, 42.1% among NH Black, 49.8% among NH Asian, and 33.9% among Hispanic adults).
  - For adults 40 to 75 years of age with 10-year predicted ASCVD risk ≥7.5%, self-reported statin use was 30.3% overall (in 2013–2014), was lower among females (26.3%) than males (33.8%), and differed by race and ethnicity (31.7% among NH White, 25.6% among NH Black, 31.5% among NH Asian, and 22.7% among Hispanic adults).
- Among 49 447 patients with LDL-C ≥190 mg/dL in the ACC NCDR PINNACLE registry of cardiology practices between 2013 and 2016, the proportions documented as receiving a statin, high-intensity statin, any lipid-lowering therapy associated with ≥50% reduction in LDL-C level, ezetimibe, or PCSK9 inhibitor were 58.5%, 31.9%, 34.6%, 8.5%, and 1.5%, respectively, with even lower treatment rates among the subset of individuals without preexisting ASCVD. After adjustment for patient and practice characteristics, there was >200% variation in treatment rates across practices for most medications.[43]
- Among 5693 participants in PALM, a nationwide registry of ambulatory community practices, females were less likely than males to receive statin dosing at the guideline-recommended intensity (36.7% versus 45.2%; *P*<0.001) and were more likely not to have ever been offered statin therapy despite being eligible (18.6% versus 13.5%; *P*<0.001) compared with males.[44]
- The REGARDS[45] study (2003–2007) showed disparities in statin use by race and sex among individuals with diabetes and LDL-C >100 mg/dL. White males had the highest rates of statin use (66.0%), followed by Black males (57.8%), White females (55.0%), and Black females (53.6%). Race-sex differences persisted after accounting for access to medical care.
- Among US adults with TC ≥240 mg/dL, rates of treatment with lipid-lowering therapy have increased over time but remain persistently lower in females compared with males (40% compared with 48% in 2001–2004 and 56% compared with 67% in 2013–2016 in females versus males, respectively).[9]
- Among 63 576 adult patients in the Veterans Affairs Health System between 2011 and 2014 with LDL-C ≥190 mg/dL but no diabetes or ASCVD, 52% received statin therapy and 9.7% received high-intensity statin therapy, with lower treatment rates among women (versus men) and patients <35 or >75 years of age (versus 35–75 years of age). High-intensity statin use increased over time from 8.6% in 2011 to 13.6% in 2014 (*P*<0.001).[46]

- Among US adults with diabetes, statin use increased from 48.3% to 60.2% between 2005 to 2006 and 2015 to 2016.[8]
- Among US adults with a 10-year predicted ASCVD risk ≥7.5%, the proportion taking a statin increased from 27.9% to 32.5% between 2005 to 2006 and 2015 to 2016.[8]

Control

- Rates of control are difficult to assess in the context of the 2018 Cholesterol Clinical Practice Guideline,[1] which is focused on treating risk and not targeting lipid levels. However:
  - — During 2013 to 2016 among US adults at increased risk because of history of CVD, significant sex differences existed in control, defined as TC <240 mg/dL (77.1% versus 91.0% of females and males were controlled; difference, −13.8% [95% CI, −21.3% to −6.4%]).[9]
  - — During 2013 to 2016 among US adults at increased risk because of type 2 diabetes, when control was defined as LDL-C <100 mg/dL in those without ASCVD and LDL-C <70 mg/dL in those with ASCVD, only 49.3% overall (56.8% of those without ASCVD and 26.4% of those with ASCVD) achieved control.[47]
- The REGARDS[45] study (2003–2007) showed disparities in LDL-C control (defined as LDL-C <100 mg/dL among those taking statins) by race and sex among individuals with diabetes. White males had the highest rates of control (75.3%), followed by White females (69.0%), Black males (62.7%), and Black females (56.0%). Race-sex differences persisted after accounting for access to medical care.

Mortality and Complications

- Among 4184 individuals free of conventional cardiovascular risk factors in the PESA study, subclinical atherosclerosis (plaque or CAC) was present in 49.7% and was associated with LDL-C at levels currently considered normal.[48]
  - — The prevalence of atherosclerosis increased linearly from the LDL-C 60 to 70 mg/dL category to the 150 to 160 mg/dL category (from 11% to 64%, respectively; *P*<0.001).
  - — A similar pattern was seen for the extent (focal, intermediate, or generalized disease) and number of vascular sites affected with atherosclerosis.
- Long-term exposure to even modestly elevated cholesterol levels can lead to CHD later in life.[49] In an analysis of time-weighted average exposures to LDL-C during young (18–39 years of age) versus later (≥40 years of age) adulthood among 36 030 participants from 6 US cohorts, CHD rates were significantly elevated among individuals who had young-adult LDL-C ≥100 mg/dL (versus <100 mg/dL), independently of later adult exposures (adjusted HR, 1.64 [95% CI, 1.27–2.11]). Specifically, compared with LDL-C <100 mg/dL, adjusted HRs were as follows: for LDL-C 100 to 129 mg/dL, HR, 1.62 (95% CI, 1.25–2.10); for LDL-C 130 to 159 mg/dL, HR, 1.89 (95% CI, 1.43–2.50); and for LDL-C ≥160 mg/dL, HR, 2.03 (95% CI, 1.47–2.82; *P* for trend across LDL-C categories <0.001).[49]
- In a large study of Health Survey for England and Scottish Health Survey participants (n=37 059), on the basis of 2250 deaths of all causes during 326 016 person-years of follow-up[50]:
  - — A U-shaped association of all-cause mortality was seen with the lowest HDL-C (<38.7 mg/dL; HR, 1.23 [95% CI, 1.06–1.44]) and highest HDL-C (≥96.7 mg/dL; HR, 1.25 [95% CI, 0.97–1.62]).
  - — Association with CVD mortality was linear, with increased risk in those with the lowest HDL-C (<38.7 mg/dL; HR, 1.49 [95% CI, 1.15–1.94]).
- A mendelian randomization analysis of data from 654 783 participants including 91 129 cases of CHD demonstrated that triglyceride-lowering variants in the lipoprotein lipase gene and LDL-C–lowering variants in the LDL receptor gene were associated with similarly lower CHD risk when evaluated per 10-mg/dL lower apoB level (OR, 0.771 [95% CI, 0.741–0.802] and 0.773 [95% CI, 0.747–0.801]), respectively. This suggested that the clinical benefit of both triglycerides and LDL-C lowering might be related to the absolute reduction in apoB-containing lipoprotein particles (very-low-density lipoprotein and LDL particles, respectively).[23]
- In a systematic review and trial-level meta-regression analysis that included 197 270 participants from 24 nonstatin trials and 25 statin trials, the RR of major vascular events was 0.80 (95% CI, 0.76–0.85) per 1-mmol/L reduction in LDL-C (or 0.79 per 40 mg/dL) and 0.84 (95% CI, 0.75–0.94) per 1-mmol/L reduction in triglycerides (0.92 per 40 mg/dL).[51]
- In a meta-analysis of individual-level data from 29 069 patients in 7 statin trials, both baseline and on-statin Lp(a) concentrations were linearly associated with risk for CVD events, defined as fatal or nonfatal CHD, stroke, or coronary or carotid revascularization. Lp(a) levels of ≥30 mg/dL at baseline or ≥50 mg/dL on statin treatment were associated with increased risks compared with levels <15 mg/dL, with adjusted HRs of 1.11 (95% CI, 1.00–1.22) for baseline levels of 30 to <50 mg/dL, 1.31 (95% CI, 1.08–1.58) for baseline levels ≥50 mg/dL, and 1.43 (95% CI, 1.15–1.76) for on-statin levels ≥50 mg/dL.[52]

Cost

- In an analysis of 2016 US health care spending, hyperlipidemia ranked the 35th most expensive health condition, with estimated spending of $26.4 billion (95% CI, 24.3–29.4 billion) overall.[53] Costs were split relatively evenly between younger and older adults (51.0% for 20–64 years of age, 48.4% for ≥65 years of age, 0.6% for <20 years of age), were higher for public versus private insurance (49.1% public insurance, 43.8% private insurance, 7.1% out-of-pocket payments), and were concentrated in prescription medications and ambulatory visits (45.6% prescribed pharmaceuticals, 33.4% ambulatory care, 5.9% inpatient care, 4.7% nursing care facility, 0.5% ED). Hyperlipidemia was among the conditions with highest annual spending growth for public insurance from 1999 to 2016 at 9.3% (95% CI, 8.2%–10.4%) per year; annual spending growth for hyperlipidemia was 5.2% overall, 4.0% for private insurance, and –0.9% for out-of-pocket payments.
- In a 2017 analysis, it was estimated that under the 2013 ACC/AHA guideline on treatment of blood cholesterol, compared with ATP III guidelines, 12.3 million more Americans would be treated with statins over the years 2016 to 2025, increasing treatment costs by $13.3 billion. Despite the higher screening and treatment costs, the 2013 ACC/AHA guideline was projected to save 43 100 lives and 183 000 QALYs and result in a net cost savings of $3.9 billion.[54] In the United States, only 47% of patients who were prescribed PCSK9 inhibitors had at least 1 prescription approved between July 2015 and August 2016.[55] Approval rates were highest for Medicare (60.9%) and lowest for private third-party payers (24.4%).

Global Burden of Hypercholesterolemia (See Chart 7-5)

- According to the GBD 2019 study of leading risk factors for global mortality among 204 participating countries, high LDL-C accounted for 4.4 million (95% UI, 3.3–5.7 million) deaths worldwide. From 1990 to 2019, the percent change in total number of deaths was 46.4 (95% UI, 35.2–55.6), and the percent change in age-standardized mortality rate was –36.7 (95% UI, –40.6 to –33.1).[56]
- In 2019, the mortality rate (per 100 000) attributable to high LDL-C was highest in Eastern Europe, Central Asia, North Africa, and the Middle East (Chart 7-5).
- A report on trends in TC in 199 countries and territories indicated that between 1980 and 2008, mean TC levels declined in high-income regions of the world (Australasia, North America, and Western Europe) and in Central and Eastern Europe but increased in East and Southeast Asia and the Pacific.[57] Nevertheless, mean TC levels in 2008 were highest in the high-income region of Australasia, North America, and Western Europe (regional mean, 202.6 mg/dL [95% CI, 196.4–208.4] for males and 202.2 mg/dL [95% CI, 194.5–210.0] for females) and lowest in sub-Saharan Africa (157.8 mg/dL [95% CI, 147.7–167.8] for males and 165.1 mg/dL [95% CI, 154.3–176.3] for females).

Table 7-1. High TC and LDL-C and Low HDL-C, United States (≥20 Years of Age)

Population group	Prevalence of TC ≥200 mg/dL, 2015–2018	Prevalence of TC ≥240 mg/dL, 2015–2018	Prevalence of LDL-C ≥130 mg/ dL, 2013–2016	Prevalence of HDL-C <40 mg/dL, 2015–2018
Both sexes	93 900 000 (38.1)	28 000 000 (11.5)	69 600 000 (28.9)	41 900 000 (17.2)
Males	41 600 000 (35.3)	12 200 000 (10.5)	34 800 000 (30.1)	31 600 000 (26.6)
Females	52 300 000 (40.4)	15 800 000 (12.1)	34 800 000 (27.6)	10 300 000 (8.5)
NH White males	35.0	10.1	29.4	26.3
NH White females	41.8	13.1	29.7	7.4
NH Black males	31.0	9.2	29.5	17.0
NH Black females	33.4	10.5	23.4	7.9
Hispanic males	37.7	12.4	33.5	32.0
Hispanic females	37.3	9.2	23.8	12.3
NH Asian males	38.6	13.0	32.2	26.4
NH Asian females	38.6	10.3	25.1	6.7

Values are number (percent) or percent. 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. Data for TC, LDL-C, and HDL-C are age adjusted.

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

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Health and Nutrition Examination Survey (2013–2016 and 2015-2018),[2] applied to 2016 population estimates for data from 2013 to 2016 and 2018 population estimates for data from 2015 to 2018.

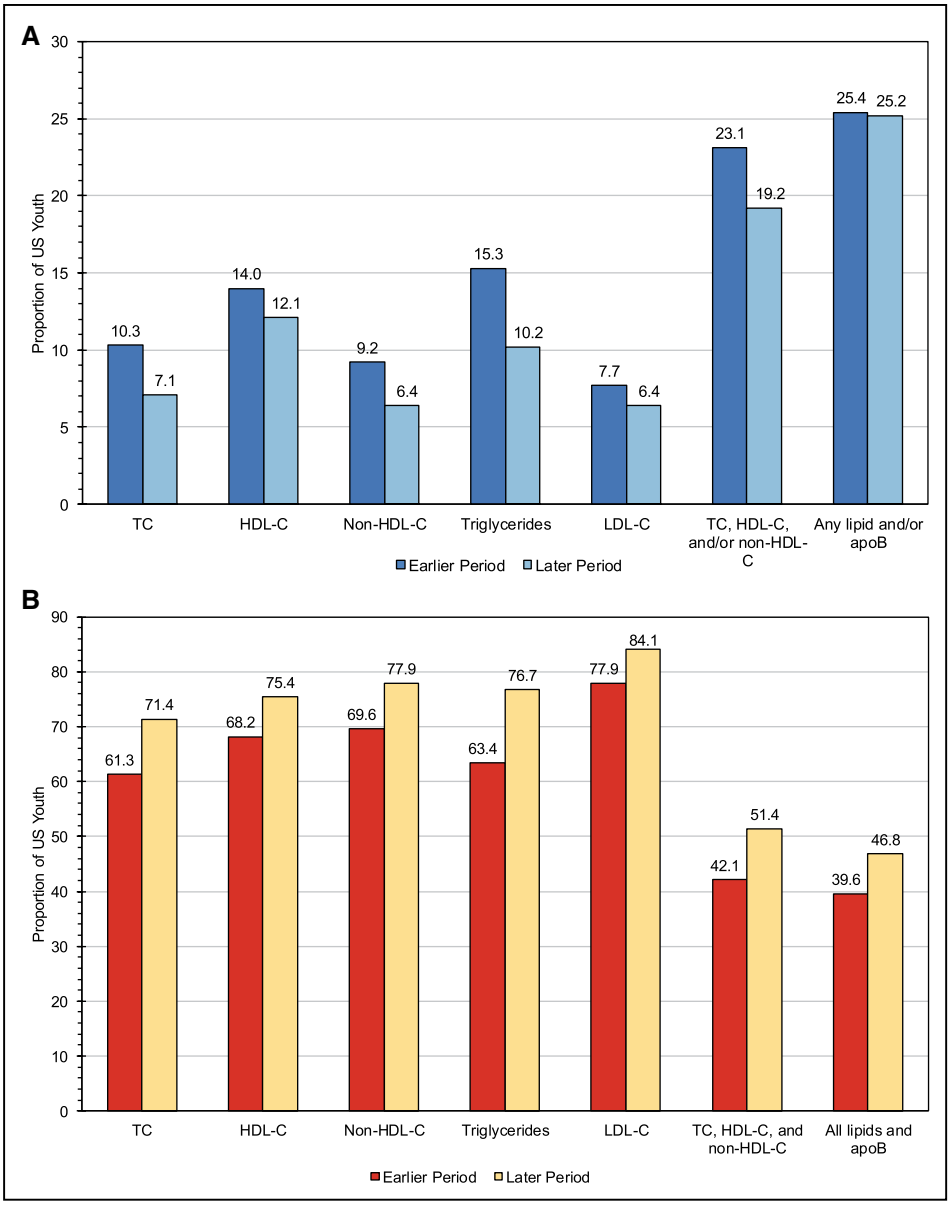

Chart 7-1. Proportions of US youth with adverse and ideal lipid levels in the period 1999 to 2016, NHANES.
A, Adverse lipid levels. **B**, Ideal lipid levels. TC, HDL-C, and non–HDL-C are shown for all youth 6 to 19 years of age, and triglycerides, LDL-C, and any/all lipids plus apoB are shown for fasting adolescents 12 to 19 years of age. **A**, For adverse lipid levels, the earlier and later periods shown for each lipid are as follows: 1999 to 2006 and 2009 to 2016 for TC; 2007 to 2010 and 2013 to 2016 for HDL-C; 2007 to 2010 and 2013 to 2016 for non–HDL-C; 1999 to 2006 and 2007 to 2014 for triglycerides; 1999 to 2006 and 2007 to 2014 for LDL-C; 2007 to 2010 and 2013 to 2016 for any of TC, HDL-C, or non–HDL-C; and 2007 to 2010 and 2011 to 2014 for any lipid or apoB. **B**, For ideal lipid levels, the earlier and later periods shown for each lipid are as follows: 1999 to 2000 and 2015 to 2016 for TC; 2007 to 2008 and 2015 to 2016 for HDL-C; 2007 to 2008 and 2015 to 2016 for non–HDL-C; 1999 to 2000 and 2013 to 2014 for triglycerides; 1999 to 2000 and 2013 to 2014 for LDL-C; 2007 to 2008 and 2015 to 2016 for TC, HDL-C, and non–HDL-C; and 2007 to 2008 and 2013 to 2014 for all lipids and apoB.
apoB indicates apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey; and TC, total cholesterol.
Source: Data derived from Perak et al.[3]

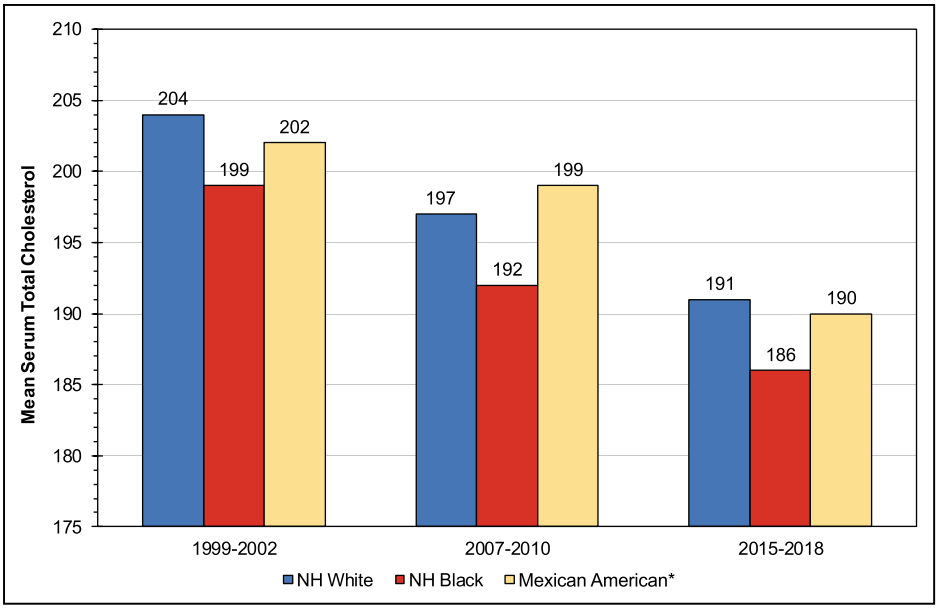

Chart 7-2. Age-adjusted trends in mean serum total cholesterol among US adults ≥20 years of age by race and survey year (NHANES, 1999–2002, 2007–2010, and 2015–2018).
Values are in milligrams per deciliter.
NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
*Data for the category of Mexican American people were consistently collected in all NHANES years, but the combined category of Hispanic people was used starting only in 2007. Consequently, for long-term trend data, the category of Mexican American people is used.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 1999 to 2018.[2]

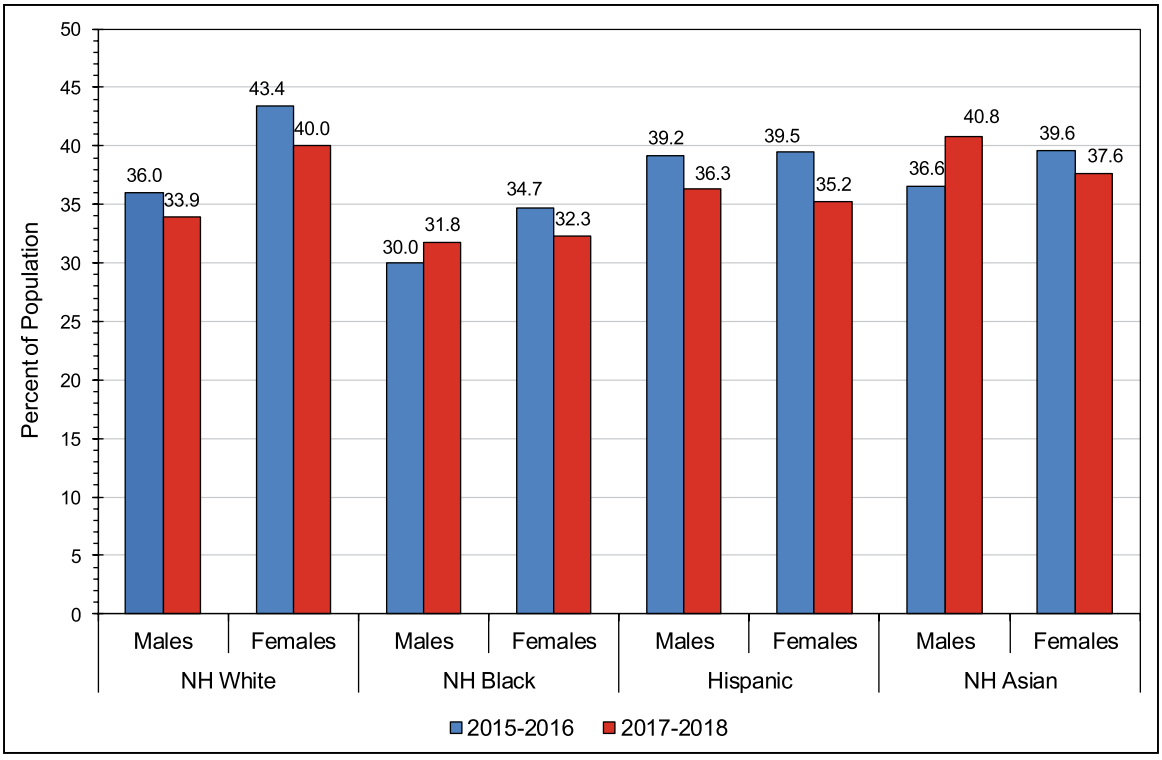

Chart 7-3. Age-adjusted trends in the prevalence of serum total cholesterol ≥200 mg/dL in US adults ≥20 years of age by race/ethnicity, sex, and survey year (NHANES, 2015–2016 and 2017–2018).
NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2015 to 2018.[2]

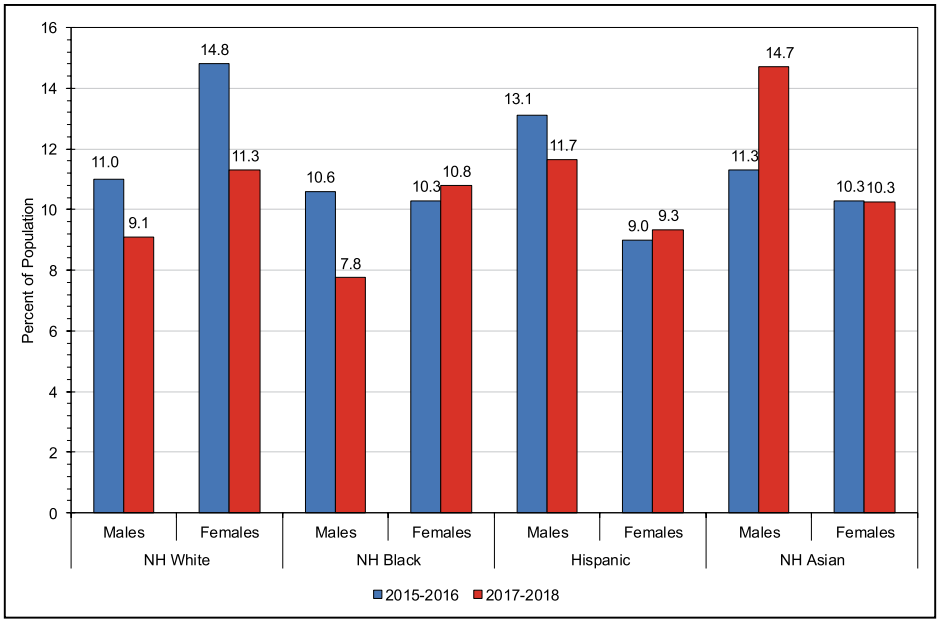

Chart 7-4. Age-adjusted trends in the prevalence of serum total cholesterol ≥240 mg/dL in US adults ≥20 years of age by race/ethnicity, sex, and survey year (NHANES, 2015–2016 and 2017–2018).
NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2015 to 2018.[2]

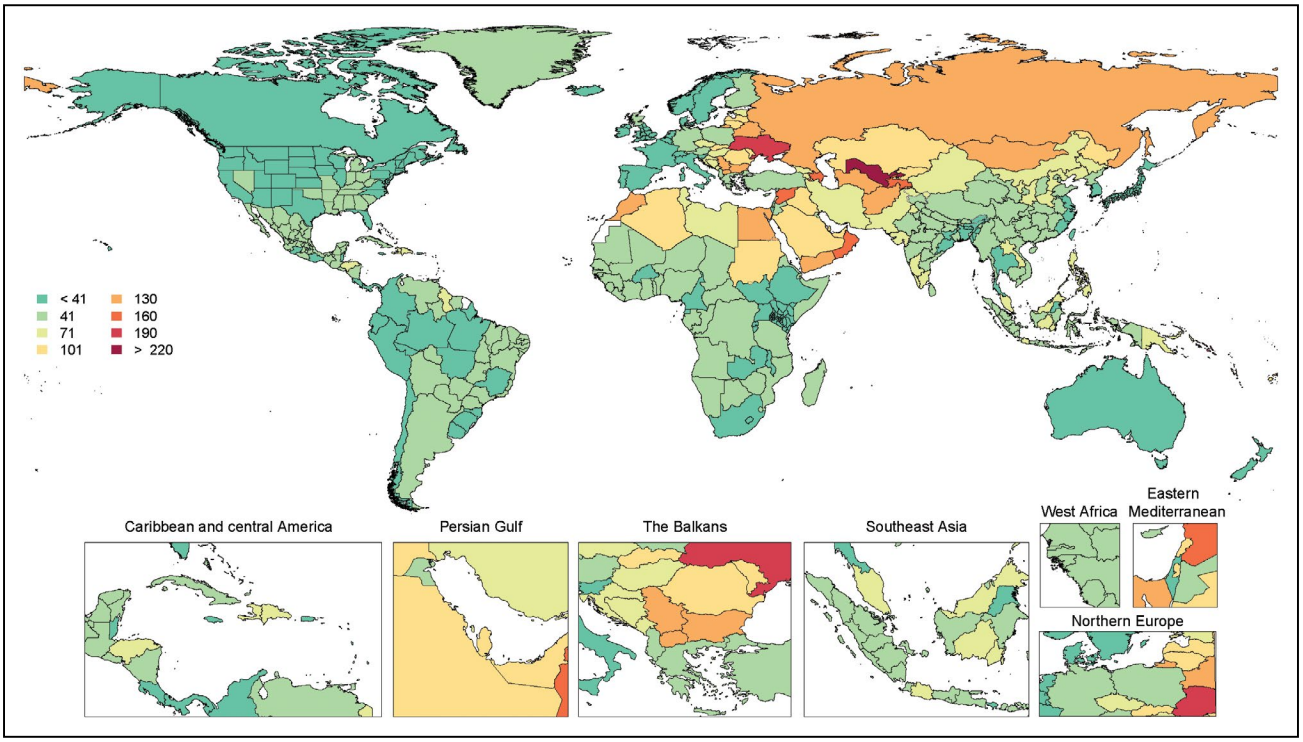

Chart 7-5. Age-standardized global mortality rates attributable to high low-density lipoprotein cholesterol per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[56] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[58]

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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 ≥20 years of age) as 1 of the 7 components of ideal CVH.[2] In 2015 to 2018, 89.1% of US children 12 to 19 years of age and 40.8% of US adults met these criteria (Chapter 2, Cardiovascular Health, Chart 2-1).

Abbreviations Used in Chapter 8

ACE	angiotensin-converting enzyme
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities study
AUC	area under the curve
BMI	body mass index
BP	blood pressure
CARDIA	Coronary Artery Risk Development in Young Adults
CDC	Centers for Disease Control and Prevention
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
CVD	cardiovascular disease
CVH	cardiovascular health
DALY	disability-adjusted life-year
DBP	diastolic blood pressure
EBP	elevated blood pressure
ED	emergency department
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
GBD	Global Burden of Disease Study
GRS	genetic risk score
GWAS	genome-wide association study

(*Continued*)

Abbreviations Used in Chapter 8 Continued

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, 9th Revision, Clinical Modification*
ICD-10	*International Classification of Diseases, 10th Revision*
ICD-10-CM	*International Classification of Diseases, 10th Revision, Clinical Modification*
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
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHDS	National Hospital Discharge Survey
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NHS	Nurses' Health Study
NVSS	National Vital Statistics System
OR	odds ratio
OSA	obstructive sleep apnea
PA	physical activity
PAF	population attributable fraction
PAR	population attributable risk
RCT	randomized controlled trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SES	socioeconomic status
SPRINT	Systolic Blood Pressure Intervention Trial
SSB	sugar-sweetened beverage
YLL	years of life lost

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Prevalence (See Table 8-1 and Charts 8-1 and 8-2)

- Although surveillance definitions vary widely in the published literature, including for the CDC

and NHLBI, as of the 2017 Hypertension Clinical Practice Guidelines, 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.
- Other important BP classifications, or phenotypes, assessed via 24-hour ambulatory BP monitoring include the following:
  - Sustained hypertension, defined as elevated clinic BP with elevated 24-hour ambulatory BP
  - White-coat hypertension, defined as elevated clinic BP with normal 24-hour ambulatory BP
  - Masked hypertension, defined as normal clinic BP with elevated 24-hour ambulatory BP
- According to 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 Hypertension Clinical Practice 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.[4]
- With the use of the most recent 2017 definition, the age-adjusted prevalence of hypertension among US adults ≥20 years of age was estimated to be 47.3% in NHANES in 2013 to 2016 (51.7% for males and 42.8% for females).[5] This equates to an estimated 121.5 million adults ≥20 years of age who have HBP (63.1 million males and 58.4 million females; Table 8-1).
- In NHANES 2015 to 2018,[5] the prevalence of HBP was 28.2% among those 20 to 44 years of age, 60.1% among those 45 to 64 years of age, and 77.0% among those ≥65 years of age (unpublished NHLBI tabulation).
- In NHANES 2015 to 2018,[5] 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; Chart 8-1).
- The prevalence of HBP in adults ≥20 years of age is presented by both age and sex in Chart 8-1.
- Data from NHANES 2015 to 2018[5] indicate that 38.8% of US adults with hypertension are not aware that they have it (unpublished NHLBI tabulation).
- The age-adjusted prevalence of hypertension in 1999 to 2002, 2007 to 2010, and 2015 to 2018 is shown in race/ethnicity and sex subgroups in Chart 8-2.
- Among 1677 participants in the IDACO cohort database 40 to 79 years of age 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.[6]
- A meta-analysis of 20 observational studies and 4 RCTs with a total sample size of 961 035 estimated the prevalence of apparent treatment-resistant hypertension in the observational studies to be 13.7% (95% CI, 11.2%–16.2%).[7]
- In a cohort of 3367 patients with established kidney disease, 40.4% had resistant hypertension, which was defined as having SBP ≥140 mm Hg or DBP ≥90 mm Hg on ≥3 antihypertensive medications or use of ≥4 antihypertensive medications and SBP <140 mm Hg and DBP <90 mm Hg.[8]
- An analysis of the Spanish Ambulatory Blood Pressure Monitoring Registry using 70 997 patients treated for hypertension estimated that 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%.[9] The prevalence of refractory hypertension (SBP/DBP ≥140/90 mm Hg on ≥5 antihypertensive medications) was 1.4%, whereas the prevalence of white-coat refractory hypertension was 26.7%.[9]
- 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.[10] From NHANES 2007 to 2012 data, it was estimated that 7.6% (95% CI, 7.0%–8.3%) of US adults (16.8 million [95% CI, 15.7–17.8 million]) met the SPRINT inclusion and exclusion criteria.[11]
- In a meta-analysis of people ≥16 years of age with HIV (49 studies with data collected from 1996–2014; n=63 554), the prevalence of hypertension was 25.2% (95% CI, 21.2%–29.6%) overall, 34.7% (95% CI, 27.4%–42.8%) among those who had been treated with antiretroviral therapy, and 12.7% (95% CI, 7.4%–20.8%) among those who had not received antiretroviral therapy.[12]

Older Adults

- The white-coat effect (clinic minus out-of-clinic BP) is larger at older ages. In IDACO, in a pooled analysis of 11 cohorts (n=656 untreated participants with white-coat hypertension and n=653 participants with sustained normotension), 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]

- Among 5236 adults in the REGARDS study ≥65 years of age currently taking antihypertensive medications and enrolled in Medicare fee-for-service, 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. The HR associated with 1 versus 0 indicators of frailty was 1.18 (95% CI, 0.99–1.40), 2 versus 0 was 1.49 (95% CI, 1.19–1.87), and ≥3 versus 0 was 2.04 (95% CI, 1.56–2.67). In contrast, on-treatment SBP, DBP, and number of antihypertensive medications were not statistically significantly associated with risk for serious fall injuries.[14]

Children and Adolescents

- In NHANES 2015 to 2016, 13.3% (SE, 1.3) of children and adolescents 8 to 17 years of age had EBP (SBP or DBP at the 90th percentile or higher) and 4.9% (SE, 0.7) had hypertension (SBP or DBP at the 95th percentile or higher) according to the 2017 guidelines from the American Academy of Pediatrics. Rates of EBP were higher among youth 13 to 17 years of age compared with those 8 to 12 years of age (15.6% and 10.8%, respectively). However, rates of hypertension were slightly higher among youth at younger ages, with a prevalence of 4.4% among youth 13 to 17 years of age and 5.3% in youth 8 to 12 years of age.[15]
- In NHANES 2015 to 2016, among youth 8 to 17 years of age, hypertension was more common among boys (5.9%) than girls (3.8%) and among Mexican American youth (9.0%) compared with NH Black youth (4.7%), and NH White youth (2.7%). Having EBP was more common among boys (16.9%) than girls (9.8%). In addition, Mexican American youth (16.9%) and NH Black youth (16.4%) were more likely to have EBP than NH White youth (10.7%).[15]
- In NHANES 2015 to 2016, the prevalence of hypertension was 11.6% among obese US adolescents (BMI ≥120% of 95th percentile of sex-specific BMI for age or BMI ≥35 kg/m^2) compared with 2.7% among normal/underweight children. The prevalence of EBP among obese versus normal/underweight youth was 16.2% compared with 8.7%.[15]
- In a retrospective study of 500 children screened for potential hypertension with ambulatory BP monitoring at a single pediatric nephrology unit in Italy, 12% had white-coat hypertension and 10% had masked hypertension.[16]
- Among 30 565 children and adolescents (3–17 years of age) 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 repeated BP measurement during the same visit had a mean BP based on 2 consecutive readings that was <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.[17]

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

- Table 8-1 includes statistics on prevalence of HBP, mortality from HBP, hospital discharges for HBP, and cost of HBP for different race, ethnicity, and sex groups.
- The prevalence of hypertension in Black people in the United States is among the highest in the world. According to NHANES 2015 to 2018 data,[5] the age-adjusted prevalence of hypertension among NH Black people was 56.6% among males and 55.3% among females (Chart 8-2).
- In an analysis of NHANES participants 22 to 79 years of age from 2003 to 2014, foreign-born NH Black individuals (n=522) had lower adjusted odds of having hypertension than US-born NH Black individuals (n=4511; OR, 0.61 [95% CI, 0.49–0.77]).[18]
- 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%).[19]
- Among >4 million adults who were overweight or obese in 10 health care systems and had continuous insurance coverage or had at least 1 primary care encounter from 2012 to 2013, the prevalence of hypertension was 47.3% among Black people, 39.6% among White people, 38.6% among Native Hawaiian/Pacific Islander people, 38.3% among American Indian/Native American people, 34.8% among Asian people, and 27.7% among Hispanic people. Within categories defined by BMI and after adjustment for age, sex, and health care system, each racial/ethnic group except Hispanic people was more likely to have hypertension than White people.[20]
- Among 441 Black people 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 Black people taking antihypertensive medication, the prevalence estimates were 23.1% for clinic hypertension, 43.0% for

daytime hypertension, and 61.7% for nighttime hypertension.[21]

Incidence

- Among 3890 adults 18 to 30 years of age participating in the CARDIA study who were free of hypertension at baseline, the incidence of hypertension (SBP ≥130 mm Hg, DBP ≥80 mm Hg, or self-reported antihypertensive medication use) by 55 years of age was 75.7% in Black females, 75.5% in Black males, 54.5% in White males, and 40.0% in White females.[22]

Lifetime Risk and Cumulative Incidence

- Data from 13 160 participants in cohorts in the Cardiovascular Lifetime Risk Pooling Project (ie, the Framingham Offspring Study, CARDIA, and ARIC) found that the lifetime risk of hypertension from 20 to 85 years of age using the 2017 Hypertension Clinical Practice Guidelines was 86.1% (95% CI, 84.1%–88.1%) for Black males, 85.7% (95% CI, 84.0%–87.5%) for Black females, 83.8% (95% CI, 82.5%–85.0%) for White males, and 69.3% (95% CI, 67.8%–70.7%) for White females.[23]
- Among 32 887 participants of the Kailuan study in Tangshan City, Hebei Province, China, with prehypertension (SBP 120–239 mm Hg or DBP 80–89 mm Hg and not taking antihypertensive medications) who were 18 to 98 years of age in 2006 to 2007 and were followed up until 2012 to 2013, the cumulative incidence of hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg, or taking antihypertensive medications) varied according to the number of ideal CVH factors. The cumulative incidence of hypertension was 78.6% for those with 0 or 1 ideal factor, 71.1% for those with 2 ideal factors, 63.2% for those with 3 ideal factors, 56.1% for those with 4 ideal factors, and 61.6% for those with ≥5 ideal factors.[24]
- In the Aerobics Center Longitudinal Study, a longitudinal study of the age-related trajectories of BP among males 20 to 90 years of age without hypertension, CVD, or cancer conducted from 1970 to 2006 at the Cooper Clinic in Dallas, TX, the mean SBP increased 0.30 mm Hg (95% CI, 0.29–0.31 mm Hg) per year. The mean increase in SBP per year was dependent on percentile of physical fitness, measured by age-specific treadmill time, with higher physical fitness associated with lower mean increases in SBP per year.[25]

Secular Trends

- In NHANES, the prevalence of prehypertension decreased in all age groups for US adults between 1999 to 2000 and 2013 to 2014, with the largest decline occurring among those 18 to 39 years of age (from 32.2% in 1999–2000 to 23.4% in 2013–2014).[26]
- With the use of 2017 guidelines from the American Academy of Pediatrics, analysis of data for children and adolescents 8 to 17 years of age (n=12 249) from NHANES 2003 to 2004 through NHANES 2015 to 2016 found that the prevalence of either EBP or hypertension (combined) significantly declined from 16.2% in 2003 to 2004 to 13.3% in 2015 to 2016 (*P* for trend <0.001) and the prevalence of hypertension declined from 6.6% to 4.5% in this age group (*P* for trend=0.005).[15]
- In NHANES, among underweight/normal-weight youth (8–17 years of age), there was a statistically significant decline in the prevalence of EBP/hypertension and hypertension between 2003 to 2004 and 2015 to 2016. There were no changes in the prevalence of EBP/hypertension or hypertension among overweight youth during this time period; among obese youth, there was a decline in the prevalence of EBP/hypertension (*P* for trend=0.03) but not hypertension. Among underweight/normal-weight adolescents, the unadjusted prevalence of EBP/hypertension was 12.9% (SE, 1.6%) and the prevalence of hypertension was 4.9% (SE, 0.9%) in 2003 to 2004; the prevalence of EBP/hypertension was 8.7% (SE, 1.7%) and that of hypertension was 2.7% (SE, 1%) in 2015 to 2016 (*P* for trend=0.001 and 0.002). Among obese youths, the unadjusted prevalence of EBP/hypertension was 30.1% (SE, 5.0%) and that of hypertension was 12.4% (SE, 3.3%) in 2003 to 2004; the unadjusted prevalence of pre-HBP was 25.5% (SE, 2.4%) and that of hypertension was 11.6% (SE, 2.1%) in 2015 to 2016.[15]
- 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.[27] No formal pooling of data was conducted.
- In NHDS data compiled by the CDC, chronic hypertension in pregnancy (defined as SBP ≥140 mm Hg or DBP ≥90 mm Hg either before pregnancy or up to the first 20 weeks during pregnancy) increased >13-fold between 1970 to 2010. Black women had a persistent 2-fold higher rate of chronic hypertension compared with White women over the 40-year period.[28]

Risk Factors

- Among 60 027 participants in the Norwegian Mother and Child Cohort Study who were normotensive before pregnancy, the PAF for pharmacologically treated hypertension within 10 years postpartum was 28.6% (95% CI, 25.5%–30.3%) for complications of pregnancy (preeclampsia/eclampsia, gestational hypertension, preterm delivery, and pregestational or gestational diabetes).[29]
- In a cohort of 58 671 parous females participating in the NHS II without CVD or hypertension at baseline, gestational hypertension and preeclampsia during first pregnancy were associated with a higher rate of self-reported physician-diagnosed chronic hypertension over a 25- to 32-year follow-up (HR, 2.8 [95% CI, 2.6–3.0] for gestational hypertension and HR, 2.2 [95% CI, 2.1–2.3] for preeclampsia).[30]
- Among 6897 Black and White individuals in the REGARDS cohort who were free from hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg) at baseline, the Southern dietary pattern accounted for 51.6% (95% CI, 18.8%–84.4%) of the excess risk of incident hypertension in Black males compared with White males and 29.2% (95% CI, 13.4%–44.9%) of the risk in Black females compared with White females.[31]
- In NHANES 2013 to 2014, among 766 participants, each additional 1000 mg of usual 24-hour sodium excretion (a marker of sodium consumption) was associated with 4.58–mm Hg (95% CI, 2.64–6.51 mm Hg) higher SBP and 2.25–mm Hg (95% CI, 0.83–3.67 mm Hg) higher DBP. Each additional 1000 mg of potassium excretion was associated with 3.72–mm Hg (95% CI, 1.42–6.01 mm Hg) lower SBP.[32]
- In a meta-analysis of 240 508 individuals enrolled in 6 prospective cohorts, participants with SSB consumption in the highest versus lowest quantile had an RR for hypertension of 1.12 (95% CI, 1.06–1.17).[33] This equated to an 8.2% increased risk for hypertension for each additional SSB consumed per day.
- In a meta-analysis of 5 studies, each additional 250 mL of SSBs per day was associated with an RR for incident hypertension of 1.07 (95% CI, 1.04–1.10).[34]
- 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.[35]
- In a meta-analysis of 24 cohort studies (n=330 222), each 10 additional MET hours per week in leisure-time PA was associated with reduced risk for hypertension (RR, 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).[36]
- 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).[37]
- In the HCHS/SOL Sueño Sleep Ancillary Study of Hispanic people (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 a 7.2% lower prevalence of hypertension.[38]
- In the JHS ancillary sleep study conducted from 2012 to 2016 among 913 participants, those with moderate or severe OSA had a 2-fold higher odds (95% CI, 1.14–3.67) of resistant hypertension than participants without sleep apnea.[39]
- 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]).[40]

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 odds of hypertension (95% CI, 1.55–2.63) observed in lower- compared with higher-educated individuals. Associations were stronger among females and in higher-income countries.[41]
- Data from 2280 Black individuals in the CARDIA study found that moving from highly segregated census tracts to low-segregation tracts, without returning to a high-segregation tract over a 25-year follow-up, was associated with a 5.71–mm Hg lower mean SBP (95% CI, 3.5–8.0 mm Hg), even after adjustment for poverty and other relevant risk factors.[42]
- Self-reported experiences of discrimination and unfair treatment have also been linked to hypertension and BP. In a meta-analysis of 44 studies (n=32 651), higher reports of discrimination were linked to a greater prevalence of hypertension (Fisher z=0.048 [95% CI, 0.013–0.087]), particularly among Black people (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.[43]

- 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 Black people, each additional social contact was associated with a 13% lower prevalence (95% CI, 0.74–1.00) of treatment-resistant hypertension in multivariable-adjusted models.[44]
- In a subsample of 528 females and males 45 to 84 years of age who did not have hypertension at baseline from the Chicago, IL, MESA field center, higher levels of self-reported neighborhood safety were associated with lower levels of SBP (1.54 mm Hg per 1-SD increase [95% CI, 0.25–2.83]) in both sexes and lower levels of DBP (1.24 mm Hg [95% CI, 0.37–2.12]) among females only.[45]

Risk Prediction

- 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, with a pooled C statistic from 35 models in meta-analysis of 0.77 (95% CI, 0.74–0.79).[46]
- Using a total study sample of ≈1.5 million individuals in the Health Information Exchange data set of Maine, which covers ≈95% of Maine residents, the additive regression tree model software XGBoost achieved an AUC of 0.87 for predicting incident hypertension cases in 2015, having been trained on data from 2013 and 2014.[47] This AUC is likely optimistic, given the high probability that the same person could be present in both the training and validation data sets.

Borderline Risk Factors/Subclinical/Unrecognized Disease

- According to data from NHANES 2011 to 2014, among US adults not taking antihypertensive medication, the prevalence of EBP (SBP 120–129 mm Hg, DBP <80 mm Hg) was 12.1% (95% CI, 11.0%–13.3%).[4]
- Among 17 747 participants in NHANES 2007 to 2012 who were 8 to 80 years of age, the yearly net transition probabilities for ideal BP (<90th percentile by age and sex for individuals 8–19 years of age; SBP <120 mm Hg and DBP <80 mm Hg for individuals 20–80 years of age) to prehypertension (90th–95th percentile or SBP ≥120 mm Hg or DBP ≥80 mm Hg for individuals 8–19 years of age; SBP 120–129 mm Hg or DBP 80–89 mm Hg for individuals 20–80 years of age) among African American and White American males were highest from 30 to 40 years of age and highest after 40 years of age among Mexican American males. Yearly net transition probabilities for ideal BP to prehypertension among females increased monotonically from 8 to 80 years of age.[48]

Genetics/Family History

- Genetic studies have been conducted to identify the genetic architecture of hypertension. Several large-scale GWASs, whole-exome, and whole-genome sequencing studies, with interrogation of common and rare variants in >1 million individuals, have established >300 well-replicated hypertension loci, with several hundred additional suggestive loci.[49–58]
- GRSs for hypertension are also associated with increased risk of CVD and MI.[49]
- Given the 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[59,60] and sodium.[61]
- The clinical implications and utility of hypertension genes remain unclear, although some genetic variants have been shown to influence response to antihypertensive agents.[62]

Prevention

- In NHANES 2011 to 2014 (n=10 958), US NH Black people (13.2%) were more likely than NH Asian people (11.0%), NH White people (8.6%), or Hispanic people (7.4%) to use home BP monitoring on a weekly basis.[63]
- Among 6328 participants in the International Childhood Cardiovascular Cohort Consortium, which included 4 cohort studies conducted from as early as 1970 with follow-up as late as 2007, the RR for adult-onset incident hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg, or antihypertensive medication use) ranged from 1.5 to 2.3 among the 4 studies for participants who were overweight or obese in childhood compared with participants who were normal weight in childhood. The pooled RR was 1.8 (95% CI, 1.5–2.1).[64]

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

- On the basis of NHANES 2015 to 2018 data,[5] the extent of awareness, treatment, and control

of HBP is provided by race/ethnicity in Chart 8-3, by age in Chart 8-4, and by race/ethnicity and sex in Chart 8-5. Awareness, treatment, and control of hypertension were higher at older ages (Chart 8-4). In all race/ethnicity groups except NH Asian people, females were more likely than males to be aware of their condition, under treatment, or in control of their hypertension (Chart 8-5).

- Analysis of NHANES 1999 to 2002, 2007 to 2010, and 2015 to 2018[5] found large increases in hypertension awareness, treatment, and control (≈10%) within each race/ethnicity and sex subgroup except for Black females. Among Black females, levels of hypertension awareness, treatment, and control increased between 1999 to 2002 and 2007 to 2010 but decreased between 2007 to 2010 and 2015 to 2018. (Table 8-2).
- In a multinational study of 63 014 adults at least 50 years of age 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.[65]
- In a cohort study of Korean people 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 RR for stroke of 1.27 (95% CI, 1.17–1.38) compared with those with high adherence (>80% of days covered by prescription fill).[66]
- According to 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 ACE inhibitors (from 29 to 105 defined daily doses), angiotensin II receptor blockers (from 13 to 73 defined daily doses), β-blockers (from 17 to 34 defined daily doses), and calcium channel blockers (from 34 to 82 defined daily doses).[67]
- Among 3358 Black people 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]).[68]
- In an analysis of 1590 health care providers who completed the DocStyles survey, a web-based survey of health care providers, 86.3% reported using a prescribing strategy to increase their patients' adherence to antihypertensive medications. 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%).[69]
- 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%.[70]

Mortality (See Table 8-1)

- According to data from the NVSS, in 2018,[71] 95 876 deaths were attributable primarily to HBP (Table 8-1). The 2018 age-adjusted death rate attributable primarily to HBP was 24.0 per 100 000. Age-adjusted death rates attributable to HBP (per 100 000) in 2018 were 24.1 for NH White males, 56.0 for NH Black males, 23.1 for Hispanic males, 17.2 for NH Asian/Pacific Islander males, 32.3 for NH American Indian/Alaska Native males, 19.6 for NH White females, 37.5 for NH Black females, 16.7 for Hispanic females, 14.9 for NH Asian/Pacific Islander females, and 22.5 for NH American Indian/Alaska Native females (unpublished NHLBI tabulation using CDC WONDER[72]).
- From 2008 to 2018, the death rate attributable to HBP increased 27.0%, and the actual number of deaths attributable to HBP rose 57.2%. During this 10-year period, in NH White people, the HBP age-adjusted death rate increased 35.2%, whereas the actual number of deaths attributable to HBP increased 57.4%. In NH Black people, the HBP death rate increased 0.2%, whereas the actual number of deaths attributable to HBP increased 34.6%. In Hispanic people, the HBP death rate increased 21.6%, and the actual number of deaths attributable to HBP increased 106.0% (unpublished NHLBI tabulation using CDC WONDER[72]).
- When any mention of HBP was present, the overall age-adjusted death rate in 2018 was 123.7

per 100 000. Death rates were 137.7 for NH White males, 231.7 for NH Black males, 95.4 for NH Asian or Pacific Islander males, 175.3 for NH American Indian or Alaska Native males (underestimated because of underreporting), and 124.2 for Hispanic males. In females, rates were 101.9 for NH White females, 155.3 for NH Black females, 70.9 for NH Asian or Pacific Islander females, 114.6 for NH American Indian or Alaska Native females (underestimated because of underreporting), and 88.2 for Hispanic females (unpublished NHLBI tabulation using CDC WONDER[72]).

- The elimination of hypertension could reduce CVD mortality by 30.4% among males and 38.0% among females.[73] 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.[73]
- In 3394 participants from the CARDIA study cohort, greater long-term visit-to-visit variability in SBP (eg, variability independent of the mean) from young adulthood through midlife was associated with greater all-cause mortality (HR, 1.24 [95% CI, 1.09–1.41]) during a median follow-up of 20 years.[74]
- 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).[75]
- In a cohort of 63 910 adult participants in the Spanish Ambulatory Blood Pressure Registry conducted from 2004 to 2014, masked hypertension had the largest HR for all-cause mortality versus sustained normotension (2.83 [95% CI, 2.12–3.79]) compared with 1.80 (95% CI, 1.41–2.31) for sustained hypertension and 1.79 (95% CI, 1.38–2.32) for white-coat hypertension.[76]
- In a meta-analysis of 64 000 participants from 27 studies, untreated white-coat hypertension was associated with an increased risk of all-cause (HR, 1.33 [95% CI, 1.07–1.67]) and cardiovascular (2.09 [95% CI, 1.23–4.48]) mortality compared with normotension.[77] There was no evidence of increased risk among those with treated white-coat hypertension.
- In 1034 participants from the JHS completing ambulatory BP monitoring, each 1-SD higher level of mean nighttime SBP (15.5 mm Hg) was associated with all-cause mortality (HR, 1.24 [95% CI, 1.06–1.45]) after multivariable adjustment including clinic BP; however, there were no associations between daytime SBP, daytime DBP, or nighttime DBP and all-cause mortality.[78]

Complications

- 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.[79]
- In a sample of 4851 adults 18 to 30 years of age at baseline from the CARDIA cohort, for those who developed hypertension before 40 years of age, incident CVD rates were 3.15 (95% CI, 2.47–4.02) for those with stage 1 hypertension (untreated SBP 130–139 mm Hg or DBP 80–89 mm Hg) per 1000 person-years and 8.04 (95% CI, 6.45–10.03) for those with stage 2 hypertension (≥140/90 mm Hg or taking antihypertensive medication) per 1000 person-years over the median follow-up of ≈19 years.[80] Over a median follow-up of 18.8 years in 4851 adults from the CARDIA cohort, among those who developed hypertension before 40 years of age, incident CVD rates were 2.74 (95% CI, 1.78–4.20) for those with EBP or prehypertension (untreated SBP 130–139 mm Hg or DBP 80–89 mm Hg) per 1000 person-years compared with 1.37 (95% CI, 1.07–1.75) among those who retained normal BP through 40 years of age.[80]
- Among 27 078 Black and White individuals in the Southern Community Cohort Study, hypertension was associated with an increased risk of HF in the full cohort (HR, 1.69 [95% CI, 1.56–1.84]), with a PAR of 31.8% (95% CI, 27.3%–36.0%).[81]
- 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 no hypertension.[82]
- In a pooled cohort of 12 497 NH Black individuals from the JHS and REGARDS, over a maximum 14.3 years of follow-up, the multivariable-adjusted HR associated with hypertension (compared with normotension) was almost 2-fold higher (HR, 1.91 [95% CI, 1.48–2.46]) for composite incident CVD and was 2.41 (95% CI, 1.59–3.66) for incident CHD, 2.20 (95% CI, 1.44–3.36) for incident stroke, and 1.52 (95% CI, 1.01–2.30) for incident HF.[83] The PAR associated with hypertension was 32.5% (95% CI, 20.5%–43.6%) for composite incident CVD, 42.7% (95% CI, 24.0%–58.4%) for incident CHD, 38.9% (95% CI, 19.4%–55.6%) for incident stroke, and 21.6% (95% CI, 0.6%–40.8%)

for incident HF. For composite CVD, the PAR for hypertension was 54.6% (95% CI, 37.2%–68.7%) among NH people <60 years of age but significantly lower, at 32% (95% CI, 11.9%–48.1%), among NH Black people ≥60 years of age.

- Among 17 312 participants with hypertension, nondipping BP was associated with an HR for CVD of 1.40 (95% CI, 1.20–1.63).[84]
- In the JHS cohort of NH Black people, masked hypertension was associated with an HR for CVD of 2.49 (95% CI, 1.26–4.93).[85] In 1034 participants from the JHS completing ambulatory BP monitoring, each 1-SD higher level of mean daytime SBP (13.5 mm Hg) was also associated with an increased incidence of CVD events (HR, 1.53 [95% CI, 1.24–1.88]) after multivariable adjustment that included clinic BP. Adjusted findings were similar for nighttime SBP (HR, 1.48 [95% CI, 1.22–1.80]) per 15.5 mm Hg, daytime DBP (HR, 1.25 [95% CI, 1.02–1.51]) per 9.3 mm Hg, and nighttime DBP (HR, 1.30 [95% CI, 1.06–1.59]) per 9.5 mm Hg.[78]
- A meta-analysis (23 cohorts with 20 445 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]).[86]
- 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 eGFR or ESRD (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]).[8]
- In an international case-control study (n=13 447 cases of stroke and n=13 472 control subjects), a 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%.[87]
- Among adults 45 years of age without HF, HF-free survival was shorter among those with versus those without hypertension in males (30.4 years versus 34.3 years), females (33.5 years versus 37.6 years), Black people (33.2 years versus 37.3 years), and White people (31.9 years versus 36.3 years).[88]
- In a prospective follow-up of the REGARDS, MESA, and JHS cohorts (n=31 856), 63.0% (95% CI, 54.9%–71.1%) of the 2584 incident CVD events occurred in participants with SBP <140 mm Hg and DBP <90 mm Hg.[89]
- Higher SBP explains ≈50% of the excess stroke risk among Black individuals compared with White individuals.[90]

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

- Beginning in 2016, a code for hypertensive crisis (*ICD-10-CM* I16) was added to the HCUP inpatient database. For 2016, hypertensive crisis is included in the total number of inpatient hospital stays for HBP. From 2006 to 2016, the number of inpatient discharges from short-stay hospitals with HBP as the principal diagnosis increased from 292 000 to 486 000. The number of discharges with any listing of HBP increased from 13 851 000 to 16 676 000 (Table 8-1).
- In 2016, there were 63 000 principal diagnosis discharges for essential hypertension (HCUP,[91] unpublished NHLBI tabulation).
- In 2016, there were 11 612 000 all-listed discharges for essential hypertension (HCUP,[91] unpublished NHLBI tabulation).
- In 2016, 32 779 000 of 883 725 000 physician office visits had a primary diagnosis of essential hypertension (*ICD-9-CM* 401; NAMCS,[92] unpublished NHLBI tabulation). A total of 1 016 000 of 145 591 000 ED visits in 2016 and 3 743 000 of 125 721 000 hospital outpatient visits in 2011 were for essential hypertension (NHAMCS,[93] unpublished NHLBI tabulation).
- 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%), or hypertension but no apparent treatment-resistant hypertension (71.8%).[94]

Cost (See Table 8-1)

- The estimated direct and indirect cost of HBP for 2016 to 2017 (annual average) was $52.4 billion (Table 8-1).
- Estimated US health care expenditures for hypertension in 2016 were $79 billion (95% CI, $72.6–$86.8 billion). Of 154 health conditions, hypertension ranked 10th in health care expenditures.[95]

- From 2003 to 2014, the annual mean additional medical cost for a person with hypertension was $1920 compared with a person without hypertension, according to data from MEPS.[96]
- According to data from MEPS for 2011 to 2014, among individuals 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.[97]
- 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.[98]

Global Burden (See Chart 8-6)

- In 2019, HBP was 1 of the 5 leading risk factors for the burden of disease (YLL and DALYs) in all regions with the exception of Oceania and eastern, central, and western sub-Saharan Africa.[99]
- In a meta-analysis of population-studies conducted in Africa, the prevalence of hypertension was 55.2% among adults ≥55 years of age.[100]
- 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 those developed in low- and middle-income countries (63.5% versus 10%).[101]
- From 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- and 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).[102]
- The GBD 2019 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 369 diseases and injuries and 87 risk factors in 204 countries and territories. Age-standardized mortality rates attributable to high SBP are generally lower in high-income countries (Chart 8-6).[99]
- 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.[103] In addition, 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, 874 million had SBP ≥140 mm Hg.[103]
- It has been estimated that 7.834 million deaths and 143.037 million DALYs in 2015 could be attributed to SBP ≥140 mm Hg.[103] 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.[103]
- 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 increase in high- and middle-income (from 1.288 to 2.176 million deaths), middle-income (from 1.044 to 2.253 million deaths), low- and middle-income (from 0.512 to 1.151 million deaths), and low-income (from 0.146 to 0.293 million deaths) countries.[103]
- Among ≈1.7 million participants from the Chinese mainland 35 to 75 years of age from 2014 to 2017, the age- and sex-standardized prevalence of hypertension was 37.2%.[104]
- In a meta-analysis of 25 studies (n=54 196 participants 2–19 years of age) 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.[105]
- Among 12 971 Turkish adults who completed the Chronic Diseases and Risk Factors Survey, a nationwide study, the age-adjusted 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.[106]

Table 8-1. HBP in the United States

Population group	Prevalence, 2015–2018, age ≥20 y	Mortality,* 2018, all ages	Hospital discharges,† 2016, all ages	Estimated cost, 2016–2017
Both sexes	121 500 000 (47.3%) (95% CI, 45.4%–49.2%)	95 876	486 000	$52.4 Billion
Males	63 100 000 (51.7%)	46 124 (48.1%)‡	246 000	…
Females	58 400 000 (42.8%)	49 752 (51.9%)‡	240 000	…
NH White males	51.0%	31 094	…	…
NH White females	40.5%	35 763	…	…
NH Black males	58.3%	9249	…	…
NH Black females	57.6%	8546	…	…
Hispanic males	50.6%	3764	…	…
Hispanic females	40.8%	3373	…	…
NH Asian males	51.0%	1389§	…	…
NH Asian females	42.1%	1629§	…	…
NH American Indian/Alaska Native	…	671	…	…

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 (SBP) was ≥130 mm Hg or diastolic blood pressure (DBP) 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.[4] The number of US adults with hypertension in this table includes both noninstitutionalized and institutionalized US individuals. In addition, 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 (SBP was ≥130 mm Hg or DBP was ≥80 mm Hg or if the subject said "yes" to taking antihypertensive medication). CIs have been added for overall prevalence estimates in key chapters. CIs have not been included in this table for all subcategories of prevalence for ease of reading.

Ellipses (…) indicate data not available; HBP, high blood pressure; 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.

†Beginning in 2016, a code for hypertensive crisis (International Classification of Diseases, 10th Revision, Clinical Modification I16) was added to the Healthcare Cost and Utilization Project (HCUP) inpatient database and is included in the total number of hospital discharges for HBP.

‡These percentages represent the portion of total HBP mortality that is for males vs females.

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

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES (2015–2018).[5] Percentages for racial/ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2018 US population estimates. Mortality: Unpublished NHLBI tabulation using National Vital Statistics System, 2018.[71] These data represent underlying cause of death only. Mortality for NH Asian people includes Pacific Islander people. Hospital discharges: Unpublished NHLBI tabulation using HCUP 2016.[91] Cost: Unpublished NHLBI tabulation using Medical Expenditure Panel Survey[107]; include estimated direct costs for 2016 to 2017 (annual average) and indirect costs calculated by NHLBI for 2016 to 2017 (annual average).

Table 8-2. Hypertension Awareness, Treatment, and Control: NHANES 1999 to 2002, 2007 to 2010, and 2015 to 2018 Age-Adjusted Percent With Hypertension in US Adults by Sex and Race/Ethnicity

	Awareness, %			Treatment, %			Control, %		
	1999–2002	2007–2010	2015–2018	1999–2002	2007–2010	2015–2018	1999–2002	2007–2010	2015–2018
Overall	48.9	61.2	61.2	37.7	52.5	50.4	12.0	24.1	21.6
NH White males	42.7	58.0	60.3	31.4	48.7	45.9	10.9	22.2	20.2
NH White females	56.7	66.1	64.8	45.9	59.2	57.7	14.8	28.7	25.4
NH Black males	46.0	60.5	63.1	33.0	47.6	48.7	9.1	18.2	15.8
NH Black females	67.7	73.5	70.1	54.9	64.3	60.9	16.4	28.2	22.8
Mexican American males*	25.9	40.6	41.9	14.0	30.5	30.3	4.1	12.7	13.3
Mexican American females*	50.4	55.6	55.8	35.4	49.3	47.8	10.4	21.2	20.7

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 (SBP) was ≥130 mm Hg or diastolic blood pressure (DBP) was ≥80 mm Hg or if the subject said "yes" to taking antihypertensive medication. Controlled hypertension is considered SBP <130 mm Hg or DBP <80 mm Hg. Total includes race/ethnicity groups not shown (other Hispanic, other race, and multiracial).

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

*The category of Mexican American people was consistently collected in all NHANES years, but the combined category of Hispanic people was only used starting in 2007. Consequently, for long-term trend data, the category of Mexican American people is used. Total includes race/ethnicity groups not shown (other Hispanic, other race, and multiracial).

Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES (1999–2002, 2007–2010, 2015–2018).[5]

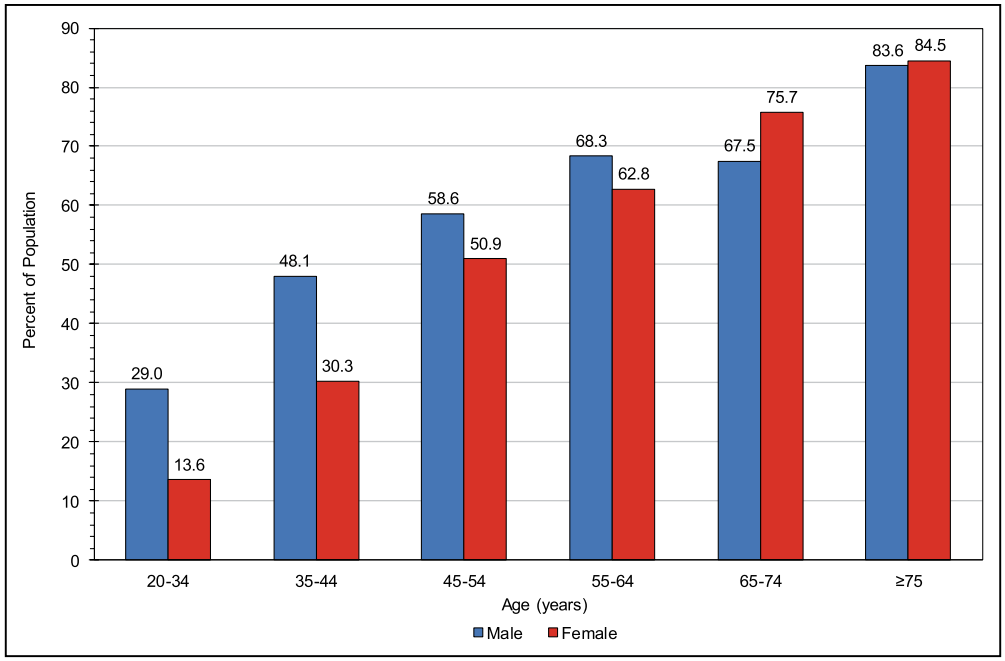

Chart 8-1. Prevalence of hypertension in US adults ≥20 years of age by sex and age (NHANES, 2015–2018).
Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A person was considered to have hypertension if he or she had systolic blood pressure ≥130 mm Hg or diastolic 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: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2015 to 2018.[5]

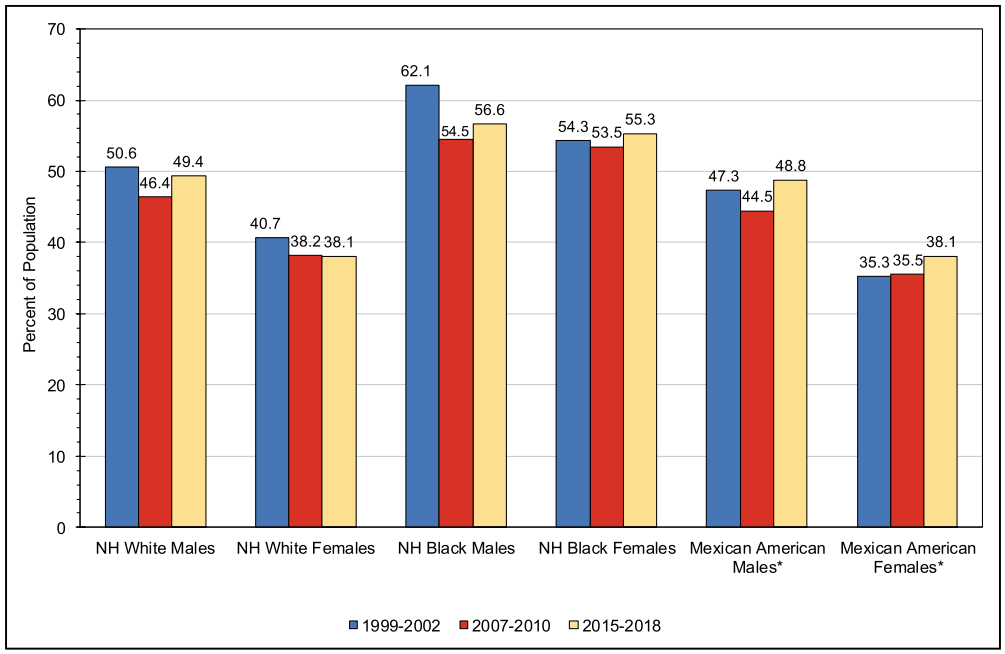

Chart 8-2. Age-adjusted prevalence trends for hypertension in US adults ≥20 years of age by race/ethnicity, sex, and survey year (NHANES, 1999–2002, 2007–2010, and 2015–2018).
Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A person was considered to have hypertension if he or she had systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg or if he or she said "yes" to taking antihypertensive medication.
NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
*The category of Mexican American people was consistently collected in all NHANES years, but the combined category of Hispanic people was used only starting in 2007. Consequently, for long-term trend data, the category of Mexican American people is used.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 1999 to 2018.[5]

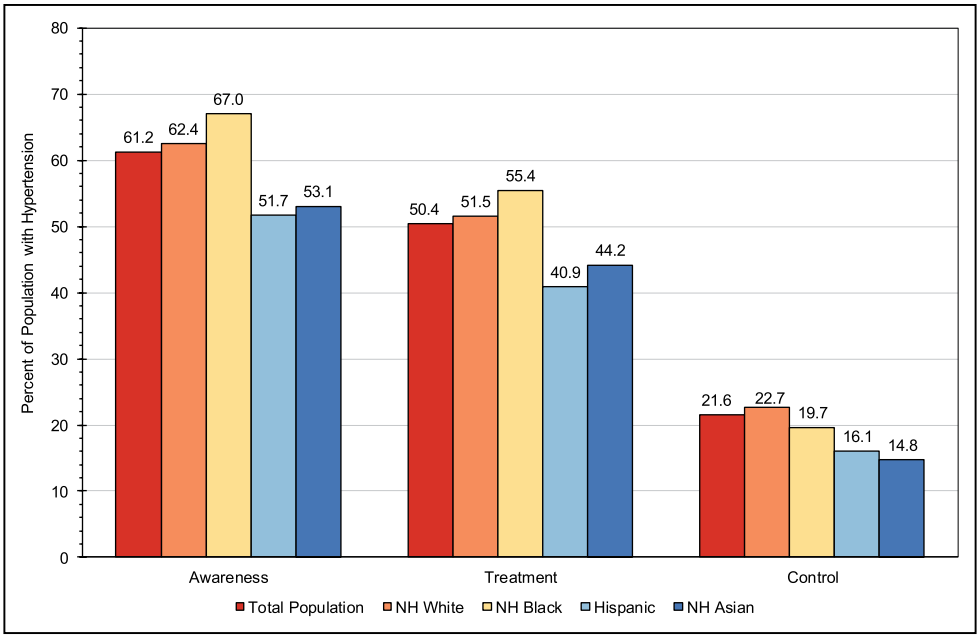

Chart 8-3. Extent of awareness, treatment, and control of high blood pressure by race/ethnicity, United States (NHANES, 2015–2018).
Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A person was considered to have hypertension if he or she had systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg or if he or she said "yes" to taking antihypertensive medication.
NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES 2015 to 2018.[5]

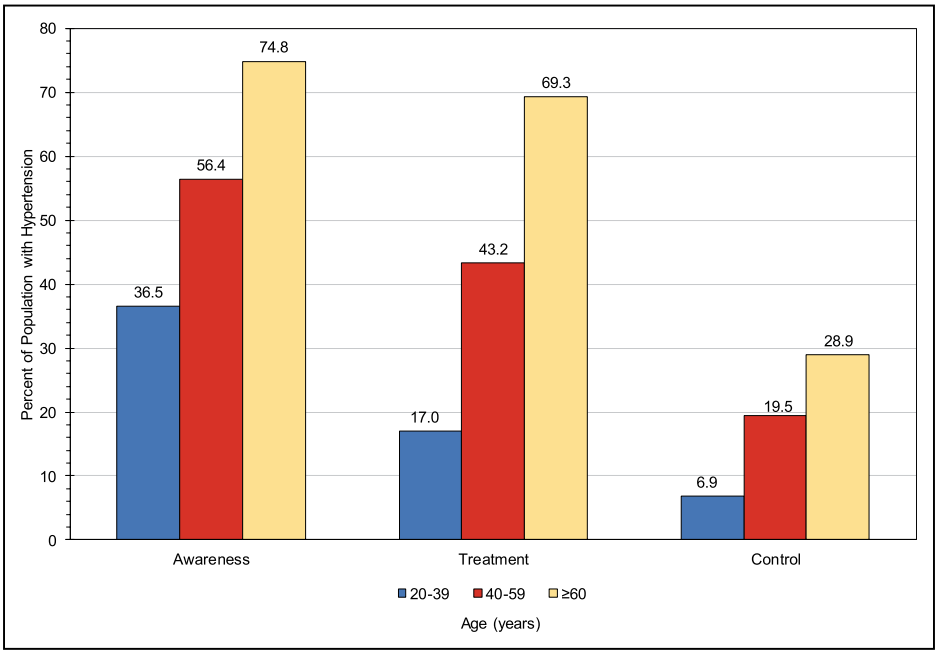

Chart 8-4. Extent of awareness, treatment, and control of high blood pressure by age, United States (NHANES, 2015–2018).
Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A person was considered to have hypertension if he or she had systolic blood pressure≥130 mm Hg or diastolic blood pressure ≥80 mm Hg or if he or she said "yes" to taking antihypertensive medication.
NHANES indicates National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES 2015 to 2018.[5]

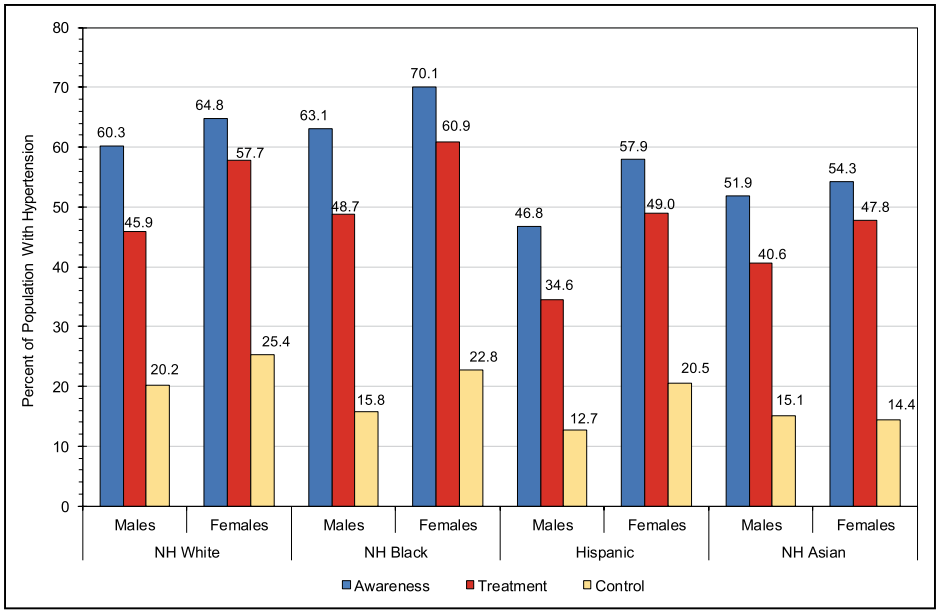

Chart 8-5. Extent of awareness, treatment, and control of high blood pressure by race/ethnicity and sex, United States (NHANES, 2015–2018).
Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A person was considered to have hypertension if he or she had systolic blood pressure≥130 mm Hg or diastolic blood pressure ≥80 mm Hg or if he or she said "yes" to taking antihypertensive medication.
NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2015 to 2018.[5]

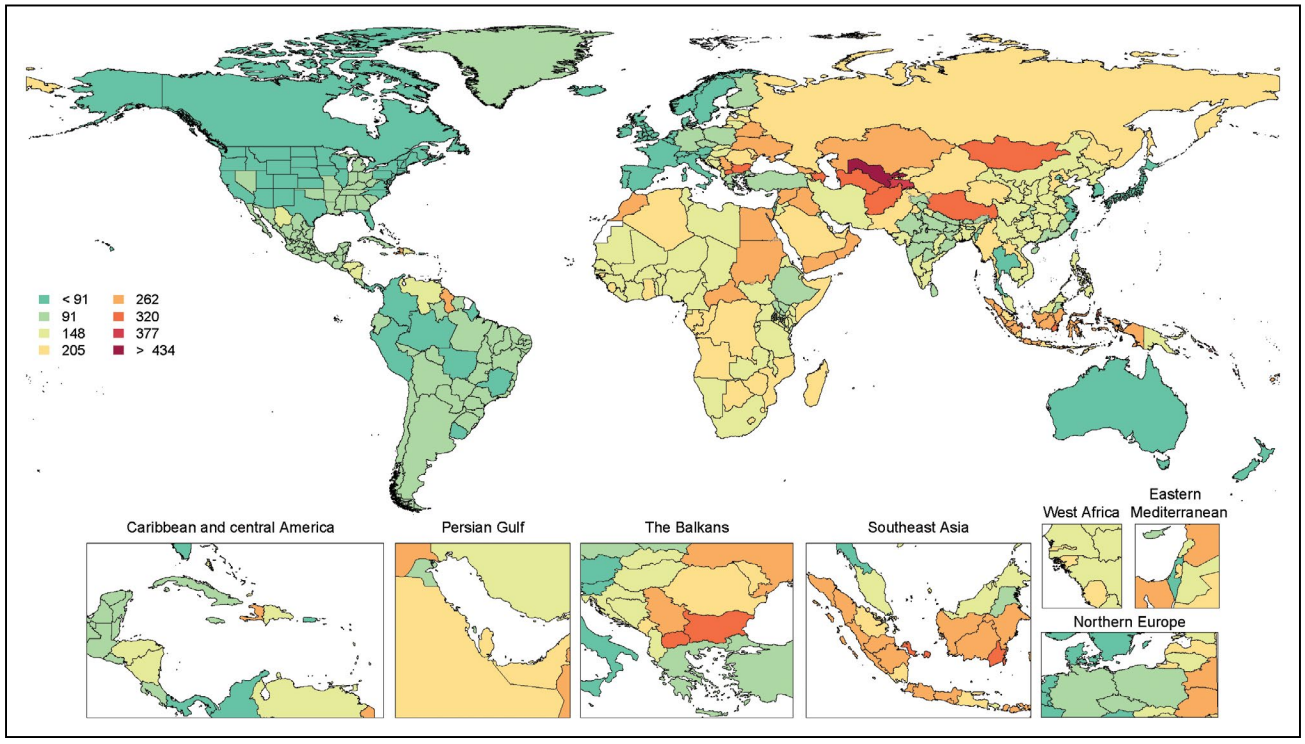

Chart 8-6. Age-standardized global mortality rates attributable to high systolic blood pressure per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[99] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[108]

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9. DIABETES

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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Diabetes is a heterogeneous mix of health conditions characterized by glucose dysregulation. In the United States, the most common forms are type 2 diabetes, which affects 90% to 95% of those with diabetes,[1] and type 1 diabetes, which constitutes 5% to 10% of diabetes.[2] Diabetes is diagnosed on the basis of FPG ≥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%.[3] Diabetes is a major risk factor for CVD, including CHD and stroke.[4] The AHA has identified untreated FPG levels of <100 mg/dL for children and adults as 1 of the 7 components of ideal CVH.[5]

Abbreviations Used in Chapter 9

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACR	albumin-to-creatinine ratio
ACS	acute coronary syndrome
AF	atrial fibrillation
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities study
ASCVD	atherosclerotic cardiovascular disease
AUC	area under the curve
BMI	body mass index
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CAC	coronary artery calcification
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research
CHD	coronary heart disease
CI	confidence interval

(*Continued*)

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Abbreviations Used in Chapter 9 Continued

CKD	chronic kidney disease
CVD	cardiovascular disease
CVH	cardiovascular health
DCCT/EDIC	Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications
ED	emergency department
eGFR	estimated glomerular filtration rate
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
FHS	Framingham Heart Study
FPG	fasting plasma glucose
GBD	Global Burden of Disease Study
GRS	genetic risk score
GWAS	genome-wide association study
GWTG	Get With The Guidelines
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
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-10	*International Classification of Diseases, 10th Revision*
IDF	International Diabetes Federation
IHD	ischemic heart disease
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
IRR	incidence rate ratio
JHS	Jackson Heart Study
KDIGO	Kidney Disease: Improving Global Outcomes
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
MI	myocardial infarction
NEDS	Nationwide Emergency Department Sample
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NHS	Nurses' Health Study
NIS	National (Nationwide) Inpatient Sample
NVSS	National Vital Statistics System
OR	odds ratio
PA	physical activity

(*Continued*)

Abbreviations Used in Chapter 9 Continued

PAF	population attributable fraction
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
SSB	sugar-sweetened beverage
TC	total cholesterol
TECOS	Trial Evaluating Cardiovascular Outcomes with Sitagliptin
TIMI	Thrombolysis in Myocardial Infarction
TODAY	Treatment Options for Type 2 Diabetes in Adolescents and Youth
UI	uncertainty interval
USRDS	United States Renal Data System
WC	waist circumference
WHI	Women's Health Initiative

Prevalence

Youth

- Approximately 210 000 people <20 years of age were diagnosed with diabetes in 2018, of whom 187 000 had type 1 diabetes.[6]
- During 2001 to 2009, the prevalence of type 1 diabetes increased 30% (1.48 per 1000 youths in 2001 to 1.93 per 1000 youths in 2009) and the prevalence of type 2 diabetes increased 30.5% (0.34 per 1000 youths in 2001 to 0.46 per 1000 youths in 2009).[7]
  - Among youths with type 1 diabetes in 2001 to 2004, 22.1% were overweight and 12.6% were obese.[8]
  - Among youths with type 2 diabetes in 2001 to 2004, 10.4% were overweight and 79.4% were obese.[8]
- Among US adolescents 12 to 19 years of age in 2005 to 2014, the prevalence of diabetes was 0.8% (95% CI, 0.6%–1.1%). Of those with diabetes, 28.5% (95% CI, 16.4%–44.8%) were undiagnosed.[9]
- Among US adolescents 12 to 18 years of age in 2005 to 2016, the prevalence of prediabetes was 18.0% (95% CI, 16.0%–20.1%). Adolescent males were more likely to have prediabetes than adolescent females (22.5% [95% CI, 19.8%–25.4%] versus 13.4% [95% CI, 10.8%–16.5%]).[10]

Adults (See Table 9-1 and Charts 9-1 through 9-3)

- Among adults ≥18 years of age in the NHIS 2016, the crude prevalence of type 1 diabetes, type 2 diabetes, and other unspecified diabetes was 0.55%, 8.58%, and 0.31%, respectively.[11]
- On the basis of data from NHANES 2013 to 2016,[12] an estimated 26 million adults (9.8%) had diagnosed diabetes, 9.4 million adults (3.7%) had undiagnosed diabetes, and 91.8 million adults (37.6%) had prediabetes.
- After adjustment for population age differences, NHANES 2013 to 2016[12] data for people ≥20 years of age indicate that the prevalence of diagnosed diabetes varied by race and sex and was highest in Hispanic males (Table 9-1 and Chart 9-1).
- On the basis of 2017 data from the US Indian Health Service, the age-adjusted prevalence of diagnosed diabetes among American Indian/Alaska Native people was 14.5% for males and 14.8% for females.[6]
- On the basis of NHANES 2013 to 2016[12] data, the age-adjusted prevalence of diagnosed diabetes 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).
- Among US adults ≥20 years of age in NHANES 2011 to 2016, the prevalence of diabetes varied within racial/ethnic subgroups. Among Hispanic subgroups, the prevalence was highest for Mexican adults (24.6%) and lowest for South American adults (12.3%). Among Asian subgroups, the prevalence was highest for South Asian adults (23.3%) and lowest for East Asian adults (14.0%).[13]
- According to NHANES 2011 to 2014 data, NH Black (OR, 2.53 [95% CI, 1.71–3.73]), Asian (OR, 6.16 [95% CI, 3.76–10.08]), and Hispanic (OR, 1.88 [95% CI, 1.19–2.99]) people were more likely to have undiagnosed diabetes than NH White people.[14]
- Geographic variations in diabetes prevalence have been reported in the United States.
  - From state-level data from BRFSS[15] 2018, West Virginia had the highest age-adjusted prevalence of diagnosed diabetes (13.5%) and Colorado had the lowest prevalence (6.6%). The age-adjusted prevalence of diagnosed diabetes was highest in the US territory of Guam (15.3%; Chart 9-3).
  - According to data from the REGARDS study, the median (range) predicted prevalence of diabetes was 14% (10% to 20%) among White individuals and 31% (28% to 41%) among Black individuals.[16] Diabetes was most prevalent in the west and central Southeast among White individuals (Louisiana, Arkansas, Mississippi, Alabama, Tennessee, and southern Kentucky, as well as parts of North Carolina and South Carolina).

Incidence

Youth

- During 2014 to 2015, an estimated 18 291 people <20 years of age in the United States were diagnosed with incident type 1 diabetes, and 5758 individuals 10 to 19 years of age were newly diagnosed with type 2 diabetes annually.[6]
- In the SEARCH study in 2014 to 2015, the incidence rate (per 100 000) of type 1 diabetes and type 2 diabetes was 22.3 (95% CI, 21.0–23.6) and 13.8 (95% CI, 12.4–15.3), respectively.[17]
  - For type 1 diabetes, the incidence rate (per 100 000) was 6.2 (95% CI, 3.0–12.9) for American Indian youth, 9.4 (95% CI, 6.6–13.3) for Asian or Pacific Islander youth, 20.8 (95% CI, 17.7–24.4) for Black youth, 16.3 (95% CI, 14.1–18.8) for Hispanic youth, and 27.3 (95% CI, 25.5–29.3) for White youth.[17]
  - For type 2 diabetes, the incidence rate (per 100 000) was 32.8 (95% CI, 20.8–51.6) for American Indian youth, 11.9 (95% CI, 7.8–18.3) for Asian or Pacific Islander youth, 37.8 (95% CI, 31.9–44.7) for Black youth, 20.9 (95% CI, 17.4–24.9) for Hispanic youth, and 4.5 (95% CI, 3.5–5.7) for White youth.[17]

Adults (See Table 9-1)

- Approximately 1.5 million US adults ≥18 years of age were diagnosed with incident diabetes in 2018 (Table 9-1).[6]
- During 2017 to 2018, the age-adjusted incidence rate of diagnosed diabetes (per 1000) was 9.7 (95% CI, 6.7–14.0) for Hispanic adults, 8.2 (95% CI, 6.0–11.0) for NH Black adults, 7.4 (95% CI, 4.9–10.9) for Asian adults, and 5.0 (95% CI, 4.3–5.8) for NH White adults.[6]
- During 2017 to 2018, adults with less than high school education had a higher age-adjusted incidence rate for diagnosed diabetes (11.5 per 1000 [95% CI, 8.3–15.9]) than adults with a high school education (6.0 per 1000 [95% CI, 4.8–7.5]) or more than high school education (5.6 per 1000 [95% CI, 4.7–6.7]).[6]

Secular Trends (See Charts 9-4 through 9-5)

- In the SEARCH study, the incidence rate of type 1 diabetes increased by 1.9% annually (from 19.5 to 22.3 cases per 100 000 youths from 2002–2015) and the incidence of type 2 diabetes increased by 4.8% annually (from 9.0–13.8 cases per 100 000 youths from 2002–2015).[17]
  - The annual increase in diabetes varied by race/ethnicity. For type 1 diabetes, the annual percent change was 2.7% for Black youth, 4.0% for Hispanic youth, 4.4% for Asian or Pacific Islander youth, and 0.7% for White youth. For type 2 diabetes, the annual percent change was 6.0% for Black youth, 6.5% for Hispanic youth, 3.7% for American Indian youth, 7.7% for Asian or Pacific Islander youth, and 0.8% for White youth.[17]
- The age-adjusted prevalence of diagnosed diabetes in adults ≥18 years of age increased from 6.4% (95% CI, 5.8%–7.0%) in 1999 to 2002 to 9.4% (95% CI, 8.6%–10.2%) in 2013 to 2016. In contrast, the age-adjusted prevalence of undiagnosed diabetes was similar from 1999 to 2002 (3.1% [95% CI, 2.6%–3.7%]) and 2013 to 2016 (2.6% [95% CI, 2.2–3.1]) (Chart 9-4).[6]
- The prevalence of diagnosed diabetes in adults was higher for both males and females in the NHANES 2013 to 2016 data than in the NHANES 1988 to 1994 data. Males had a higher prevalence of both diagnosed diabetes and undiagnosed diabetes than females in 2013 to 2016. Prevalence of diagnosed and undiagnosed diabetes increased for both males and females between study periods (Chart 9-5). During this time period, 2 diagnostic changes occurred: The threshold definition for diagnosed diabetes was lowered from ≥140 to ≥126 mg/dL in 1997,[18] and HbA_{1c} ≥6.5% was added as a diagnostic test in 2010.[3]
- The prevalence of prediabetes has been stable among US adults ≥18 years of age. The age-adjusted prevalence of prediabetes was 33.6% in 2005 to 2008 and 33.3% in 2013 to 2016.[6]

Risk Factors

- In a meta-analysis of 76 513 individuals from 16 studies, progression from prediabetes to diabetes was 23.7 per 1000 person-years for FPG 100 to 125 mg/dL, 43.8 per 1000 person-years for 2-hour postchallenge glucose 140 to 199 mg/dL, and 45.2 per 1000 person-years for HbA_{1c} 5.7 to 6.4%.[19]
- In MESA, the incidence rate of diabetes per 1000 person-years associated with having 0, 1, 2, 3, 4, and 5 to 6 ideal CVH factors (TC, BP, dietary intake, tobacco use, PA, and BMI) was 21.8, 18.6, 13.0, 11.2, 4.7, and 3.6, respectively.[20] Lower diabetes risk was associated with more ideal CVH factors for Asian, Hispanic, NH Black, and NH White people.
- In CARDIA, Black males and females were more likely to develop diabetes than White males and females (for males: HR, 1.67 [95% CI, 1.28–2.17]; for females: HR, 2.86 [95% CI, 2.19–3.72]) in sex-stratified analyses. Adjustment for FPG, BMI, WC, SBP, use of antihypertensive medications, ratio of

triglycerides to HDL-C, and parental history of diabetes explained the higher incidence of diabetes observed for Black adults compared with White adults over 30 years of follow-up.[21]

- In the WHI, the risk of diabetes varied by metabolic status. Compared with females who were metabolically healthy and normal weight, the risk of diabetes was increased among those who were metabolically unhealthy and obese (HR, 4.51 [95% CI, 3.82–5.35]), those who were metabolically unhealthy and normal weight (HR, 2.24 [95% CI, 1.74–2.88]), and those who were metabolically healthy and obese (HR, 1.68 [95% CI, 1.40–2.00]).[22]
- In JHS, the risk of diabetes was increased for adults with obesity who were insulin resistant (IRR, 2.35 [95% CI, 1.53–3.60]), for adults without obesity who were insulin resistant (IRR, 1.59 [95% CI, 1.02–2.46]), and for adults with obesity who were insulin sensitive (IRR, 1.70 [95% CI, 0.97–2.99]) compared with those without obesity and who were insulin sensitive.[23]
- In a meta-analysis, each 1-SD higher BMI in childhood was associated with an increased risk for developing diabetes 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 children 7–11 years of age; and 1.70 [95% CI, 1.30–2.22] for those 12–18 years of age).[24]
- Compared with birth weight of 3.63 to 4.5 kg, low birth weight (<2.72 kg) increased the risk of type 2 diabetes (OR, 2.15 [95% CI, 1.54–3.00]), with 47% of this association mediated by insulin resistance.[25]
- Of the 20.9 million new cases of diabetes predicted to occur over 10 years in the United States, 1.8 million could be attributable to consumption of SSBs. A meta-analysis showed that each 1–serving per day higher consumption of SSBs was associated with an 18% increased risk for diabetes.[26]
- In a meta-analysis, 600 to 3999, 4000 to 7999, and ≥8000 MET minutes per week of PA versus <600 MET minutes per week was associated with a decreased risk for developing diabetes 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.[27]
- Systematic reviews have found an association between sedentary time and diabetes even after adjustment for PA.[28,29] For example, Biswas et al[28] analyzed 5 studies and found that higher sedentary time was associated with elevated risk of diabetes (RR, 1.91 [95% CI, 1.64–2.22]).
- In NHANES 2007 to 2014, the prevalence of gestational diabetes was 7.6%, with 19.7% having a subsequent diagnosis of diabetes. Age-standardized prevalence of gestational diabetes was highest among Hispanic females (9.3%) and lower among NH White females (7.0%) and NH Black females (6.9%).[30]
- In the NHS II, the risk of diabetes was increased for females with a history of gestational hypertension (HR, 1.65 [95% CI, 1.42–1.91]) or preeclampsia (HR, 1.75 [95% CI, 1.58–1.93]) during first pregnancy compared with females with normotension.[31]

Risk Prediction

- Several risk prediction algorithms for type 2 diabetes have been developed.[32–35] In 2017, an updated version of the QDiabetes risk prediction algorithm was published, with C statistics between 0.81 and 0.89.[36]
- Risk prediction algorithms for CVD among individuals with diabetes have also been developed.[37,38] A meta-analysis found an overall pooled C statistic of 0.67 for 15 algorithms developed in populations with diabetes and 0.64 for 11 algorithms originally developed in a general population.[38]
- The TIMI risk score for CVD events performed moderately well among adults with type 2 diabetes and high CVD risk. The C statistic was 0.71 (95% CI, 0.69–0.73) for CVD death and 0.66 (95% CI, 0.64–0.67) for a composite end point of CVD death, MI, or stroke.[39]

Family History and Genetics

- Diabetes is heritable; twin or family studies have demonstrated a range of heritability estimates from 30% to 70%, depending on age at onset.[40,41] In the FHS, having a parent or sibling with diabetes conferred a 3.4 times increased risk of diabetes, which increased to 6.1 if both parents were affected.[42] In Danish registries, there was a greater risk of diabetes if the affected parent was a mother versus a father.[43] On the basis of data from NHANES 2009 to 2014, individuals with diabetes had an adjusted prevalence ratio for family history of diabetes of 4.27 (95% CI, 3.57–5.12) compared with individuals without diabetes or prediabetes.[44]
- There are monogenic forms of diabetes such as maturity-onset diabetes of the young and latent autoimmune diabetes in adults. In the TODAY study of overweight and obese children and adolescents with type 2 diabetes, 4.5% of individuals were found to have monogenic diabetes.[45] Genetic testing can be considered if maturity-onset diabetes is suspected and can guide management and screening of family members.

- The majority of diabetes is a complex disease characterized by multiple genetic variants with gene-gene and gene-environment interactions. Genome-wide genetic studies of common diabetes conducted in large sample sizes through meta-analyses have identified >100 genetic variants associated with diabetes, with the most consistent being a common intronic variant in the *TCF7L2* (transcription factor 7 like 2) gene.[46–49] Several of these variants have also been associated with gestational diabetes.[50]
- Other risk loci for diabetes identified from GWASs include variants in the *SLC30A8* and *HHEX* genes (related to β-cell development or function) and in the *NAT2* (N-acetyltransferase 2) gene, associated with insulin sensitivity.[48,51]
- Genetic studies in non-European ethnicities have also identified significant risk loci for diabetes, including variants in the *KCNQ1* gene (identified from a GWAS in Japanese individuals and replicated in other ethnicities),[48,52] a variant in the *G6PD* gene,[53] and a rare variant in the *HBB* gene[54] associated with hemoglobin in individuals of African descent, as well as a locus in the *ZRANB3* gene associated with diabetes found in sub-Saharan African individuals.[55] 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* gene (specific to European ancestry).[46,47]
- Lifestyle appears to overcome risk conferred by a GRS composed of a combination of these common variants. In a study of the UK Biobank, genetic composition and combined health behaviors had a log-additive effect on the risk of developing diabetes, but ideal lifestyle returned the risk of incident diabetes toward the referent (low genetic risk) group in both the intermediate- and high-genetic-risk groups.[56]
- Genetic variants associated with traits that are risk factors for diabetes have themselves been shown to be associated with diabetes. For example, in a genome-wide study in the UK Biobank, polygenic risk scores associated with body fat distribution were associated with a higher risk of diabetes.[57] However, the utility of clinical genetic testing for common type 2 diabetes is currently unclear.
- In the ACCORD trial, 2 genetic markers were identified with excess CVD mortality in the intensive treatment arm. A polygenic risk score has been developed that includes these genetic markers and was found to be associated with the effect of intensive glycemic treatment of cardiovascular outcomes.[58]
- Although most variants identified from GWASs are common, genes that harbor rare variants associated with common diabetes have also been identified.[59] These include rare loss-of-function variants in the *SLC30A8* gene that protect against diabetes risk,[59] with carriers having a 65% lower risk,[60] as well as a variant in the *CCND2* gene (encoding a protein that helps regulate the cell cycle) that reduces the risk of diabetes by half[61] and variants in the *ANGPTL4* gene associated with reduced diabetes risk.[62]
- Type 1 diabetes 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.[63] More recent studies have identified additional genes associated with type 1 diabetes risk.[64]
- A GRS composed of 9 type 1 diabetes–associated risk variants has been shown to be able to discriminate type 1 diabetes from type 2 diabetes (AUC 0.87), which could be clinically useful given the increasing prevalence of obesity in young adults.[65]
- Shared genetic architectures of diabetes-related diseases may exist. For example, there are shared genes between polycystic ovarian syndrome and diabetes; another study found that a diabetes-associated GRS was also associated with FPG levels in pregnancy[66]; and a GWAS in latent autoimmune diabetes in adults found overlap of many genetic signals with type 1 and type 2 diabetes.[67]
- The risk of complications from diabetes 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.[68] Genetic variants have also been identified that increase risk of CAD or dyslipidemia in patients with diabetes[69,70] and that are associated with end-organ complications in diabetes (retinopathy,[71] nephropathy,[72] and neuropathy[73]).

Prevention

- Among adults without diabetes in NHANES 2007 to 2012, 37.8% met the moderate-intensity PA goal of ≥150 min/wk and 58.6% met the weight loss or maintenance goal for diabetes prevention. Adults with prediabetes were less likely to meet the PA and weight goals than adults with normal glucose levels.[74]
- In NHANES 2011 to 2014 data, among adults with prediabetes, 36.6% had hypertension, 51.2% had dyslipidemia, 24.3% smoked, 7.7% had albuminuria, and 4.6% had reduced eGFR.[75]
- 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 diabetes 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.[76]

Awareness, Treatment, and Control (See Chart 9-6)

- In 2013 to 2016, the awareness of prediabetes was low, with only 13.3% of adults with prediabetes reporting being told that they had prediabetes by a health care professional.[6]
- On the basis of NHANES 2013 to 2016 data for adults with diabetes, 20.9% had their diabetes treated and controlled (Chart 9-6).
- 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 having no risk factors at goal.[77]
- Among adults with diagnosed diabetes in NHANES 2013 to 2016, 9.9% had an HbA_{1c} ≥10.0% and this was more prevalent among adults 18 to 44 years of age (16.3% [95% CI, 10.8%–23.9%]) than adults ≥65 years of age (4.3% [95% CI, 2.9%–6.5%]).[6]
- In NHANES 2013 to 2016, 13.2% of adults 40 to 75 years of age with diagnosed diabetes used statins.[6]
- In NHANES 2011 to 2016, 50.4% of adults with diabetes who were taking antihypertensive medications did not meet BP treatment goals according to both the 2017 Hypertension Clinical Practice Guidelines and the American Diabetes Association standards of medical care.[78]
- In NHIS 2013 to 2017, adults with diabetes <65 years of age were more likely to report overall financial hardship from medical bills (41.1%) than adults with diabetes ≥65 years of age (20.7%). The prevalence of cost-related medication nonadherence was 34.7% and of delayed medical care was 55.5% among adults with diabetes <65 years of age.[79]
- In NHANES 2011 to 2016, 83.4% of adults with diabetes had an HbA_{1c} test in the past year. Testing rates were higher for individuals with health insurance (86.6%) than for those without health insurance (55.9%).[80]
- According to data from BRFSS 2013, individuals with private insurance were more likely than those without insurance to have had HbA_{1c} testing (OR, 2.60 [95% CI, 2.02–3.35]), a foot examination (OR, 1.72 [95% CI, 1.32–2.25]), or an eye examination (OR, 2.01 [95% CI, 1.56–2.58]) in the past year.[81]
- In the SEARCH study (Washington and South Carolina sites), the prevalence of food insecurity among individuals with type 1 diabetes was 19.5%. Youth and young adults from food-insecure households were more likely to have an HbA_{1c} >9.0% (OR, 2.37 [95% CI, 1.10–5.09]).[82]
- Among young adults with type 2 diabetes in the SEARCH study, those who transferred from pediatric care to an adult care provider or no care provider were more likely to have an HbA_{1c} >9% (OR, 4.5 [95% CI, 1.8–11.2] for transfer to adult care provider; OR, 4.6 [95% CI, 1.4–14.6] for transfer to no care provider).[83]
- Among HCHS/SOL study participants with diabetes, 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.[84] 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]).[85]
- In the AHA's GWTG program, patients with ACS and diabetes were less likely to have LDL-C checked or a statin prescribed than patients with ACS but without diabetes.[86]
- In the IMPROVE-IT trial, adults with diabetes randomized to ezetimibe plus statin versus placebo plus statin had a lower risk of the composite end point of CVD death, CHD, and stroke (HR, 0.85 [95% CI, 0.78–0.94]).[87]
- In MEPS, 70% (95% CI, 68%–71%), 67% (95% CI, 66%–69%), and 68% (95% CI, 66%–71%) of US adults with diabetes received appropriate diabetes care (HbA_{1c} measurement, foot examination, and an eye examination) in 2002, 2007, and 2013, respectively[88]; however, only 39.6% of adults with diabetes reported receiving dilated eye examinations annually.[89]
- Among Medicare Advantage patients with diabetes from 2006 to 2013, use of metformin increased from 47.6% to 53.5%, use of dipeptidyl peptidase 4 inhibitors increased from 0.5% to 14.9%, insulin use increased from 17.1% to 23.0%, use of sulfonylureas decreased from 38.8% to 30.8%, and thiazolidinedione use decreased from 28.5% to 5.6%.[90]

Mortality (See Table 9-1)

- Diabetes was listed as the underlying cause of mortality for 84 946 people (47 551 males and

37 395 females) in the United States in 2018 (Table 9-1).[91]

- The 2018 overall age-adjusted death rate attributable to diabetes was 21.4 per 100 000. For males, the age-adjusted death rates per 100 000 population were 24.3 for NH White people, 46.9 for NH Black people, 29.8 for Hispanic people, 20.2 for NH Asian/Pacific Islander people, and 49.4 for NH American Indian/Alaska Native people. For females, the age-adjusted death rates per 100 000 population were 14.3 for NH White people, 32.7 for NH Black people, 20.4 for Hispanic people, 13.5 for NH Asian/Pacific Islander people, and 35.6 for NH American Indian/Alaska Native people (unpublished NHLBI tabulation using CDC WONDER[92]). In 2018, diabetes was the seventh leading cause of death in the United States.[6]
- In NHIS 1997 to 2011, diabetes was the underlying cause for 3.3% of deaths and a contributing cause for 10.8% of deaths. The PAF for death associated with diabetes was 11.5%. Although diabetes was more often cited as an underlying and contributing cause of death for NH Black individuals and Hispanic individuals than for NH White individuals, the PAF was similar in each racial/ethnic group.[93]
- In a collaborative meta-analysis of 980 793 individuals from 68 prospective studies, diabetes was associated with all-cause mortality among both males (RR, 1.59 [95% CI, 1.54–1.65]) and females (RR, 2.00 [95% CI, 1.90–2.11]).[94] In another meta-analysis of 2 314 292 individuals from 35 prospective cohort studies, diabetes was associated with all-cause mortality among both males (HR 2.33 [95% CI, 2.02–2.69]) and females (HR 1.91 [95% CI, 1.72–2.12]).[95]
- In NHIS 2000 to 2011, males and females with diagnosed diabetes had 1.56 and 1.69 times higher risk of all-cause mortality compared with those without diagnosed diabetes (HR, 1.56 [95% CI, 1.49–1.64] and 1.69 [95% CI, 1.61–1.78], respectively).[96]
- In the Swedish National Diabetes Register, there was a significant decline in all-cause mortality from 1998 to 2014 among individuals with type 1 diabetes (HR, 0.71 [95% CI, 0.66–0.78]), but this decline was not statistically different from the decline observed among individuals without diabetes (HR, 0.77 [95% CI, 0.72–0.83]). In contrast, the decline in all-cause mortality from 1998 to 2014 among individuals with type 2 diabetes (HR, 0.79 [95% CI, 0.78–0.80]) was less than the decline observed among individuals without diabetes (HR, 0.69 [95% CI, 0.68–0.70]).[97]
- In the Swedish National Diabetes Register, compared with individuals without diabetes, the adjusted HR for all-cause mortality for individuals with type 1 diabetes who met all risk factor targets was 1.31 (95% CI, 0.93–1.85), whereas the HR for individuals with type 1 diabetes who met no risk factor targets was 7.33 (95% CI, 5.08–10.57).[98] Individuals with type 2 diabetes who met all risk factor targets (HbA_{1c}, LDL-C, BP, urine ACR, and nonsmoker) had similar risks of death, MI, and stroke compared with those without diabetes.[99]
- The association of new-onset type 2 diabetes and all-cause mortality exhibited a U-shaped relationship by BMI, with the strongest associations comparing those with diabetes with those without diabetes observed among those with BMI ≥40 kg/m^2 (HR, 1.37 [95% CI, 1.11–1.71] for short-term mortality risk within 5 years; HR, 2.00 [95% CI, 1.58–2.54] for long-term mortality risk >5 years).[100]
- In the NHIS from 1985 to 2014, there was a decrease in major CVD deaths, with 25% greater percentage reduction among adults with diabetes than among adults without diabetes.[101]
- Age at diagnosis is an important factor in mortality rates among individuals with type 1 diabetes. In the Swedish National Diabetes Register, those who developed type 1 diabetes before 10 years of age experienced 17.7 YLL (95% CI, 14.5–20.4) for females and 14.2 YLL (95% CI, 12.1–18.2) for males compared with those without type 1 diabetes.[102]

Complications (See Chart 9-7)

Microvascular Complications

- Among those ≤21 years of age with newly diagnosed diabetes in a US managed care network, 20% of youth with type 1 diabetes and 7.2% of youth with type 2 diabetes developed diabetic retinopathy over a median follow-up of 3 years.[103]
- In DCCT/EDIC, over >30 years of follow-up, the rates of ocular events per 1000 person-years were 12 for proliferative diabetic retinopathy, 14.5 for clinically significant macular edema, and 7.6 for ocular surgeries.[104]
- Among adults ≥18 years of age with diagnosed diabetes in 2018, the prevalence of a vision disability was 11.7% (95% CI, 11.0%–12.5%).[6]
- Among American Indian and Alaska Native individuals with diabetes using primary care clinics of the US Indian Health Service, tribal, and urban Indian health care facilities, 17.7% had nonproliferative diabetic retinopathy, 2.3% had proliferative diabetic retinopathy, and 2.3% had diabetic macular edema.[105]
- On the basis of analyses of data from the NIS, the USRDS, and the US NVSS, between 1995 and 2015 (Chart 9-7), substantial declines were observed in the age-standardized rates of diabetes-related

complications among those with diagnosed diabetes.[106]

- Among adults with diabetes 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.[107] The prevalence of CKD was 58.7% in US adults with diabetes ≥65 years of age, 25.7% in those <65 years of age, 43.5% in NH Black people and Mexican American people, and 38.7% in NH White people.[107]
- With the use of the KDIGO classification for CKD among adults with type 2 diabetes in NHANES 2007 to 2014, the prevalence of stage 3a CKD (mildly to moderately decreased kidney function) was 10.4% (95% CI, 9.1%–11.7%), stage 3b CKD (moderately to severely decreased) was 5.4% (95% CI, 4.5%–6.4%), stage 4 CKD (severely decreased) was 1.8% (95% CI, 1.3%–2.4%), and stage 5 CKD (kidney failure) was 0.4% (95% CI, 0.2%–0.7%).[108]
- According to data from NHANES 1988 through 2014, the prevalence of any diabetic kidney disease, defined as persistent albuminuria, persistent reduced eGFR, or both, did not significantly change from 1988 to 1994 (28.4% [95% CI, 23.8%–32.9%]) to 2009 to 2014 (26.2% [95% CI, 22.6%–29.9%]). Comparing the 2 times periods shows that the prevalence of albuminuria decreased from 20.8% (95% CI, 16.3%–25.3%) to 15.9% (95% CI, 12.7%–19.0%), whereas the prevalence of reduced eGFR increased from 9.2% (95% CI, 6.2%–12.2%) to 14.1% (95% CI, 11.3%–17.0%).[109]
- In the Swedish National Diabetes Register using data from 1998 to 2013, type 1 diabetes was associated with an HR for amputation of 40.1 (95% CI, 32.8–49.1) compared with no diabetes. The incidence has been decreasing and was 3.09 per 1000 person-years in 1998 to 2001 compared with 2.64 per 1000 person-years in 2011 to 2013.[110]

CVD Complications

- Among male NHIS participants enrolled in 2000 to 2009 and followed up through 2011, diabetes was associated with increased risk for HD mortality (HR, 1.72 [95% CI, 1.53–1.93]), cerebrovascular mortality (HR, 1.48 [95% CI, 1.18–1.85]), and CVD mortality (HR, 1.67 [95% CI, 1.51–1.86]). Among female participants, diabetes was also associated with increased risk for HD mortality (HR, 2.02 [95% CI, 1.81–2.25]), cerebrovascular mortality (HR, 1.43 [95% CI, 1.15–1.77]), and CVD mortality (HR, 1.85 [95% CI, 1.69–1.96]).[96]
- In the TECOS trial of adults with type 2 diabetes and ASCVD, females with diabetes had a lower risk of MI (HR, 0.70 [95% CI, 0.55–0.90]) and stroke (HR, 0.52 [95% CI, 0.38–0.71]) than males with diabetes.[111]
- On the basis of analyses of data from the NHIS, between 1995 and 2015, the rate of hospitalizations for IHD and stroke declined among patients with diabetes (Chart 9-7).[106]
- The HRs of CHD events comparing participants with diabetes only, diabetes and prevalent CHD, and neither diabetes 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.[112] Compared with participants who had prevalent CHD, the HR of CHD events for participants with severe diabetes (defined as insulin use or presence of albuminuria) was 0.88 (95% CI, 0.72–1.09).
- In data from the Cardiovascular Disease Lifetime Risk Pooling Project, the 30-year risk of CVD was positively associated with fasting glucose at midlife, even within the range of nondiabetic values. Among females, the absolute risk of CVD was 15.3% (95% CI, 12.3%–18.3%) for fasting glucose <5.0 mmol/L and 18.6% (95% CI, 13.1%–24.1%) for fasting glucose 6.3 to 6.9 mmol/L. Among males, the absolute risk of CVD was 23.5% (95% CI, 19.7%–27.3%) for fasting glucose <5.0 mmol/L and 31.0% (95% CI, 25.6%–36.3%) for fasting glucose 6.3 to 6.9 mmol/L.[113]
- In the Veterans Affairs Diabetes Trial, a 1-SD increase in glucose variability increased the risk of CVD (HR, 1.11 [95% CI, 1.01–1.23] for coefficient of variation; HR, 1.14 [95% CI, 1.04–1.25] for average real variability) after adjustment for risk factors and mean glucose.[114]
- In the Pittsburgh Epidemiology of Diabetes Complications Study, a prospective cohort study of individuals with childhood-onset type 1 diabetes, a 1% increase in HbA_{1c} was associated with a 1.26-fold increase in incident CVD (95% CI, 1.07–1.45).[115]
- In MESA, 63% of participants with diabetes had a CAC score >0 compared with 48% of those without diabetes.[116] A longer duration of diabetes 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, in the CARDIA Study.[117]
- In the Swedish National Diabetes Register from 2001 to 2013, the IRR for AF compared with diabetes and matched controls was 1.35 (95% CI, 1.33–1.36).[118]
- Post hoc analysis of data from the EVEREST randomized trial of patients hospitalized with decompensated systolic HF demonstrated that diabetes 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.[119]

Hypoglycemia

- Hypoglycemia is a major factor that limits glycemic control in diabetes. In 2010, among Medicare beneficiaries with diabetes, hospitalizations for hypoglycemia and hyperglycemia occurred at a rate of 612 and 367 per 100 000 person-years, respectively.[120]
- In the Veterans Affairs Diabetes Trial, severe hypoglycemia within the prior 3 months was associated with an increased risk of a CVD event (HR, 1.9 [95% CI, 1.06–3.52]), CVD mortality (HR 3.7 [95% CI 1.3–10.4]), and all-cause mortality (HR, 2.4 [95% CI, 1.1–5.1)].[121]
- In the LEADER trial, patients with type 2 diabetes who experienced a severe hypoglycemic event had an increased risk of MACEs (HR, 2.2 [95% CI, 1.6–3.0]) and CVD death (HR, 3.7 [95% CI, 2.6–5.4]).[122] Similarly, in the EXAMINE trial, severe hypoglycemia was associated with an increased risk of MACEs (HR, 2.42 [95% CI, 1.27–4.60]).[123]
- 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]).[124]
- Severe hypoglycemia is more common with increasing age, with use of insulin or sulfonylureas, and in those with impaired renal function, type 1 diabetes, multiple comorbidities, and prior severe hypoglycemia.[125–127] Higher rates of hypoglycemia have also been reported in NH Black people compared with NH White people.[126,128]
- With the use of data from the Optum Labs Data Warehouse, 6419 index hospitalizations for hypoglycemia were identified among individuals with diabetes from 2009 to 2014. The 30-day readmission rate was 10%, with the majority of these readmissions being for other primary causes and only 12% for recurrent hypoglycemia.[129]
- A simple risk prediction tool for hypoglycemia based on age, renal function, insulin and sulfonylurea use, history of severe hypoglycemia, and ED use had C statistics between 0.79 and 0.83.[127,130]

Health Care Use (See Table 9-1)

- In 2016, there were 580 000 principal diagnosis discharges for diabetes (HCUP,[131] unpublished NHLBI tabulation; Table 9-1).
- Among Medicare beneficiaries with type 2 diabetes enrolled in Medicare Advantage prescription drug plans hospitalized between 2012 and 2014, there was a 17.1% 30-day readmission rate.[132] According to data from the Optum Labs Data Warehouse, individuals with type 2 diabetes hospitalized between 2009 and 2014 had a 10.8% 30-day readmission rate.[133]
- According to the 2016 NHIS, the rate of hospitalization among adults with diabetes was 339.0 per 1000 people with diabetes for any cause (7.8 million discharges), 75.3 per 1000 people with diabetes for major CVD (1.7 million discharges), 5.6 per 1000 people with diabetes for lower-extremity amputation (130 000 discharges), 9.1 per 1000 people with diabetes for hyperglycemic crisis (209 000 discharges), and 2.5 per 1000 people with diabetes for hypoglycemia (57 000 discharges).[1,6]
- According to the 2016 NEDS, the rate of ED visits was 69.1 per 1000 people with diabetes for diabetes as any listed diagnosis (16.0 million visits), 10.2 per 1000 people with diabetes for hypoglycemia (235 000 visits), and 9.7 per 1000 people with diabetes for hyperglycemia (224 000 visits).[6]
- Among participants in the ARIC study without a prior diagnosis of diabetes, 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 diabetes, 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.[134]

Cost

- In 2016, of 154 health conditions evaluated, diabetes had the highest public insurance spending ($55.4 billion [95% CI, 49.3–62.7 billion]).[135]
- In 2017, the cost of diabetes was estimated at $327 billion, up 26% from 2012, accounting for 1 in 4 health care dollars.[136] Of these costs, $237 billion were direct medical costs and $90 billion resulted from reduced productivity. Medical costs for patients with diabetes were 2.3 times higher than for people without diabetes, with an average medical expenditure of $16 752 per year for people with diabetes, of which $9601 was attributed to diabetes.[136]
- Informal care is estimated to cost $1192 to $1321 annually per person with diabetes.[137]
- According to 2001 to 2013 MarketScan data, the per capita total excess medical expenditure for individuals with diabetes in the first 10 years after diagnosis is $50 445.[138]
- In 2014, the cost for diabetes-related preventable hospitalizations was $5.9 billion. Between 2001 and 2014, this cost increased annually by 1.6%, of

which 25% was attributable to an increase in the cost per hospitalization and 75% was attributable to an increase in the number of hospitalizations.[139] The diabetes-related preventable hospitalization rate has decreased slightly[139] or stayed stable.[140]

- A systematic review estimated that CVD costs account for 20% to 49% of the total direct costs of diabetes care.[141]

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

- The GBD 2019 Study used bayesian meta-regression tools and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 369 diseases and injuries and 87 risk factors in 204 countries and territories.[142] The prevalence of diabetes increased 199.3% for males and 179.8% for females between 1990 and 2019. Overall, 237.9 million males and 222.0 million females worldwide have diabetes (Table 9-2).
  - Age-standardized mortality rates attributable to high FPG are generally lower in high-income countries (Chart 9-8).
  - Age-standardized mortality attributable to diabetes is highest in Oceania, southern Sub-Saharan Africa, Central Latin America, and Southeast Asia (Chart 9-9).
  - The age-standardized prevalence of diabetes is highest in Oceania, Central Latin America, Caribbean, high-income North America, and parts of North Africa and the Middle East (Chart 9-10).
- According to the IDF Atlas, the global prevalence of diabetes was 451 million (95% CI, 367–585 million) for adults 18 to 99 years of age in 2017 and is projected to increase to 693 million (95% CI, 522–903 million) by 2045.[143] The IDF Atlas global prevalence estimate did not include all ages and used a different methodology from the GBD prevalence estimate reported here.
- The global economic burden of diabetes was $1.3 trillion in 2015. It is estimated to increase to $2.1 to $2.5 trillion by 2030.[144]

Table 9-1. Diabetes in the United States

Population group	Prevalence of diagnosed diabetes, 2013–2016: age ≥20 y	Prevalence of undiagnosed diabetes, 2013–2016: age ≥20 y	Prevalence of prediabetes, 2013–2016: age ≥20 y	Incidence of diagnosed diabetes, 2018: age ≥18 y	Mortality, 2018: all ages*	Hospital discharges, 2016: all ages	Cost, 2017
Both sexes	26 000 000 (9.8%)	9 400 000 (3.7%)	91 800 000 (37.6%)	1 500 000	84 946	580 000	$327 Billion
Males	13 700 000 (10.9%)	5 500 000 (4.6%)	51 700 000 (44.0%)	…	47 551 (56.0%)†	319 000	…
Females	12 300 000 (8.9%)	3 900 000 (2.8%)	40 100 000 (31.3%)	…	37 395 (44.0%)†	261 000	…
NH White males	9.4%	4.7%	43.7%	…	32 182	…	…
NH White females	7.3%	2.6%	32.2%	…	23 591	…	…
NH Black males	14.7%	1.7%	31.9%	…	7802	…	…
NH Black females	13.4%	3.3%	24.0%	…	7463	…	…
Hispanic males	15.1%	6.3%	48.1%	…	5115	…	…
Hispanic females	14.1%	4.0%	31.7%	…	4271	…	…
NH Asian males	12.8%	6.1%	47.1%	…	1695	…	…
NH Asian females	9.9%	2.1%	29.4%	…	1490	…	…
NH American Indian or Alaska Native	…	…	…	…	1073	…	…

Undiagnosed diabetes is defined as those whose fasting glucose is ≥126 mg/dL but who did not report being told by a health care provider that they had diabetes. Prediabetes is a fasting blood glucose of 100 to <126 mg/dL (impaired fasting glucose); prediabetes includes impaired glucose tolerance.

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 diabetes mortality that is for males vs females.

Sources: Prevalence: Prevalence of diagnosed and undiagnosed diabetes: unpublished National Heart Lung and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey, 2013 to 2016.[12] Percentages for sex and racial/ethnic groups are age adjusted for Americans ≥20 years of age. Incidence: Centers for Disease Control and Prevention, National Diabetes Statistics Report, 2020.[6] Mortality: unpublished NHLBI tabulation using National Vital Statistics System, 2017.[91] These data represent diabetes as the underlying cause of death only. Mortality for NH Asian people includes Pacific Islander people. Hospital discharges: Healthcare Cost and Utilization Project, 2016.[131] Cost: American Diabetes Association.[2]

Table 9-2. Global Prevalence and Mortality of Diabetes, 2019

	Both sexes combined		Males		Females	
	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)
Total number (millions)	1.6 (1.4 to 1.7)	459.9 (423.5 to 498.0)	0.8 (0.7 to 0.8)	237.9 (219.4 to 258.0)	0.8 (0.7 to 0.9)	222.0 (203.6 to 240.4)
Percent change in total number 1990 to 2019	134.4 (120.2 to 149.1)	189.6 (185.8 to 193.2)	153.0 (134.2 to 172.9)	199.3 (194.1 to 204.7)	119.1 (100.3 to 136.7)	179.8 (176.4 to 183.1)
Percent change in total number 2010 to 2019	32.9 (27.0 to 39.0)	39.1 (36.0 to 42.7)	33.8 (26.0 to 41.6)	40.2 (36.8 to 43.9)	32.1 (23.9 to 40.7)	38.0 (34.6 to 41.5)
Rate per 100 000, age standardized	19.5 (18.1 to 20.7)	5555.4 (5118.8 to 6013.8)	21.0 (19.5 to 22.5)	5970.4 (5514.6 to 6462.8)	18.2 (16.5 to 19.7)	5168.9 (4748.1 to 5600.7)
Percent change in rate, age standardized 1990 to 2019	8.6 (2.3 to 14.9)	47.8 (46.0 to 49.3)	15.0 (7.1 to 23.7)	51.8 (49.6 to 54.0)	3.0 (−5.8 to 11.1)	43.7 (41.8 to 45.2)
Percent change in rate, age standardized 2010 to 2019	1.9 (−2.6 to 6.4)	12.2 (9.6 to 15.1)	2.2 (−3.6 to 7.7)	13.0 (10.2 to 16.0)	1.5 (−4.7 to 8.1)	11.2 (8.5 to 14.2)

UI indicates uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[142] Printed with permission. Copyright © 2020, University of Washington.

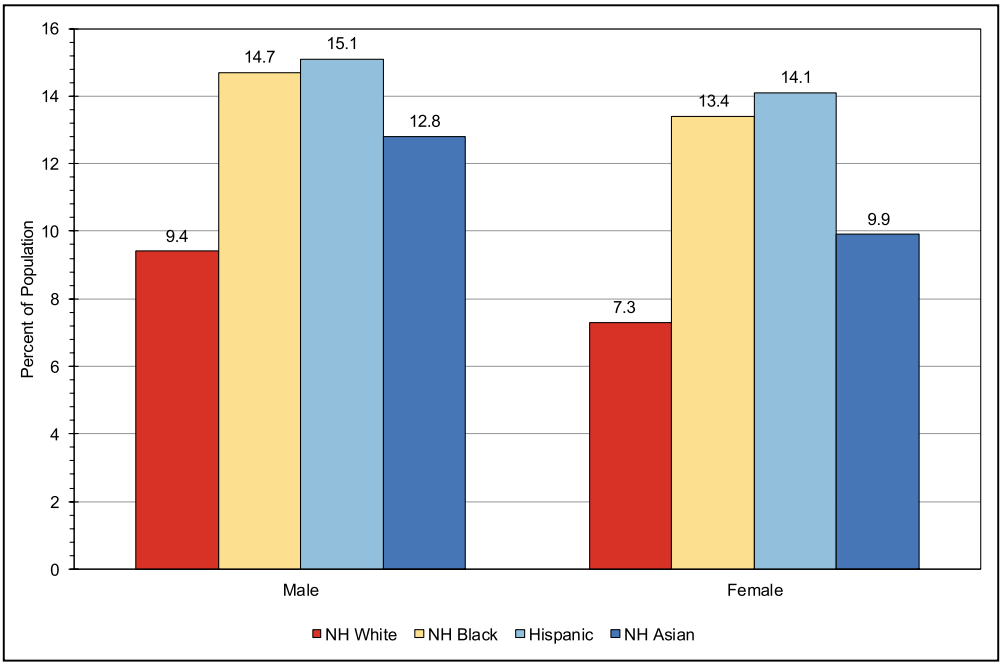

Chart 9-1. Age-adjusted prevalence of diagnosed diabetes in US adults ≥20 years of age by race/ethnicity and sex (NHANES, 2013–2016).

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

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.[12]

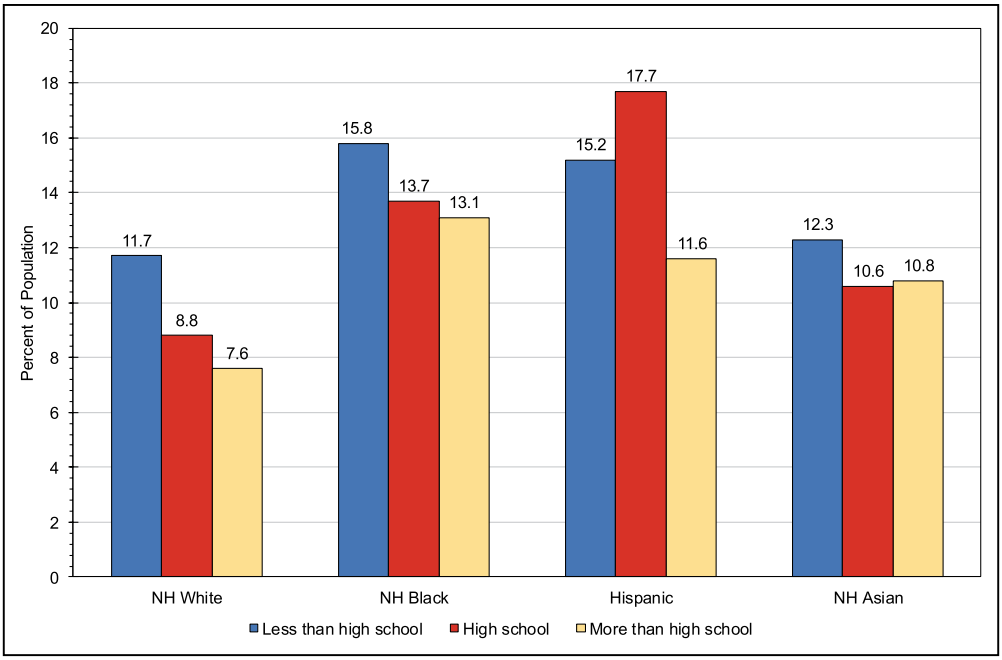

Chart 9-2. Age-adjusted prevalence of diagnosed diabetes in US adults ≥20 years of age by race/ethnicity and years of education (NHANES, 2013–2016).

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

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.[12]

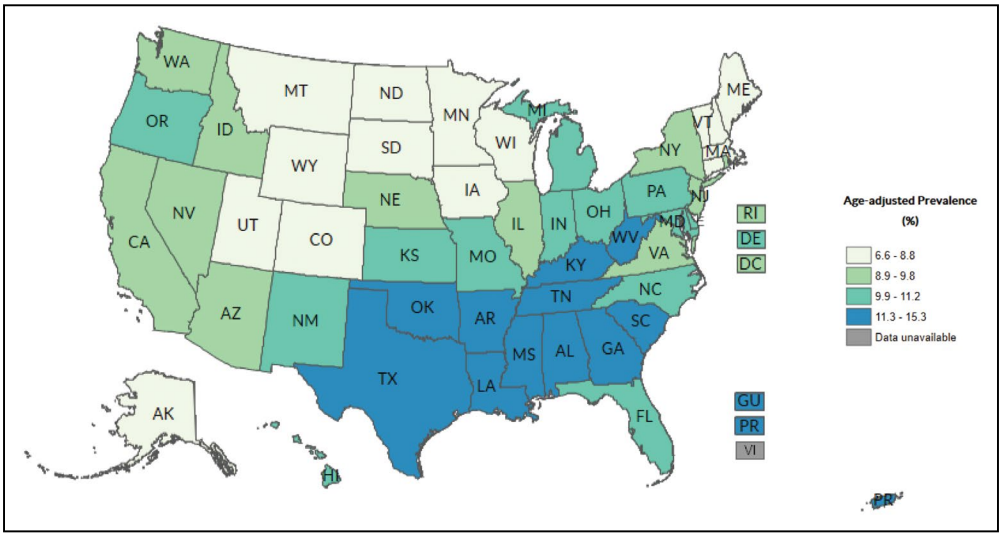

Chart 9-3. Age-adjusted percentage of adults with diagnosed diabetes, US states and territories, 2018.

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Source: Reprinted from Behavioral Risk Factor Surveillance System prevalence and trends data.[15]

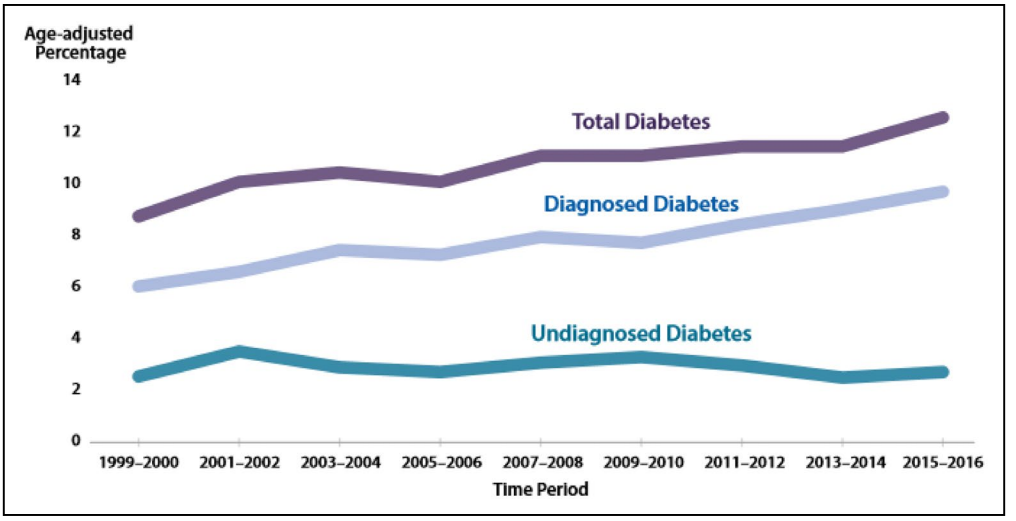

Chart 9-4. Trends in age-adjusted prevalence of diagnosed diabetes, undiagnosed diabetes, and total diabetes among US adults ≥18 years of age (NHANES, 1999–2016).

Diagnosed diabetes was based on self-report. Undiagnosed diabetes was based on fasting plasma glucose and hemoglobin A_{1c} levels among people self-reporting no diabetes.

NHANES indicates National Health and Nutrition Examination Survey.

Source: Reprinted Figure 1 from Centers for Disease Control and Prevention 2020 National Diabetes Report6 using NHANES, 1999 to 2016.[12]

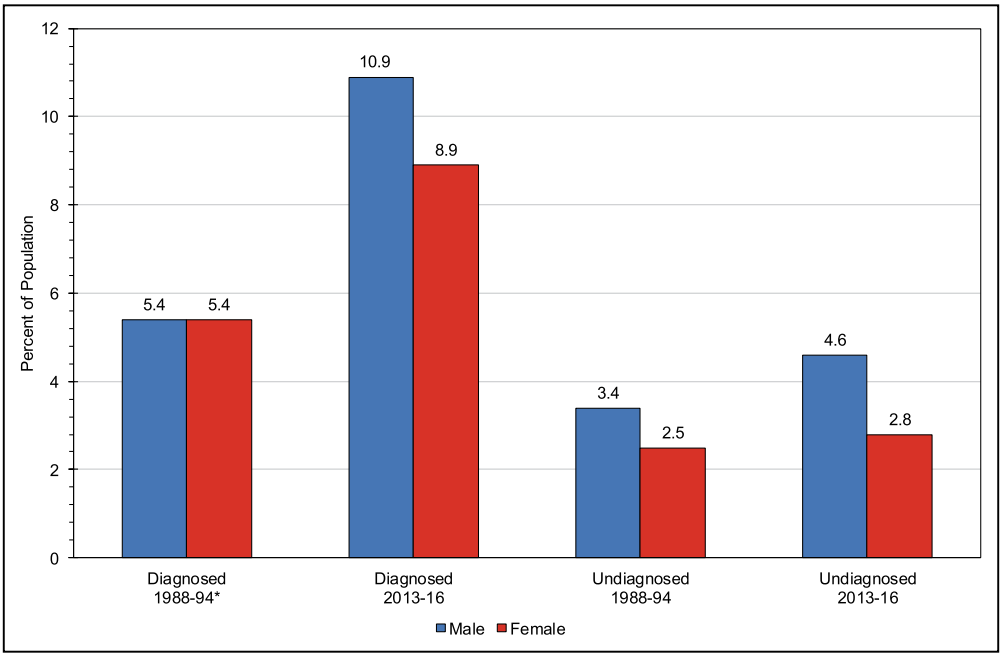

Chart 9-5. Trends in diabetes prevalence in US adults ≥20 years of age by sex (NHANES, 1988–1994 and 2013–2016).

The definition of diabetes changed in 1997 (from glucose ≥140 to ≥126 mg/dL).

NHANES indicates National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 1988 to 1994 and 2013 to 2016.[12]

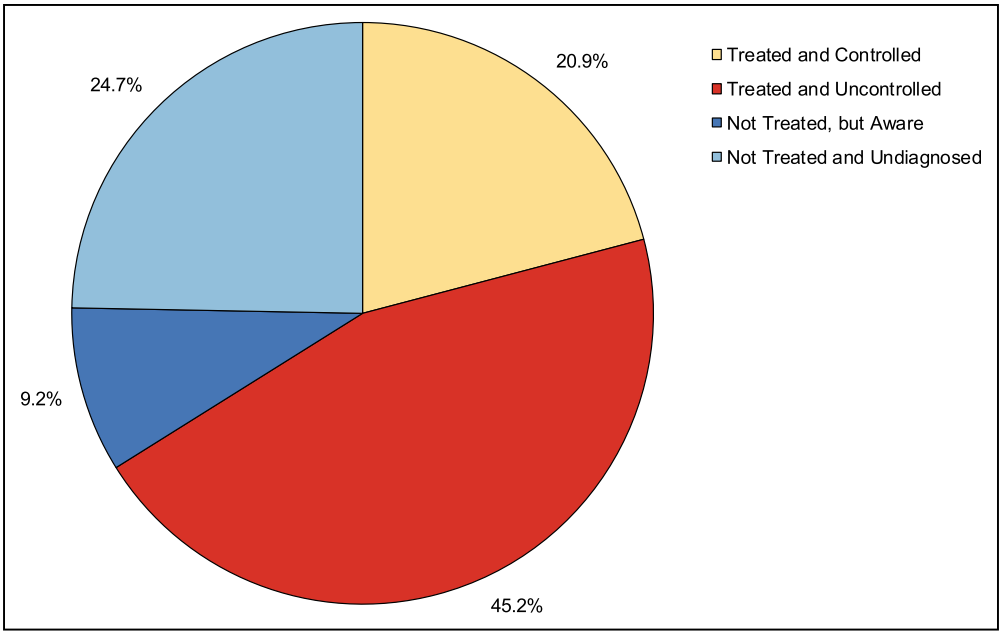

Chart 9-6. Awareness, treatment, and control of diabetes in US adults ≥20 years of age (NHANES, 2013–2016).
NHANES indicates National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.[12]

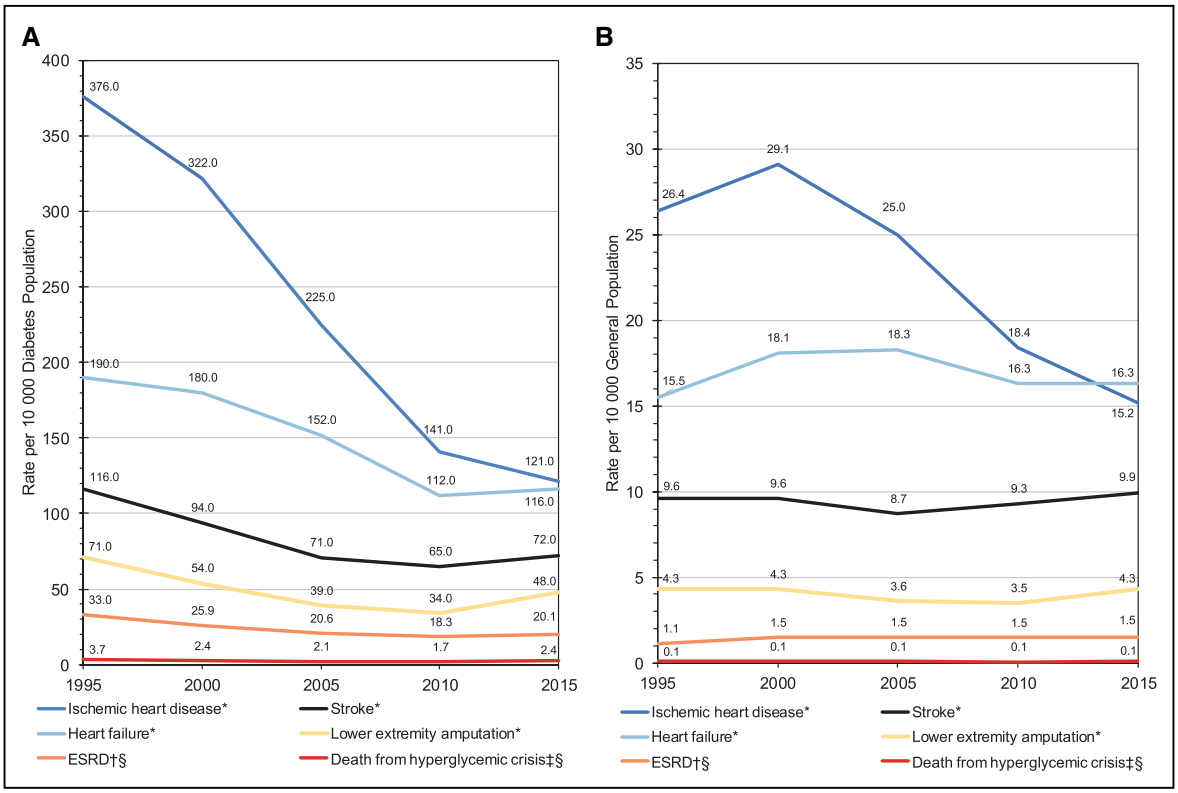

Chart 9-7. Trends in age-standardized rates of diabetes-related complications among US adults ≥18 years of age from 1995 to 2015.
A, Data include the population with diabetes. **B**, Data include the general population (with or without diabetes). Age adjustment is to the 2000 US standard population using age groups <45, 45 to 64, 65 to 74, and ≥75 years of age.
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.
§Hyperglycemic crisis and ESRD rates are for all ages.
Source: Centers for Disease Control and Prevention Diabetes Atlas[106] using data sources listed in the symbol notes.

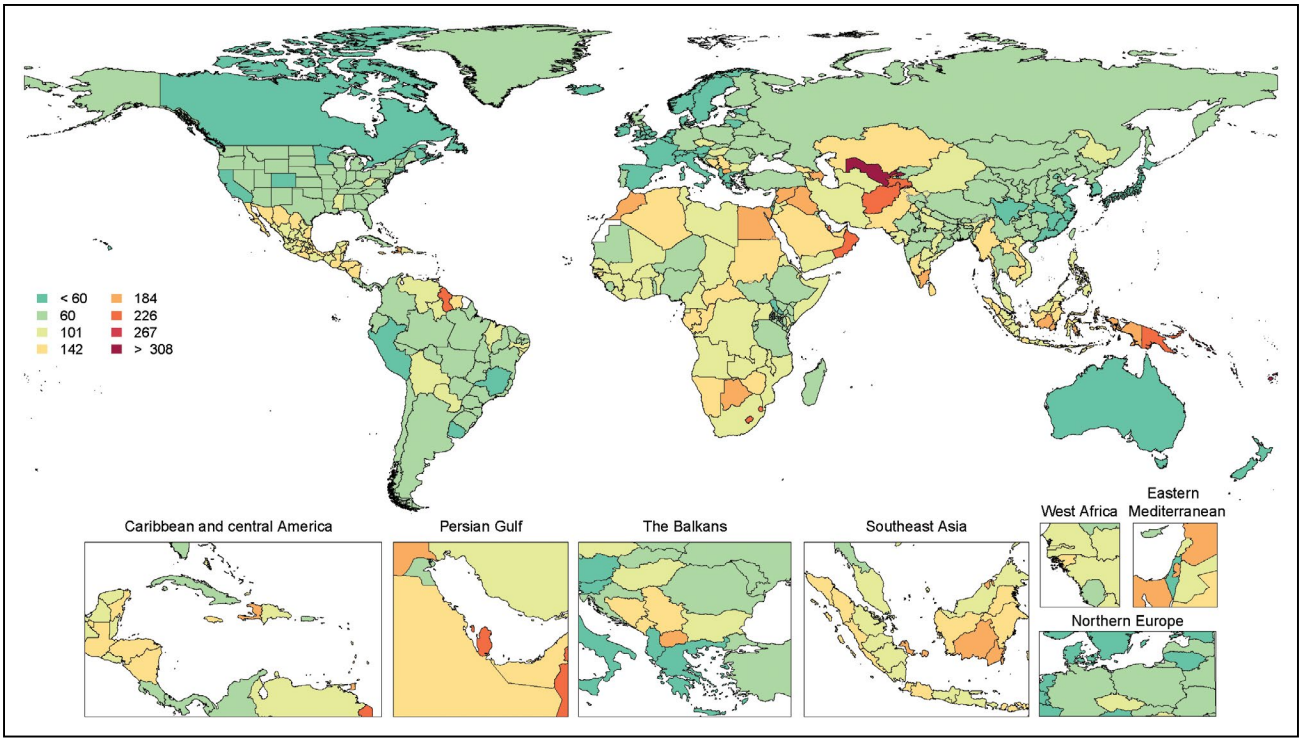

Chart 9-8. Age-standardized global mortality rates attributable to high fasting plasma glucose per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[145] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[146]

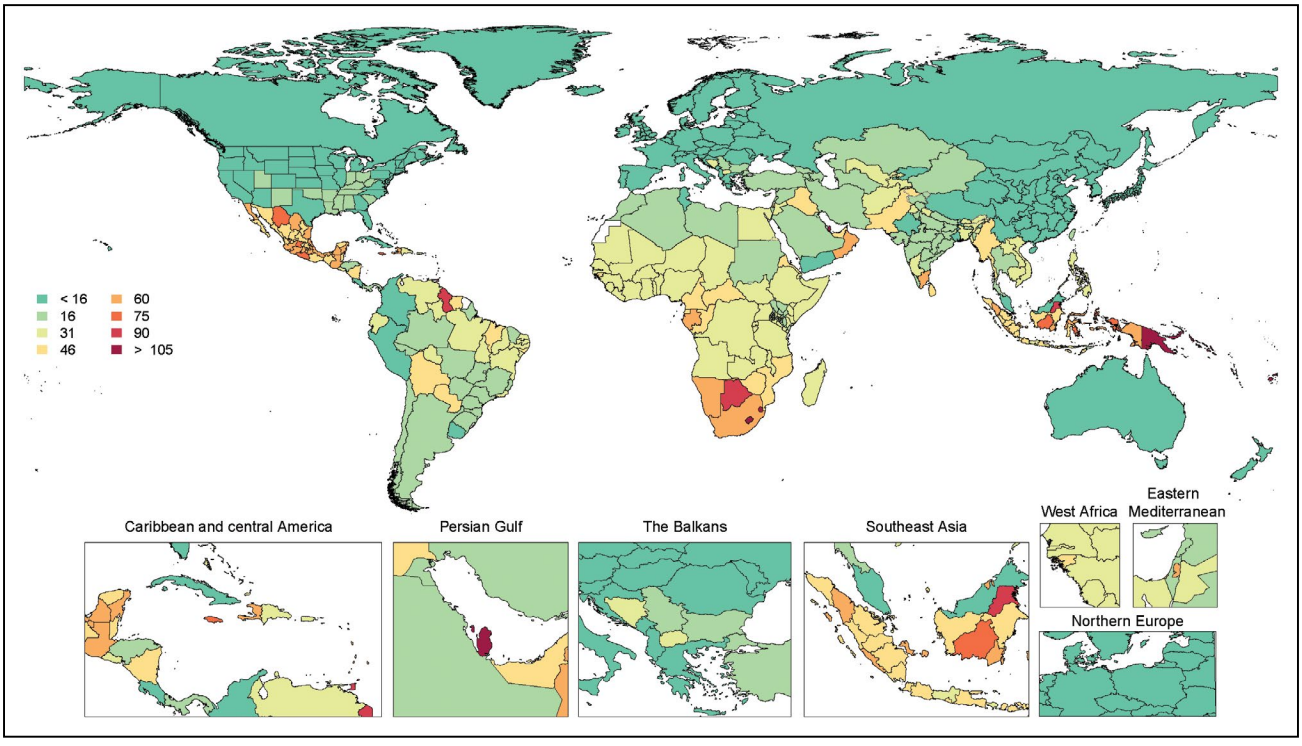

Chart 9-9. Age-standardized global mortality rates attributable to diabetes per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[142] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[146]

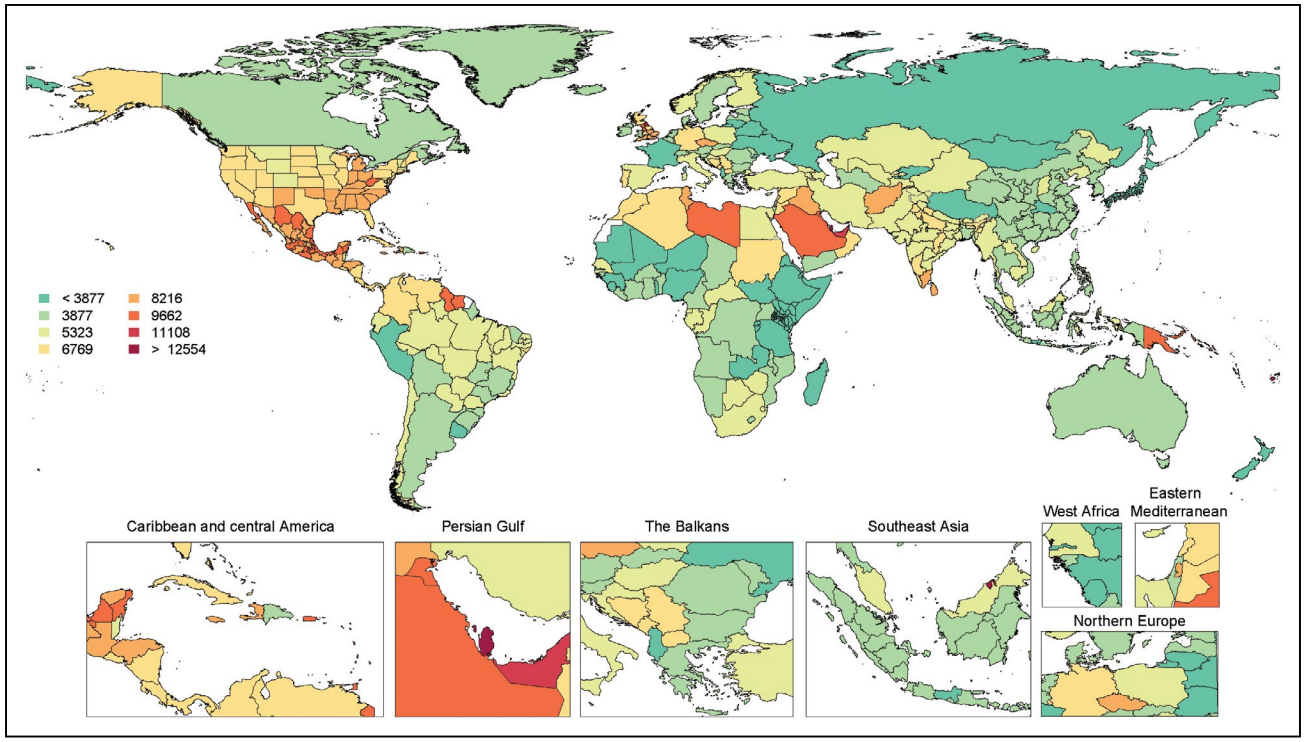

Chart 9-10. Age-standardized global prevalence rates of diabetes per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[142] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[146]

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10. METABOLIC SYNDROME

See Charts 10-1 through 10-8

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Definition

- MetS is a multicomponent risk factor for CVD and type 2 diabetes that reflects the clustering of individual cardiometabolic risk factors related to abdominal obesity and insulin resistance. MetS is a

Abbreviations Used in Chapter 10

AF	atrial fibrillation
AHA	American Heart Association
aHR	adjusted hazard ratio
AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes
ANP	atrial natriuretic peptide
aOR	adjusted odds ratio
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
CABG	coronary artery bypass grafting
CAC	coronary artery calcification
CAD	coronary artery disease
cAMP	cyclic adenosine monophosphate
Carbs	carbohydrates
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CHRIS	Collaborative Health Research in South Tyrol Study
CI	confidence interval
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
EBP	elevated blood pressure
EF	ejection fraction

(*Continued*)

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Abbreviations Used in Chapter 10 Continued

EGCUT	Estonian Genome Center of the University of Tartu
ERICA	Study of Cardiovascular Risks in Adolescents
FPG	fasting plasma glucose
GFR	glomerular filtration rate
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
HCUP	Healthcare Cost and Utilization Project
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
IDF	International Diabetes Federation
IL	interleukin
IMT	intima-media thickness
JHS	Jackson Heart Study
KORA	Cooperative Health Research in the Region of Augsburg
LDL	low-density lipoprotein
LV	left ventricular
MESA	Multi-Ethnic Study of Atherosclerosis
MET	metabolic equivalent
MetS	metabolic syndrome
MHO	metabolically healthy obesity
MI	myocardial infarction
MICROS	Microisolates in South Tyrol Study
MORGAM	MONICA, 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
NIH-AARP	National Institutes of Health–American Association of Retired Persons
NIPPON DATA	National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in Aged
NL	the Netherlands
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
RENIS-T6	Renal Iohexol-Clearance Survey in Tromsø 6
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
TNF	tumor necrosis factor
UA	United Arab
VTE	venous thromboembolism
WC	waist circumference
WHO	World Health Organization

useful entity for communicating the nature of lifestyle-related cardiometabolic risk to both patients and clinicians. Although multiple definitions for MetS have been proposed, the IDF, NHLBI, AHA, and others recommended a harmonized definition for MetS based on the presence of any 3 of the following 5 risk factors[1]:

- FPG ≥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 Asian individuals and individuals of non-European ancestry who have resided predominantly 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

- Several adverse health conditions are related to MetS 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]
- Type 2 diabetes, defined as FPG ≥126 mg/dL, random or 2-hour postchallenge glucose ≥200 mg/dL, HbA_{1c} ≥6.5%, or taking hypoglycemic medication, is a separate clinical diagnosis distinct from MetS; however, many of those with type 2 diabetes also have MetS.

Prevalence

Youth
(See Chart 10-1)

- On the basis of NHANES 1999 to 2014, the prevalence of MetS in adolescents 12 to 19 years of age in the United States varied by geographic region and was higher in adolescent males versus females across all regions (Chart 10-1).[3]
- In HCHS/SOL Youth, the prevalence of MetS among children 10 to 16 years of age varied according to the clinical definition used, with only 1 participant being classified as having MetS by all 3 clinical definitions.[4]
- Although MetS categorization is generally unstable at younger ages, a single grouping of cardiometabolic risk factors (ie, abdominal obesity, insulin resistance, dyslipidemia, and EBP) was identified in a confirmatory factor analysis and shown to be present across the age spectrum from children to adults.[5] However, a separate confirmatory factor analysis in HCHS/SOL Youth showed that SBP and FPG did not cluster with other MetS components.[4]
- Uncertainty remains concerning the definition of the obesity component of MetS in the pediatric population because it is age dependent. Therefore, use of BMI percentiles[6] and waist-height ratio[7] has been recommended. When CDC and FitnessGram standards are used for pediatric obesity, the prevalence of MetS in obese youth ranges from 19% to 35%.[6]

Adults
(See Chart 10-2)

The following estimates include many who also have diabetes, in addition to those with MetS without diabetes:

- On the basis of NHANES 2007 to 2014, the overall prevalence of MetS was 34.3% and was similar for males (35.3%) and females (33.3%).[8] The prevalence of MetS 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 meta-analysis of 26609 young adults (18–30 years of age) across 34 studies, the prevalence of MetS was 4.8% to 7.0%, depending on the definition used.[9]
- The age-standardized prevalence of MetS by age and sex from 2008 to 2011 in Hispanic/Latino people in HCHS/SOL is shown in Chart 10-2.[10]
- Among Black people in the JHS, the overall prevalence of MetS was 34%, and it was higher in females than in males (40% versus 27%, respectively).[11]
- The prevalence of MetS has been noted to be high in individuals with certain conditions, including schizophrenia spectrum disorders[12] and bipolar disorder[13]; use of atypical antipsychotic drugs[14]; prior solid organ transplantations[15]; prior hematopoietic cell transplantation[16,17]; HIV infection[18]; prior treatment for blood cancers[17,19]; systemic inflammatory disorders such as psoriasis,[20,21] systemic lupus erythematosus,[22] ankylosing spondylitis,[23] and rheumatoid arthritis[24]; multiple sclerosis[25]; type 1 diabetes[26,27]; latent autoimmune diabetes in adults[27]; hypopituitarism[28]; prior gestational diabetes[29]; prior pregnancy-induced hypertension[30]; cerebral palsy[31]; war-related bilateral lower-limb amputation[32] or spinal cord injury[33] in veterans; and chronic opiate dependence,[34] as well as individuals in select professions, including law enforcement[35] and firefighting.[36]

Secular Trends

Youth

(See Chart 10-3)

- In NHANES 1999 to 2012, the prevalence of MetS decreased among youth 12 to 19 years of age. This was most evident when considering a MetS severity *z* score (slope=–0.015; *P*=0.030) (Chart 10-3).[37]

Adults

(See Charts 10-4 through 10-6)

- Secular trends in MetS differ according to the definition used.[8,38,39] Chart 10-4[38] demonstrates trends using the harmonized MetS criteria in NHANES 1988 to 2012; Chart 10-5[8] demonstrates trends using ATP III criteria in NHANES 2007 to 2014.
- In the ARIC study (1987–1998), prevalence of MetS increased from 33% to 50% over the mean 10-year follow-up, with differences by age and sex (Chart 10-6).[40]

Risk Factors

Youth

- In the PREMA study, independent predictors of MetS from childhood to adolescence were low birth weight, small head circumference, and a parent with overweight or obesity.[41] When all 3 of these predictors were present, the sensitivity and specificity of identifying MetS were 91% and 98%, respectively, in both the derivation and validation cohorts.
- In an RCT of health care worker assistance to promote longer duration of exclusive breastfeeding in mother-child pairs, the risk of childhood MetS after 11.5 years of follow-up was increased among boys who received longer breastfeeding (OR, 1.49 [95% CI, 1.01–2.22]) but not girls (OR, 0.94 [95% CI, 0.63–1.42]) who received longer breastfeeding compared with control groups.[42]
- In NHANES 2007 to 2010, higher exposure to secondhand smoke was associated with prevalent MetS (OR, 5.4 [95% CI, 1.7–16.9]) among adolescents 12 to 19 years of age. In addition, higher secondhand smoke exposure interacted with low exposure to certain nutrients (vitamin E and omega-3 PUFAs) to increase the odds of MetS.[43]
- Daily intake of added sugar >186 g/d was associated with prevalent MetS (OR, 8.4 [95% CI, 4.7–12.1]) among adolescents 12 to 19 years of age in NHANES 2005 to 2012.[44]
- Among Chinese adolescents 12 to 16 years of age, the aspartate aminotransferase/alanine aminotransferase ratio was inversely associated with prevalent MetS. Students in the lowest tertile of aspartate aminotransferase/alanine aminotransferase ratio had a 6-fold higher odds of MetS compared with those in the highest tertile (aOR, 6.02 [95% CI, 1.93–18.76]).[45] In addition, a lower ratio of insulin-like growth factor 1 to insulin-like growth factor binding protein 3 was an independent risk factor for prevalent MetS (OR, 2.35 [95% CI, 1.04–5.30]) in Chinese adolescents age 12 to 16 years of age. Lower baseline ratio of insulin-like growth factor 1 to insulin-like growth factor binding protein 3 in adolescence was an independent risk factor for MetS in adulthood (OR, 10.72 [95% CI, 1.03–11.40]).[46]
- In ERICA, serum adiponectin levels were inversely associated with MetS *z* score among Brazilian adolescents 12 to 17 years of age (β=–0.40, [95% CI, – 0.66 to – 0.14]; *P*=0.005).[47]

Adults

Incident MetS

Diet

- Dietary habits are also directly associated with incident MetS, including a Western diet[48] and consumption or intake of soft drinks,[49] diet soda,[50] energy-dense beverages,[51] SSBs,[52] fructose,[53] magnesium,[54,55] carbohydrates,[56] total fat,[57] meats (total, red, and processed but not white meat),[58,59] and fried foods.[50] In addition, skipping breakfast,[60] restrained and emotional eating behaviors,[61] and a problematic relationship with eating and food[62] are risk factors.
- Dietary habits are also inversely associated with incident MetS, including alcohol use,[63] fiber intake,[64,65] consumption of fruits and vegetables,[66] white fish intake,[67] Mediterranean diet,[68–70] dairy consumption (particularly yogurt and low-fat dairy products),[50,71] consumption of fermented milk with *Lactobacillus plantarum*,[72] consumption of animal or fat protein,[73] hot tea consumption (but not sugar-sweetened iced tea),[74] coffee consumption[75], vitamin D intake,[76] intake of tree nuts,[77] walnut intake,[78] avocado intake,[79] intake of long-chain omega-3 PUFAs,[80] potassium intake,[81] and ability to interpret nutrition labels.[82]

Physical Activity

- In prospective or retrospective cohort studies, low levels of PA[83] and physical fitness[84] are directly associated with incident MetS.
- In a meta-analysis that included 76 699 participants and 13 871 incident cases of MetS, there was a negative linear relationship between leisure-time PA and development of MetS.[85] For every increase of 10 MET hours per week (equal to ≈150 minutes of moderate PA per week), risk of MetS was reduced by 10% (RR, 0.90 [95% CI, 0.86–0.94]).
- The following factors have been reported as being inversely associated with incident MetS, defined by 1 of the major definitions, in prospective or retrospective cohort studies: increased PA or physical fitness,[86]

aerobic training,[87] cardiorespiratory fitness (eg, maximal oxygen uptake),[88] and living at geographically higher elevation.[89] Each 1000–steps per day increase is associated with lower odds of having MetS (OR, 0.90 [95% CI, 0.83–0.98]) in American men.[90]

Blood Biomarkers

- Blood biomarkers that are inversely associated with incident MetS include insulin sensitivity,[91] ratio of aspartate aminotransferase to alanine aminotransferase,[92] total testosterone,[91,93,94] serum 25-hydroxyvitamin D,[95] sex hormone–binding globulin,[91,93,94] and Δ5-desaturase activity.[96]

Other

- There is a bidirectional association between MetS and depression. In prospective studies, depression increases the risk of MetS (OR, 1.49 [95% CI, 1.19–1.87]), and MetS increases the risk of depression (OR, 1.52 [95% CI, 1.20–1.91]).[97]
- Other risk direct factors for incident MetS include age,[98] smoking[99,100] and parental smoking,[101] parental history of diabetes,[102] childhood MetS,[102,103] obesity or high BMI,[104] intra-abdominal fat,[93] weight gain,[105] weight fluctuation,[106] and heart rate.[107]
- Prior studies have reported higher MetS incidence among individuals with lower educational attainment, lower SES,[108] more experiences of everyday discrimination,[109] and long-term work stress. In HCHS/SOL, perceived discrimination was not associated with MetS prevalence when all Hispanic/Latino groups were evaluated in aggregate. However, among individuals of Central American background, increased perceived ethnicity-associated threat to oneself or one's property was related to increased MetS prevalence.[110]
- In a pooled population of 117 020 patients from 20 studies who were followed up for a median of 5 years (range, 3–14.7 years), NAFLD was associated with an increased risk of incident MetS when alanine aminotransferase (RR, 1.80 [95% CI, 1.72–1.89] for highest versus lowest quartile or quintile), γ-glutamyltransferase (RR, 1.98 [95% CI, 1.89–2.07] for highest versus lowest quartile or quintile), or ultrasonography (RR, 3.22 [95% CI, 3.05–3.41]) was used to assess NAFLD.[111]

Prevalent MetS

Diet

- In cross-sectional studies, prevalent MetS is directly associated with a high-salt diet,[112] white rice consumption,[113] a high dietary inflammatory index,[114] a long-chain food supply (compared with a short-chain food supply),[115] excessive dietary calcium (>1200 mg/d) in males,[116] and inadequate energy intake among patients undergoing dialysis.[117] Prevalent MetS is inversely associated with a vegetarian diet,[118] total antioxidant capacity from diet and dietary supplements,[119] and organic food consumption.[120]

Physical Activity

- In cross-sectional studies, prevalent MetS is directly associated with low cardiorespiratory fitness[121] and is inversely associated with increased standing,[122] "weekend warrior" and regular PA patterns,[123] and handgrip strength.[124]

Blood Biomarkers

- Blood biomarkers directly associated with prevalent MetS include proinflammatory cytokines such as IL-6 and TNF-α[125]; retinol binding protein 4[126]; cancer antigen 19-9[121,127]; erythrocyte parameters[128] such as hemoglobin level and red blood cell distribution width; blood parameters such as hemoglobin, platelet, and white blood cell counts[129]; non–HDL-C[130]; and ratio of lymphocyte to HDL-C.[131]
- In cross-sectional studies, prevalent MetS is inversely associated with anti-inflammatory cytokines (IL-10),[125] ghrelin,[125] adiponectin,[125] and antioxidant factors (paraoxonase-1).[125]
- In NHANES 1999 to 2004, high serum anti-Mullerian hormone was inversely associated with specific MetS components, including WC, diabetes status, and insulin resistance, in overweight and obese US adult men.[132] However, anti-Mullerian hormone was not associated with having ≥3 MetS components (aOR, 1.00 [95% CI, 0.96–1.04]) or with the specific components of hypertension, HDL-C, triglycerides, or hyperglycemia in US adult men regardless of weight status.[132]

Other

- Prevalent MetS is also directly associated with stress[133]; elevated intraocular pressure among people without glaucoma[134]; exposure to pesticides[135]; poor sleep characteristics[136]; sarcopenia in middle-aged and older nonobese adults[137]; and OSA.[138]
- In cross-sectional studies, prevalent MetS is inversely associated with subclinical hypothyroidism in males,[139] muscle mass to visceral fat ratio in college students,[140] and marijuana use.[141]
- In NHANES 2003 to 2008, high neighborhood racial/ethnic diversity[142] was associated with a lower MetS prevalence (OR, 0.71 [95% CI, 0.52–0.96]) after adjustment for neighborhood-level poverty and individual factors.

Subclinical Disease (See Chart 10-6)

- In the ARIC study (1987–1998), with the use of a sex- and race/ethnicity-specific MetS severity score, 76% of ARIC participants progressed over a mean 10-year follow-up, with faster progression

observed in younger participants and in females (Chart 10-6).[40]
- Isolated MetS, which could be considered an earlier form of overt MetS, has been defined as ≥3 MetS components but without overt hypertension and diabetes. In a population-based random sample of 2042 residents of Olmsted County, MN, those with isolated MetS had a higher incidence of hypertension, diabetes, diastolic dysfunction, and reduced renal function (GFR <60 mL/min) compared with healthy control subjects (P<0.05).[143]

Genetics and Family History

- 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*), cAMP signaling (*ADCY5*), and oxidative LDL metabolism (*COLEC12*), as well as expression of liver-specific genes (*HNF1A*), have been identified across various racial/ethnic populations that could explain some of the correlated architecture of MetS traits.[144–148]
- The minor G allele of the ANP genetic variant rs5068, which is associated with higher levels of circulating ANP, has been associated with lower prevalence of MetS in White and Black people.[149]
- SNPs of inflammatory genes (encoding IL-6, IL-1β, and IL-10) and plasma fatty acids, as well as interactions among these SNPs, are differentially associated with odds of MetS.[150]

Prevention and Awareness of MetS

- Identification of MetS represents a call to action for the healthcare provider and patient to address underlying lifestyle-related risk factors. A multidisciplinary team of health care professionals is desirable to adequately address PA, healthy diet, and healthy weight for attainment of ideal BP, serum cholesterol, and FPG levels in patients with MetS.[152]
- Despite the high prevalence of MetS, the public's recognition of MetS is limited.[153] Communicating with patients about MetS and its clinical assessment may increase risk perception and motivation toward a healthier behavior.[154]

Morbidity and Mortality

Adults

CVD Morbidity and Mortality

- MetS is associated with CVD morbidity and mortality. A meta-analysis of 87 studies comprising 951 083 subjects showed that MetS increased the risk of CVD (summary RR, 2.35 [95% CI, 2.02–2.73]), with significant increased risks (RRs ranging from 1.6–2.9) for all-cause mortality, CVD mortality, MI, and stroke, even for those with MetS without diabetes.[155]
- The cardiovascular risk associated with MetS varies on the basis of the combination of MetS components present. Of all possible ways to have 3 MetS components, the combination of central obesity, EBP, 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.[104]
- In the INTERHEART case-control study of 26 903 subjects from 52 countries, MetS was associated with an increased risk of MI, according to both the WHO (OR, 2.69 [95% CI, 2.45–2.95]) and the IDF (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 were similar across all regions and ethnic groups. In addition, the presence of ≥3 risk factors with above-threshold values was associated with increased risk of MI (OR, 1.50 [95% CI, 1.24–1.81]) compared with having <3 risk factors with above-threshold values. Similar results were observed when the IDF definition was used.[156]
- In the Three-City Study, among 7612 participants ≥65 years of age who were followed up for 5.2 years, MetS 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, MetS was not associated with CHD beyond its individual risk components.[157]
- Among 3414 patients with stable CVD and atherogenic dyslipidemia who were treated intensively with statins in the AIM-HIGH trial, neither the presence of MetS nor the number of MetS components was associated with cardiovascular outcomes, including coronary events, ischemic stroke, nonfatal MI, CAD death, or the composite end point.[158]
- With the use of the 36 cohorts represented in the MORGAM Project, the risk of CVD in MetS declined with greater age in females but not males.[159]
- It is estimated that 13.3% to 44.0% of the excess CVD mortality in the United States, compared with other countries such as Japan, is explained by MetS or MetS-related existing CVD.[160]
- MetS is associated with risk of stroke.[161] In a meta-analysis of 16 studies including 116 496 participants who were initially free of CVD, those with MetS had an increased risk of stroke (pooled RR, 1.70 [95% CI, 1.49–1.95]) compared with those without MetS. The magnitude of the effect was stronger among females (RR, 1.83 [95% CI, 1.31–2.56]) than males

(RR, 1.47 [95% CI, 1.22–1.78]). Finally, those with MetS 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]).

- In the ARIC study, among 13 168 participants with a median follow-up of 23.6 years, MetS was independently associated with an increased risk of SCD (aHR, 1.70 [95% CI, 1.37–2.12]; *P*<0.001).[162] The risk of SCD varied according to the number of MetS components (HR, 1.31 per 1 additional component of the MetS [95% CI, 1.19–1.44]; *P*<0.001), independently of race or sex.

All-Cause Mortality

- In patients with impaired LV systolic function (EF <50%) who undergo CABG, MetS is associated with increased risk of all-cause in-hospital mortality (OR, 5.99 [95% CI, 1.02–35.15]).[163]
- In a meta-analysis of 20 prospective cohort studies that included 57 202 adults ≥60 years of age, MetS was associated with increased risk of all-cause mortality (RR, 1.20 [95% CI, 1.05–1.38] for males; RR, 1.22 [95% CI, 1.02–1.44] for females) and CVD mortality (RR, 1.29 [95% CI, 1.09–1.53] for males; RR, 1.20 [95% CI, 0.91–1.60] for females).[164] 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 MetS with CVD and all-cause mortality varied by geographic location, sample size, definition of MetS, and adjustment for frailty.
- The impact of MetS on mortality has been shown to be modified by objective sleep duration.[165] 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 mortality (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 mortality (HR, 1.29 [95% CI, 0.89–1.87]) or CVD mortality (HR, 1.49 [95% CI, 0.75–2.97]) among participants with MetS.

Complications

Youth

- Among 771 participants 6 to 19 years of age from the NHLBI's Lipid Research Clinics Princeton Prevalence Study and the Princeton Follow-Up Study, the risk of CVD was substantially higher among those with MetS than among those without MetS (OR, 14.6 [95% CI, 4.8–45.3]) who were followed up for 25 years.[166]
- 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 Minnesota Insulin Study) with a mean follow-up period of 22.3 years, childhood MetS and overweight were associated with a >2.4-fold risk for adult MetS from 5 years of age onward.[103] The risk for type 2 diabetes was increased beginning at 8 years of age (RR, 2.6 [95% CI, 1.4–6.8]) on the basis of international cutoff values for definition of childhood MetS. Risk of carotid IMT was increased beginning at 11 years of age (RR, 2.44 [95% CI, 1.55–3.55]) using the same definition.
- Among 1757 youths from the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study, those with MetS in youth and adulthood were at 3.4 times increased risk of high carotid IMT and 12.2 times increased risk of type 2 diabetes in adulthood compared with those without MetS at either time. Adults whose MetS had resolved after their youth did not have an increased risk of having high IMT or type 2 diabetes.[167]
- In the Princeton Lipid Research Cohort Study, MetS 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 of age) to those who developed CVD later in life (mean, 50 years of age).[168] MetS severity score was also strongly associated with early onset of diabetes.[169]
- MetS score, based on the number of components of MetS, was associated with biomarkers of inflammation, endothelial damage, and CVD risk in a separate cohort of 677 prepubertal children.[170]

Adults

MetS and Subclinical CVD

- MetS has also been associated with incident AF,[171,172], HF,[173] and PAD.[174]
- In MESA, among 6603 people 45 to 84 years of age (1686 [25%] with MetS without diabetes and 881 [13%] with diabetes), subclinical atherosclerosis assessed by CAC was more severe in people with MetS and diabetes than in those without these conditions, and the extent of CAC was a strong predictor of CHD and CVD events in these groups.[175] There appears to be a synergistic relationship between MetS, NAFLD, and prevalence of CAC,[176,177] as well as a synergistic relationship with smoking.[178] Furthermore, the progression of CAC was greater in people with MetS and diabetes than in those without, and progression of CAC predicted future CVD event risk both in those with MetS and in those with diabetes.[179] In MESA, the prevalence of thoracic calcification was 33% for people with MetS compared with 38% for those with diabetes (with and without MetS) and 24% of those with neither diabetes nor MetS.[180]

- In the DESIR cohort, MetS 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 MetS.[181] In MESA, MetS was associated with major and minor electrocardiographic abnormalities, although this varied by sex.[182] MetS is associated with reduced heart rate variability and altered cardiac autonomic modulation in adolescents.[183]
- Individuals with MetS have a higher degree of endothelial dysfunction than individuals with a similar burden of traditional cardiovascular risk factors.[184] Furthermore, individuals with both MetS and diabetes have demonstrated increased microvascular and macrovascular dysfunction.[185] MetS is associated with increased thrombosis, including increased resistance to aspirin[186] and clopidogrel loading.[187]
- In a meta-analysis of 8 population-based studies that included 19696 patients (22.2% with MetS), MetS 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 MetS (pooled OR, 1.61 [95% CI, 1.29–2.01]; *P*<0.0001).[188]
- In modern imaging studies using echocardiography, MRI, cardiac CT, and positron emission tomography, MetS has been shown to be closely related to increased epicardial adipose tissues,[189] regional neck fat distribution,[190] increased visceral fat in other locations,[191] increased ascending aortic diameter,[192] high-risk coronary plaque features including increased necrotic core,[193] impaired coronary flow reserve,[194] abnormal indexes of LV strain,[195,196] LV diastolic dysfunction,[197] LV dyssynchrony,[198] and subclinical RV dysfunction.[199]

MetS and Non-CVD Complications

Diabetes

- In data from ARIC and JHS, MetS was associated with an increased risk of diabetes (HR, 4.36 [95% CI, 3.83–4.97]), although the association was attenuated after adjustment for the individual components of the MetS.[200] However, use of a continuous sex- and race-specific MetS severity *z* score was associated with an increased risk of diabetes that was independent of individual MetS components, with increases in this score over time conferring additional risk for diabetes.
- In data from the Korean Genome Epidemiology Project, incident MetS and persistent MetS over 2 years were significantly associated with 10-year incident diabetes even after adjustment for confounding factors (aHR, 1.75 [95% CI, 1.30–2.37] and 1.98 [95% CI, 1.50–2.61], respectively), whereas resolved MetS over 2 years did not significantly increase the risk of diabetes after adjustment for confounders (aHR, 1.28 [95% CI, 0.92–1.75]).[201]

Kidney Disease

- Among 633 nondiabetic Chinese adults receiving a first renal transplantation, presence of pretransplantation MetS was an independent predictor of development of prevalent (aOR, 1.28 [95% CI, 1.04–1.51]) and incident (aOR, 2.75, [95% CI, 1.45–6.05]) posttransplantation diabetes.[202]
- In RENIS-T6, MetS was associated with a mean 0.30–mL/min per year (95% CI, 0.02–0.58 mL/min per year) faster decline in GFR than in individuals without MetS.[203]

Cancer

- MetS is also associated with cancer (in particular, breast, endometrial, prostate, pancreatic, hepatic, colorectal, and renal),[204–206] as well as gastroenteropancreatic neuroendocrine tumors.[207]
- MetS is linked to poorer cancer outcomes, including increased risk of recurrence and overall mortality.[205,208] In a meta-analysis of 24 studies that included 132589 males with prostate cancer (17.4% with MetS), MetS was associated with worse oncological outcomes, including biochemical recurrence and more aggressive tumor features.[209] Among 94555 females free of cancer at baseline in the prospective NIH-AARP cohort, MetS was associated with increased risk of breast cancer mortality (HR, 1.73 [95% CI, 1.09–2.75]), particularly among postmenopausal females (HR, 2.07 [95% CI, 1.32–3.25]).[210]
- In a meta-analysis of 17 prospective longitudinal studies that included 602195 women and 15945 cases of breast cancer, MetS was associated with increased risk of incident breast cancer in postmenopausal women (adjusted RR, 1.25 [95% CI, 1.12–1.39]) but significantly reduced breast cancer risk in premenopausal women (adjusted RR, 0.82 [95% CI, 0.76–0.89]). Further analyses showed that the association between MetS and increased risk of breast cancer was observed only among White and Asian women, whereas there was no association in Black women.[211]
- In data obtained from HCUP, hospitalized patients with a diagnosis of MetS and cancer had significantly increased odds of adverse health outcomes, including increased postsurgical complications (OR, 1.20 [95% CI, 1.03–1.39] and OR, 1.22 [95% CI, 1.09–1.37] for breast and prostate cancer, respectively).[212]

- In 25038 Black and White individuals in the REGARDS study, MetS was associated with increased risk of cancer-related mortality (HR, 1.22 [95% CI, 1.03–1.45]).[204] For those with all 5 MetS components present, the risk of cancer mortality was 59% higher than for those without a MetS component present (HR, 1.59 [95% CI, 1.01–2.51]).
- In NHANES III, MetS 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]).[213]
- In Japanese men and women 18 to 90 years of age who were registered between 1992 and 1995 as part of the Jichi Medical School Cohort Study and followed up for a mean of 18.5 years, MetS was associated with cancer mortality in women (HR, 1.69 [95% CI, 1.21–2.36]) but not in men (HR, 1.21 [95% CI, 0.90–1.62]).[208]
- MetS was associated with a higher incidence of hepatocellular carcinoma in males (RR, 1.75 [95% CI, 1.28–2.38]) but not in females (RR, 1.18 [95% CI, 0.76–1.84]).[214]

Gastrointestinal

- 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 MetS. On the basis of data from NHANES 2011 to 2014, the overall prevalence of NAFLD among US adults was 21.9%.[215] The global prevalence of NAFLD is estimated at 25.2%.[216] In a prospective study of 4401 Japanese adults 21 to 80 years of age who were free of NAFLD at baseline, the presence of MetS increased the risk for NAFLD in both males (OR, 4.00 [95% CI, 2.63–6.08]) and females (OR, 11.20 [95% CI, 4.85–25.87]).[217] In cross-sectional studies, an increase in the number of MetS components was associated with underlying nonalcoholic steatohepatitis and advanced fibrosis in NAFLD in adults and children.[215,218,219]
- MetS has been associated with cirrhosis,[220] colorectal adenomas,[221] and Barrett esophagus.[222]

Other

- Among 725 Chinese adults ≥90 years of age, MetS was associated with prevalent disability in activities of daily living (OR, 1.65 [95% CI, 1.10–3.21]) and instrumental activities of daily living (OR, 2.09 [95% CI, 1.1 7–4.32]).[223]
- MetS is associated with dementia,[224] cognitive decline,[225] and possibly VTE[226] and incident asthma.[227]
- MetS is also associated with erectile dysfunction.[228] In MESA, the prevalence of erectile dysfunction among participants 55 to 65 years of age with MetS was 16% compared with 10% in their counterparts without MetS (P<0.001).[228]
- MetS is associated with higher bone mineral density and, in some but not all studies, a decreased risk of bone fractures, depending on the definition of MetS used, fracture site, and sex.[229,230] Among adults from a population-based risk factor surveillance program in Vorarlberg Austria, MetS z scores were inversely associated with hip fracture risk only in women (HR, 0.80 [95% CI, 0.88–0.96]), and this relationship was no longer significant after adjustment for BMI, suggesting that the relationship between MetS and fracture risk may be explained by BMI.[231]

Cost and Health Care Use

- MetS is associated with increased health care use and health care–related costs among individuals with and without diabetes. Overall, health care costs increase by ≈24% for each additional MetS component present.[232]
- The presence of MetS 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.[212,233,234]

Global Burden of MetS (See Charts 10-7 and 10-8)

- MetS is becoming hyperendemic around the world. Published evidence has described the prevalence of MetS in Canada,[235] Latin America,[236] India,[237–240] Bangladesh,[241], Iran,[242,243] Nigeria,[244] Ghana,[245] the Gaza Strip,[246] South Africa,[247] Ecuador,[248] Nigeria,[249] and Vietnam,[250] as well as many other countries.
- On the basis of data from NIPPON DATA (1990–2005), the age-adjusted prevalence of MetS in a Japanese population was 19.3%.[160] In a partially representative Chinese population, the 2009 age-adjusted prevalence of MetS in China was 21.3%,[251] whereas in northwest China, the prevalence for 2010 was 15.1%,[252] and in 2018, the prevalence in Chinese adults in Hong Kong was 14.1%.[253]
- The prevalence of MetS and MHO in obese subjects varied considerably by European country in the BioSHaRE consortium, which harmonizes modern data from 10 different population-based cohorts in 7 European countries (Chart 10-7).[254]
- The prevalence of MetS 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.[255]

- In a systematic review of 10 Brazilian studies, the weighted mean prevalence of MetS in Brazil was 29.6%.[256]
- In a meta-analysis of 10 191 subjects across 6 studies, the prevalence of MetS in Argentina was 27.5% (95% CI, 21.3%–34.1%), and the prevalence was higher in males than in females (29.4% versus 27.4%; *P*=0.02).[257]
- In a report from a representative survey of the northern state of Nuevo León, Mexico, the prevalence of MetS in adults (≥16 years of age) 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%).[258] Among older Mexican adults (≥65 years of age), the prevalence was 72.9% (75.7% in males, 70.4% in females).[259]
- MetS is highly prevalent in modern indigenous populations, notably in Brazil and Australia. The prevalence of MetS was estimated to be 41.5% in indigenous groups in Brazil,[256,258] 33.0% in Australian Aborigines, and 50.3% in Torres Strait Islanders.[260]
- In a meta-analysis of cross-sectional studies that assessed the prevalence of MetS in 15 Middle Eastern countries, the pooled prevalence estimate for MetS was 31.2% (95% CI, 28.4%–33.9%). Pooled prevalence estimates ranged from a low of 23.6% in Kuwait up to 40.1% in the United Arab Emirates, depending on the time frame, country studied, and definition of MetS used (Chart 10-8). There was high heterogeneity among the 61 included studies.[261]

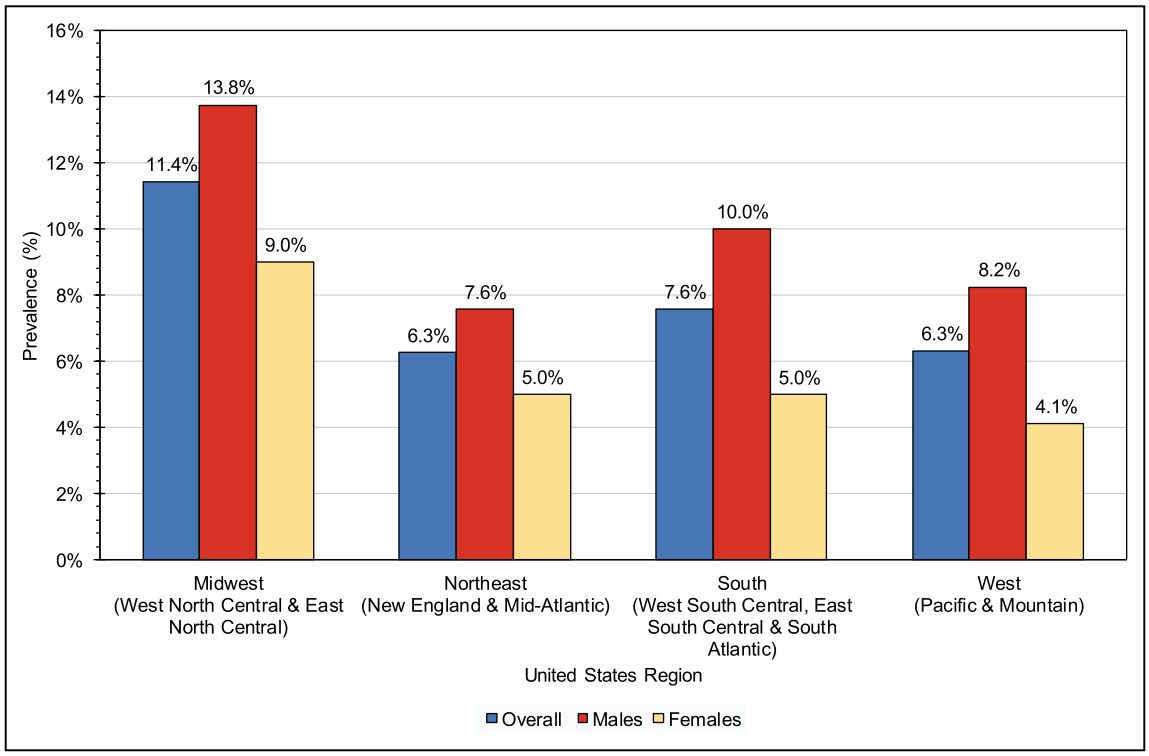

Chart 10-1. Prevalence of metabolic syndrome by sex and US region among adolescents 12 to 19 years of age (NHANES, 1999–2014).
NHANES indicates National Health and Nutrition Examination Survey.
Source: Data derived from DeBoer et al.[3]

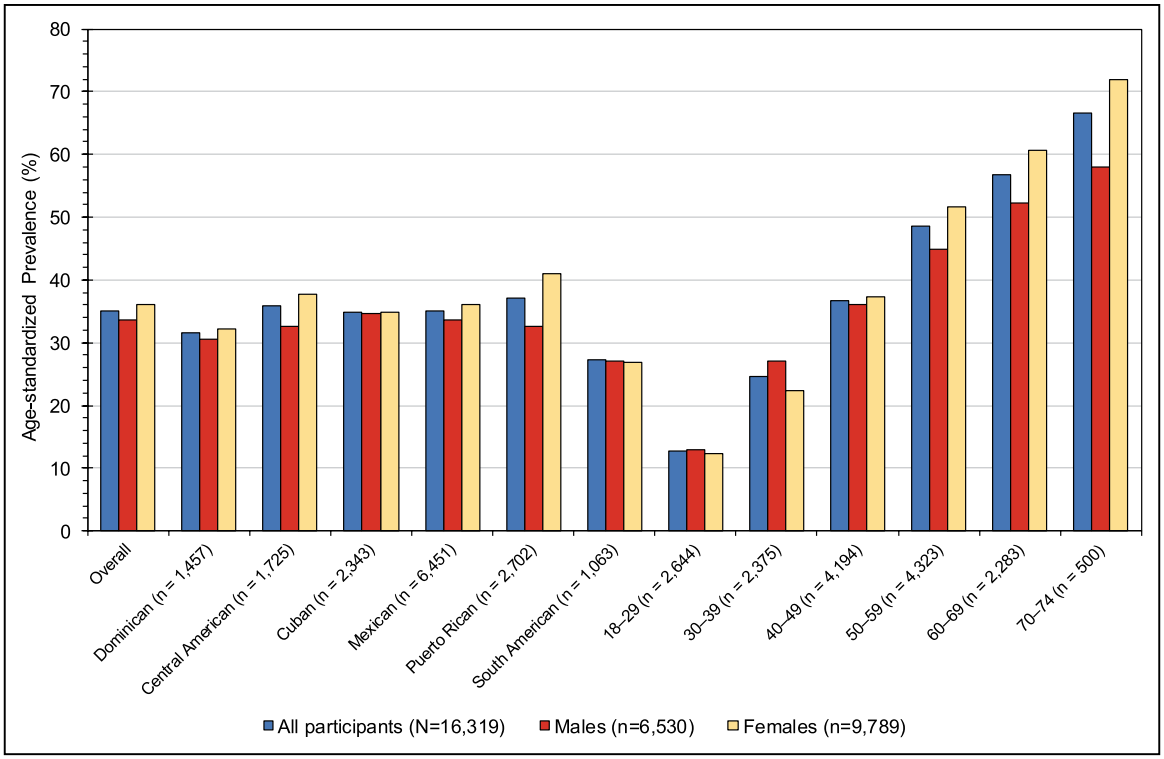

Chart 10-2. Age-standardized prevalence of metabolic syndrome by age and sex in Hispanic/Latino people in HCHS/SOL, United States, 2008 to 2011.
Values were weighted for survey design and nonresponse and were age standardized to the population described by the 2010 US census.
HCHS/SOL indicates Hispanic Community Health Study/Study of Latinos.
Source: Data derived from Heiss et al.[10]

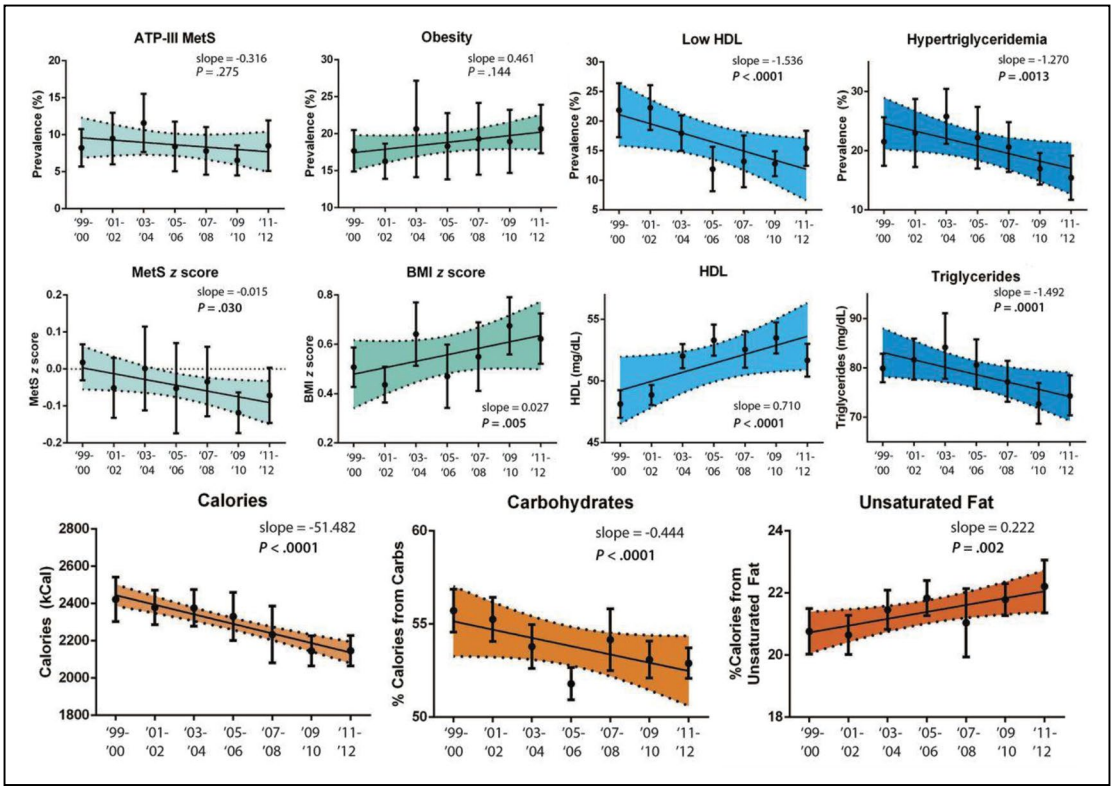

Chart 10-3. Prevalence of MetS in US youth (NHANES, 1999–2012).
ATP III indicates Adult Treatment Panel III; BMI, body mass index; Carbs, carbohydrates; HDL, high-density lipoprotein; MetS, metabolic syndrome; and NHANES, National Health and Nutrition Examination Survey.
Source: Reproduced with permission from Lee et al.[37] Copyright © 2016, by the American Academy of Pediatrics.

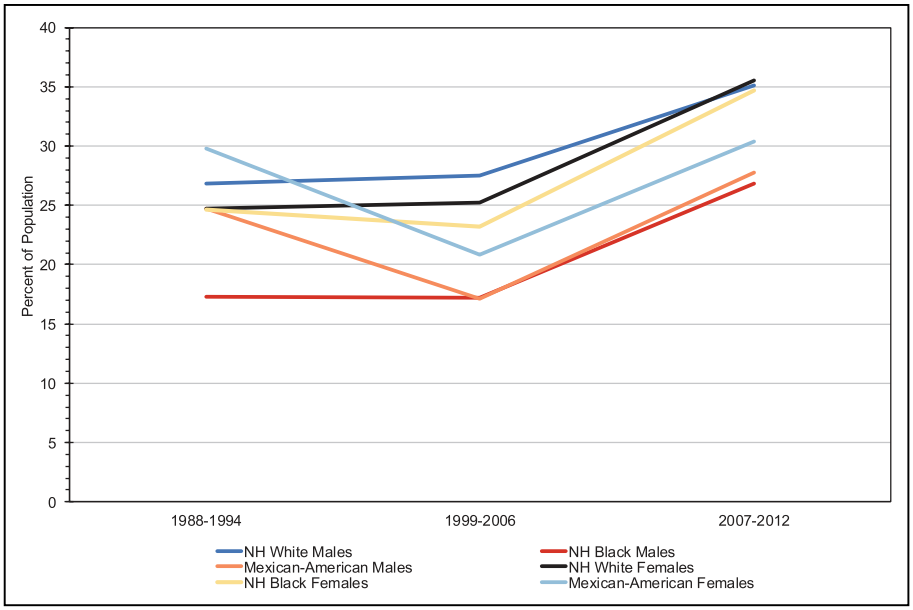

Chart 10-4. Prevalence of metabolic syndrome (MetS) among US adults using the harmonized MetS criteria (NHANES, 1998–2012).
MetS was defined using the criteria agreed to jointly by the International Diabetes Federation; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity.
NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
Source: Data derived from Moore et al.[38]

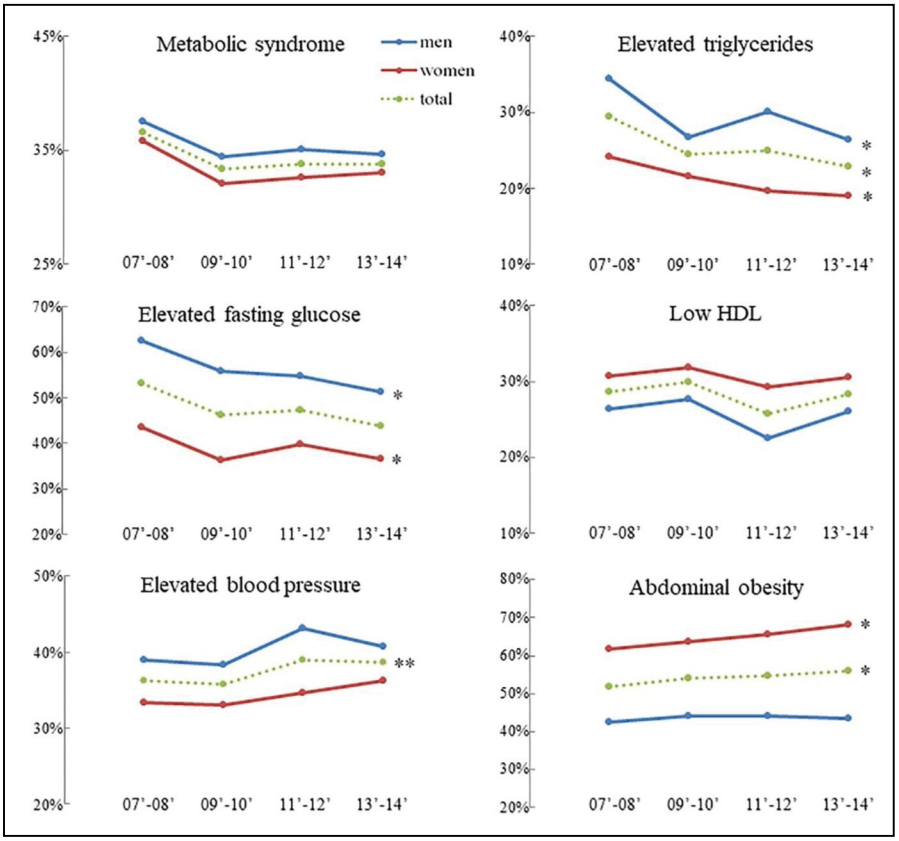

Chart 10-5. Sex-stratified trends in the age-adjusted weighted prevalence of metabolic syndrome (MetS) using Adult Treatment Panel III (ATP III) criteria and its components among US adults (NHANES, 2007–2014).
MetS was defined using modified National Cholesterol Education Program–ATP III criteria.
HDL indicates high-density lipoprotein; and NHANES, National Health and Nutrition Examination Survey.
**P* for trend <0.05.
***P* for trend=0.05 after adjustment for age, sex, and race, as appropriate.
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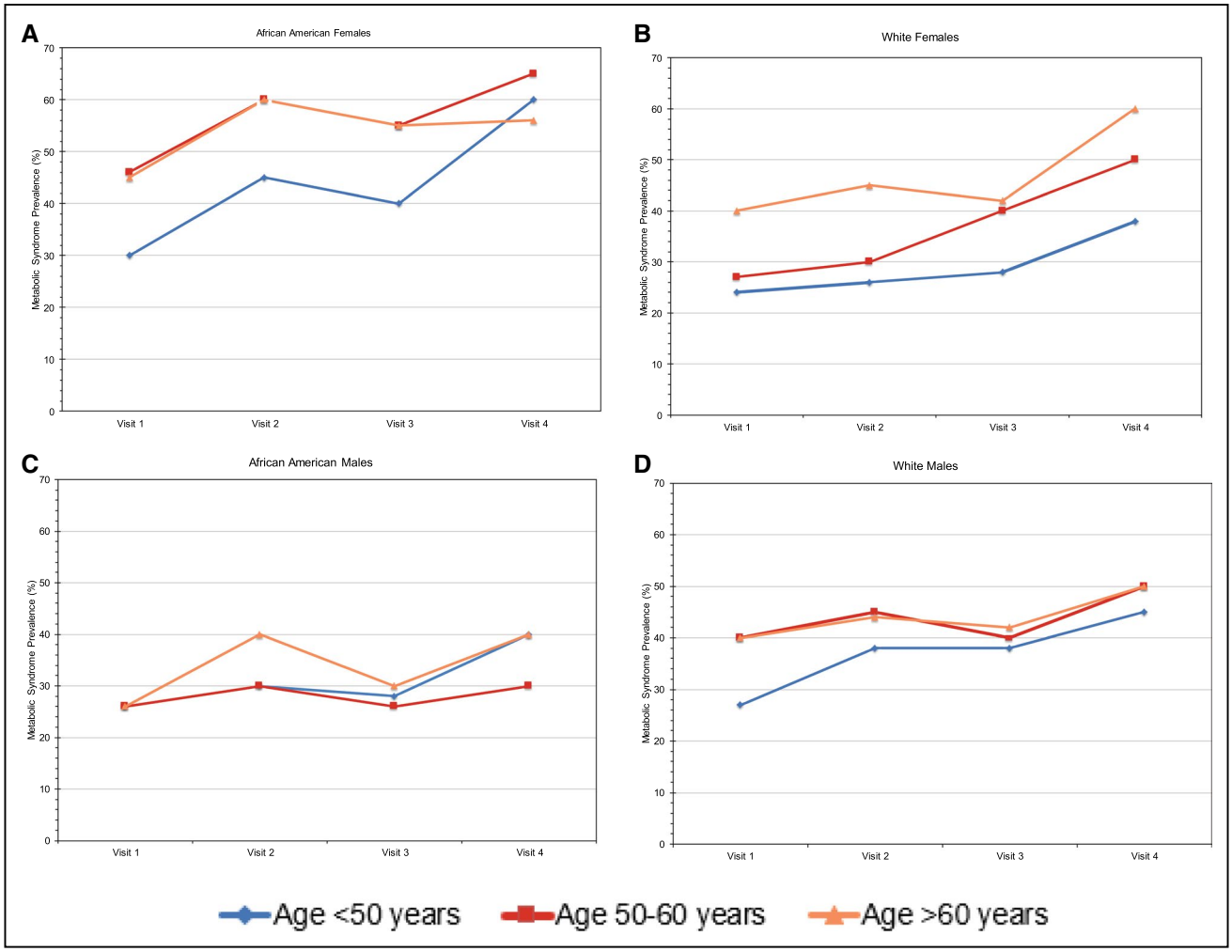

Chart 10-6. Ten-year progression of metabolic syndrome in the ARIC study, stratified by age, sex, and race/ethnicity, United States, 1987 to 1998.
A, African American females. **B**, White females. **C**, African American males. **D**, White males. Data obtained from visit 1 (1987–1989), visit 2 (1990–1992), visit 3 (1993–1995), and visit 4 (1996–1998).
ARIC indicates Atherosclerosis Risk in Communities.
Source: Data derived from Vishnu et al.[40]

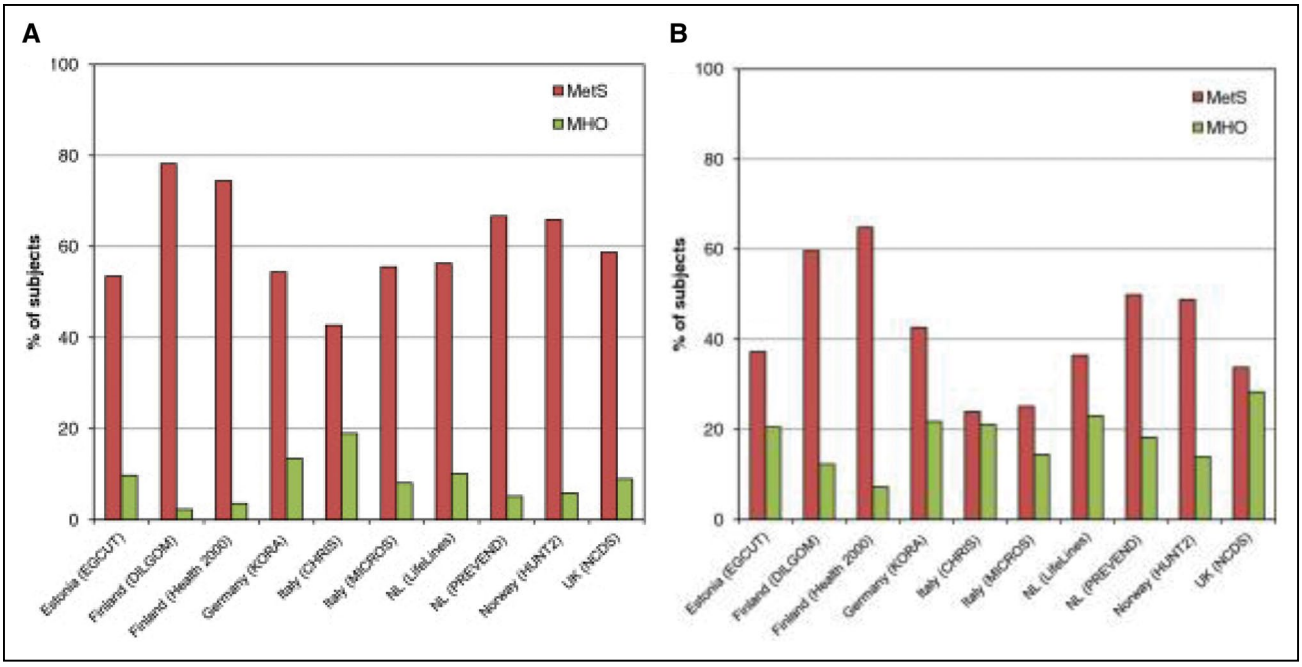

Chart 10-7. Age-standardized prevalence of MetS and MHO among obese (body mass index ≥30 kg/m2) people in different European cohorts, 1995 to 2012 (global data).

A, Males. **B**, Females.

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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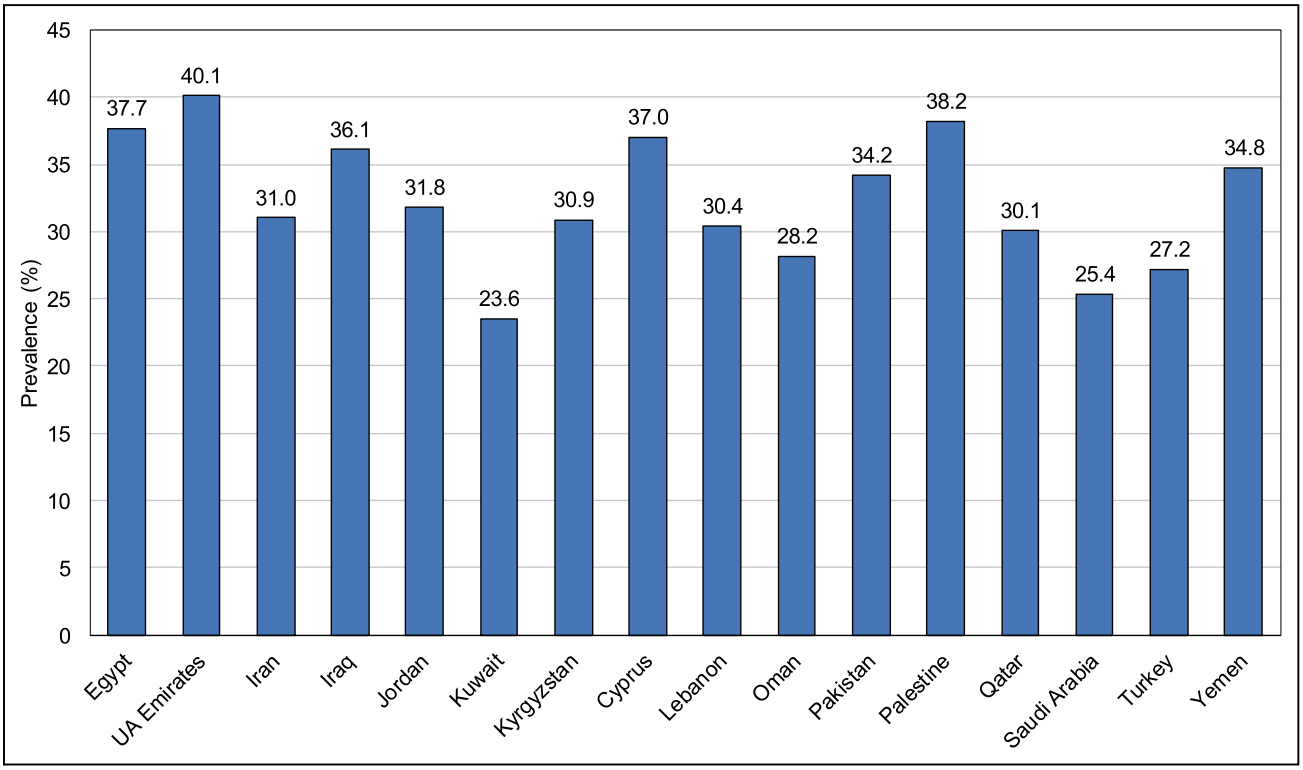

Chart 10-8. Estimated pooled prevalence* of metabolic syndrome in countries in the Middle East (2001–2018).

UA indicates United Arab.

*Pooled prevalence estimates obtained using random-effects model.

Source: Data derived from Ansari-Moghaddam et al.[261]

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11. ADVERSE PREGNANCY OUTCOMES

See Table 11-1 and Charts 11-1 through 11-9

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APOs include gestational hypertension, preeclampsia, gestational diabetes, preterm birth, and delivery of an SGA infant. These interrelated disorders reflect a response to the "stress test" of pregnancy, and they are associated with risk of poor future maternal and offspring CVH outcomes, including CHD, stroke, and HF. Furthermore, growing rates of maternal mortality in the United States are attributed predominantly to CVD. Because of this, the AHA has recognized the importance of these disorders in comprehensive CVH promotion and CVD prevention in females.[1] Furthermore, the AHA has encouraged collaboration between cardiologists and obstetricians/gynecologists to promote CVH in females across the reproductive life course with a special focus on pregnancy, given the intergenerational impact on both maternal and offspring health.[2]

This chapter focuses only on maternal and offspring complications of mortality, CVD, CVH (risk factors), and brain health; complications in other organ systems are important sources of APO-related maternal (eg, acute kidney injury) and offspring (eg, necrotizing enterocolitis) morbidity and mortality but are beyond the scope of this chapter. In addition, pregnancy complications related to PPCM and risk associated with congenital malformations are addressed elsewhere (see Chapter 21 for pregnancy-related HF and PPCM and Chapter 16 for pregnancy-related risk factors for congenital HD).

Abbreviations Used in Chapter 11

ACC	American College of Cardiology
AHA	American Heart Association
aHR	adjusted hazard ratio
aOR	adjusted odds ratio
APO	adverse pregnancy outcomes
BMI	body mass index
CAC	coronary artery calcification
CARDIA	Coronary Artery Risk Development in Young Adults Study
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
CVD	cardiovascular disease
CVH	cardiovascular health
DBP	diastolic blood pressure
DCM	dilated cardiomyopathy
ED	emergency department
FMD	flow-mediated dilation
FVL	factor V Leiden
GBD	Global Burden of Disease Study
GRS	genetic risk score
GWAS	genome-wide association study
GWG	gestational weight gain
HAPO	Hyperglycemia and Adverse Pregnancy Outcome
HD	heart disease
HDP	hypertensive disorders of pregnancy
HF	heart failure
HR	hazard ratio
MET	metabolic equivalent
MetS	metabolic syndrome
NAFLD	nonalcoholic fatty liver disease
NCHS	National Center for Health Statistics
NH	non-Hispanic
NHS	Nurses' Health Study
OR	odds ratio
OSA	obstructive sleep apnea
PA	physical activity
PAF	population attributable fraction
PAR	population attributable risk
PPCM	peripartum cardiomyopathy
PTB	preterm births
RCT	randomized controlled trial
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SDB	sleep disordered breathing
SGA	small for gestational age
WHI	Women's Health Initiative
WHO	World Health Organization

(*Continued*)

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Classification of APOs

- HDP
  - — Gestational hypertension: de novo hypertension that develops after week 20 of pregnancy

without protein in the urine or evidence of end-organ involvement
  - — Preeclampsia/eclampsia: hypertension after week 20 of pregnancy, most often de novo, with protein in the urine or other evidence of end-organ involvement is defined as preeclampsia and may progress to the convulsive phase or eclampsia
- Gestational diabetes: de novo diabetes that develops after week 20 of pregnancy
- PTB: spontaneous or indicated delivery before 37 weeks' gestation
- SGA infant: birth weight ≤10th percentile for gestational age; called intrauterine growth restriction during gestation; alternative definition for a low-birth-weight infant includes birth weight <2500 g
- Pregnancy loss: spontaneous loss of a nonviable, intrauterine pregnancy; further categorized according to gestational age at which loss occurs
  - — Stillbirth: loss occurs at ≥20 weeks' gestational age; also called late fetal death and intrauterine fetal demise
  - — Miscarriage: loss occurs before 20 weeks' gestational age; also called spontaneous abortion

Any APO

Incidence

- APOs (including HDP, gestational diabetes, PTB, and SGA at birth) occur in 10% to 20% of pregnancies.[3]

Risk Factors (See Chart 11-1)

- Chart 11-1 shows risks for any APO (including HDP, gestational diabetes, PTB, and SGA or large size for gestational age at birth) according to maternal weight categories based on a meta-analysis of individual participant data from 265 270 females from 39 European, North American, and Oceanic cohort studies. Risk of APO was greater with higher categories of prepregnancy BMI as well as greater degree of GWG with an aOR of 2.51 (95% CI, 2.31–2.74) for women with prepregnancy obesity and high (≥1.0 SD) GWG.[4]
- Similar findings were observed in a separate meta-analysis of individual participant data from 196 670 females from 25 European and North American cohort studies with estimates that 23.9% of pregnancy complications were attributable to maternal overweight or obesity defined as BMI ≥25.0 kg/m^2.[5]
- Examination of state Medicaid expansion noted an association with improvement in relative disparities between Black people and White people in rates of PTB and low-birth-weight infants among states that expanded compared with those that did not. Difference in difference models between 2011 and 2016 estimated a decline of −0.43 percentage points (95% CI, −0.84 to −0.002) for PTB and −0.53 percentage points (95% CI, −0.96 to −0.10) for low birth weight for Black infants compared with White infants.[6]

Social Determinants

- Socioeconomic disparities in births exist; 42.3% of females had Medicaid listed as source of payment for delivery in 2018.[7]
- In a French multicenter study of 464 females, individual social deprivation (based on factors such as economic position, health insurance, marital status, family support, and leisure activity) was associated with higher risk for a composite APO of preterm delivery, gestational diabetes, or HDP, with an aOR of 1.95 (95% CI, 1.15–3.29).[8]

Complications: Maternal Mortality and CVD

Mortality

- The maternal mortality rate was 17.4 per 100 000 live births in 2018.[9] Maternal mortality is defined by the NCHS as death while pregnant or within 42 days of being pregnant; late maternal deaths occurring between 43 days and 1 year are not included as part of the definition.
  - — Maternal mortality rates were higher in older age groups for females ≥40 years of age compared with females <25 years of age (81.9 versus 10.6 per 100 000 live births) in 2018.
  - — Significant disparities were present with the maternal mortality rate for NH Black females 2.5-fold and 3-fold greater than NH White and Hispanic females, respectively (37.1 versus 14.7 and 11.8 per 100 000 live births) in 2018.
- Cardiovascular deaths are the most common cause of maternal mortality, accounting for 26.5% of deaths according to an observational study using 2011 to 2013 data from the CDC Pregnancy Mortality Surveillance System.[10,11]

Cardiovascular Disease

- Among 4484 females from the Nulliparous Pregnancy Outcomes Study Monitoring Mothers-to-be Heart Health Study, a prospective observational cohort, APO occurred in 1017 females (22.7%). In short-term follow-up over a mean of 3.2 years, the overall incidence of hypertension was 5.4% (95% CI, 4.7%–6.1%) with an increased risk among females with any APO (RR, 2.4 [95% CI, 1.8–3.1]) and by subtype (HDP: RR, 2.7 [95% CI, 2.0–3.6]; preeclampsia: RR, 2.8 [95% CI, 2.0–4.0]; PTB; RR, 2.7 [95% CI, 1.9–3.8]). Females who experienced both HDP and PTB had the highest risk of incident hypertension (RR, 4.3 [95% CI, 2.7–6.7]).[12]

Hypertensive Disorders of Pregnancy

Incidence, Prevalence, and Secular Trends (See Chart 11-2)

- Rates of overall HDP are increasing. Analysis of delivery hospitalizations from the National Readmission Database reported a rate of HDP of 912.4 per 10 000 delivery hospitalizations in 2014 compared with 528.9 in 1993 in the United States (Chart 11-2).[13]

Risk Factors (Including Social Determinants)

- Among 9470 nulliparous pregnant females (60.4% NH White, 13.8% NH Black, 16.7% Hispanic, 4.0% Asian, 5.0% other), NH Black females were significantly more likely to experience HDP compared with NH White females (16.7% versus 13.4%, respectively; OR, 1.30 [95% CI, 1.10–1.53]), whereas Hispanic females and Asian females were less likely to experience HDP (10.6%, OR, 1.77 [95% CI, 0.64–0.91]; and 8.5%, OR, 0.60 [95% CI, 0.41–0.87] versus NH White females, respectively).[14] These differences were largely attenuated after adjustment for age, BMI, smoking, and medical comorbidities.
- In a meta-analysis of 25 356 688 pregnancies from 92 studies published between 2000 and 2015, the following factors at ≤16 weeks' gestation were associated with significantly elevated risks for preeclampsia (reported as pooled unadjusted RR [95% CI]): maternal age >35 years (versus <35 years) (1.2 [95% CI, 1.1–1.3]), prior preeclampsia (8.4 [95% CI, 7.1–9.9]), chronic hypertension (5.1 [95% CI, 4.0–6.5]), prepregnancy diabetes (3.7 [95% CI, 3.1–4.3]), prepregnancy obesity (BMI >30 kg/m^2 versus <30 kg/m^2) (2.8 [95% CI, 2.6–3.1]), prior stillbirth (2.4 [95% CI, 1.7–3.4]), multifetal pregnancy (2.9 [95% CI, 2.6–3.1]), nulliparity (2.1 [95% CI, 1.9–2.4]), CKD (1.8 [95% CI, 1.5–2.1]), systemic lupus erythematosus (2.5 [95% CI, 1.0–6.3]), antiphospholipid antibody syndrome (2.8 [95% CI, 1.8–4.3]), and conception by assisted reproductive techniques (1.8 [95% CI, 1.6–2.1]). PAF was highest for nulliparity (32.3% [95% CI 27.4%–37.0%]), followed by prepregnancy BMI >25 kg/m^2 (23.8% [95% CI, 22.0%–25.6%]) and prior preeclampsia (22.8% [95% CI, 19.6%–26.3%]).[15]
- In a meta-analysis of 13 studies including 156 170 singleton pregnancies in females who delivered at term, higher-than-recommended GWG per the 2009 National Academy of Medicine (Institute of Medicine) guidelines (12.5–18 kg for underweight [BMI <18.5 kg/m^2], 11.5–16 kg for normal weight [BMI, 18.5–24.9 kg/m^2], 7.0–11.5 kg for overweight [BMI, 25.0–29.9 kg/m^2], and 5.0–9.0 kg for obese [BMI >30.0 kg/m^2]) was associated with higher risks for overall HDP (OR, 1.79 [95% CI, 1.61–1.99]), gestational hypertension (OR, 1.67 [95% CI, 1.43–1.95]), and preeclampsia (OR, 1.92 [95% CI, 1.36–2.72]).[16]
- In a meta-analysis of 25 studies, polycystic ovary syndrome was associated with higher risks for preeclampsia (RR, 2.79 [95% CI, 2.29–3.38]) and gestational hypertension (RR, 2.46 [95% CI, 1.95–3.09]).[17]
- There is evidence of intergenerational transmission of HDP risk. According to multigenerational birth records for 17 302 nulliparous females in the Aberdeen Intergenerational Cohort, being born of a pregnancy complicated by preeclampsia or gestational hypertension was associated with higher risk for preeclampsia (adjusted RR ratio, 2.55 [95% CI, 1.87–3.47] and 1.44 [95% CI, 1.23–1.69], respectively) and gestational hypertension (adjusted RR ratio, 1.37 [95% CI, 1.09–1.71] and 1.36 [95% CI, 1.24–1.49], respectively).[18]
- In meta-analyses, immigrant (versus nonimmigrant) status has been associated with lower risk of HDPs (RR, 0.74 [95% CI, 0.67–0.82]),[19] and rural (versus urban) residence has been associated with no significant difference in preeclampsia (OR, 0.98 [95% CI, 0.87–1.11]) but higher risk of eclampsia (OR, 2.70 [95% CI, 1.80–4.07]).[20]

Genetics/Family History

- HDP may have genetic risk factors. Preeclampsia is a heritable disease with heritability estimates ranging from 31% to 54%.[21,22] In 1 study, daughters of women who had preeclampsia had a >2 times higher risk of preeclampsia themselves compared with other women (OR, 2.2 [95% CI, 2.0–2.4]).[23]
- However, in a study of 2 birth cohorts of female monozygotic and dizygotic twin pairs (n=2362 pairs), no concordance for preeclampsia or eclampsia was found,[24] suggesting the influence of nonmaternal genetic factors. This is supported by data from the Swedish Birth and Multi-Generation Registries of 244 564 sibling pairs in which 35% of the variance in liability of preeclampsia was attributable to maternal genetic effects, 20% to fetal genetic effects (with similar contribution of maternal and paternal genetic effects), 13% to the couple effect, and <1% to shared sibling environment.[25]
- Studies have identified variants associated with preeclampsia, some of which share susceptibility with cardiovascular risk. A GWAS of preeclampsia analyzed 4380 offspring of women with preeclampsia and 310 238 control subjects and identified a locus near the *FLT1* gene with strongest association in offspring from pregnancies in which preeclampsia developed during late gestation.[26] *FLT1* encodes a transmembrane tyrosine

kinase receptor that mediates angiogenesis by binding placental growth factor.

- Familial DCM is a single-gene (monogenic) trait; the same genes and genetic mutations that cause familial cardiomyopathy have been shown to predispose to PPCM. The prevalence of truncating variants in DCM genes was significantly greater in a cohort of 172 women with PPCM than in a general reference population (15% versus 4.7%; $P=1.3\times10^{-7}$) but similar to a cohort of patients with DCM (17%; $P=0.81$). Two-thirds of these identified truncating variants were in the *TTN* gene.[27] Furthermore, *TTN* variants are enriched in patients with preeclampsia, suggesting a shared genetic architecture among preeclampsia, PPCM, and DCM. In a study of 181 primarily White women with preeclampsia, the prevalence of loss-of-function variants in cardiomyopathy genes was higher in preeclampsia cases compared with controls (5.5% versus 2.5%; $P=0.014$), with most mutations found in the *TTN* gene[28] (see Chapter 21, Cardiomyopathy and Heart Failure).

Prevention

Lifestyle Modifications

- PA is recommended for pregnant females without obstetric or medical complications.[29–31] Several reviews of the literature that supported these guidelines indicate that PA (600 MET-min/wk of moderate-intensity exercise) during pregnancy can decrease the odds of HDP by 25%.[32]
- Aerobic exercise for ≈30 to 60 minutes 2 to 7 times per week during pregnancy was associated with a significantly lower risk of gestational hypertension in a systematic review from 17 trials including 5075 pregnant females (RR, 0.70 [95% CI, 0.53–0.83] for HDP).[33]

Aspirin

- Low-dose aspirin started in early pregnancy reduces risk for some APOs among higher-risk females. In a meta-analysis of 42 RCTs including 27 222 nulliparous females at high risk for preeclampsia (based on medical history or ultrasonographic indicators), low-dose aspirin started at ≤16 weeks' gestation reduced the risks for preeclampsia (7.6% versus 17.9%; RR, 0.47 [95% CI, 0.36–0.62]), severe preeclampsia (1.5% versus 12.3%; RR, 0.18 [95% CI, 0.08–0.41]), fetal growth restriction (8.0% versus 17.6%; RR, 0.46 [95% CI, 0.33–0.64]), preterm delivery (4.8% versus 13.4%; RR, 0.35 [95% CI, 0.22–0.57]), and perinatal death (fetal death after 16 weeks' gestation or neonatal death before 28 days of age; 1.1% versus 4.0%; RR, 0.41 [95% CI, 0.19–0.92]).[34]
- Data on aspirin use in at-risk pregnant females are limited. In a retrospective cohort study at a single tertiary care hospital in Toronto, overall rate of documented aspirin use was 3.0% (95% CI, 2.6%–3.3%) among 8176 females. However, appropriate use of aspirin was low (prescribed in only 131 of 1727 pregnancies in females identified to be at risk for preeclampsia, 7.6% [95% CI, 6.3%–8.9%]).[35]

Complications: Maternal CVD

- According to a meta-analysis of 9 studies, gestational hypertension was associated with a 67% (95% intrinsic CI, 1.28%–2.19%) higher risk of subsequent CVD, and preeclampsia was associated with a 75% (95% intrinsic CI, 1.46%–2.06%) higher risk of subsequent CVD-related mortality.[36,37]
- On the basis of data on 1.3 million females abstracted between 1997 and 2016 in the clinical practice research datalink in the United Kingdom, females with preeclampsia had an increased risk of hypertension (HR, 4.47 [95% CI, 4.3–4.62]) and a variety of CVD subtypes (stroke: HR, 1.9 [95% CI, 1.53, 2.35]; atherosclerotic CVD, 1.67 [95% CI, 1.54–1.81]; HF: HR, 2.13 [95% CI, 1.64–2.76]; atrial fibrillation: HR, 1.73 [95% CI, 1.38–2.16]; and cardiovascular mortality: HR, 2.12 [95% CI, 1.49–2.99]).[38]
- In a systematic review identifying 37 studies that examined FMD before, during, or after pregnancy, females with preeclampsia had lower FMD before preeclampsia onset (between 20 and 29 weeks' gestation), at the time of preeclampsia diagnosis, and up to 3 years postpartum with varying magnitude of effect (0.5–3 SD), suggesting a mechanistic link between vascular dysfunction and risk of preeclampsia and future CVD.[39]

Complications: Offspring Morbidity and Mortality

- Among 6410 individuals born from 1934 to 1944 in the Helsinki Birth Cohort Study, in utero exposure to HDPs was significantly associated with risk of stroke (n=272 cases; for preeclampsia: HR, 1.9 [95% CI, 1.2–3.0]; for gestational hypertension: HR, 1.4 [95% CI, 1.0–1.8]; $P=0.03$) but not with the risk of CHD (n=464 cases; for preeclampsia: HR, 1.4 [95% CI, 0.9–2.1]; for gestational hypertension: HR, 1.0 [95% CI, 0.8–1.3]).[40]
- In a 2019 meta-analysis of studies reporting outcomes in childhood or young adulthood (up to 30 years of age), exposure to preeclampsia in utero was associated with higher SBP (pooled mean difference, 5.17 mm Hg [95% CI, 1.60–8.73]; 15 studies, 53 029 individuals, 1599 exposed), DBP (4.06 mm Hg [95% CI, 0.67–7.44]; 14 studies, 52 993 individuals, 1583 exposed), and BMI (0.36 kg/m^2 [95% CI, 0.04–0.68 kg/m^2]; 13 studies, 53 293 individuals, 1752 exposed).[41] No significant pooled associations were found for offspring lipids, glucose, or insulin.

Gestational Diabetes

Incidence, Prevalence, and Secular Trends (See Table 11-1 and Chart 11-3)

- National prevalence of gestational diabetes was 6.0% in 2016, an increase of 0.4% from 2012 according to birth data from the National Vital Statistics System. In 2016, maternal prevalence of preexisting diabetes complicating pregnancies was 0.9% (Table 11-1).[42]
  - The prevalence of gestational diabetes was highest in NH Asian females (11.1%) compared with Hispanic (6.6%), NH White (5.3%), and NH Black (4.8%) females.
  - Although data on disaggregated Asian subgroups are limited on the national level, data on 24 195 pregnant females identified through California State birth certificate records between 2007 and 2012 could be examined. Similar to the higher prevalence of type 2 diabetes, rates of gestational diabetes in females were more prevalent among almost all Asian American subgroups (Asian Indian, 19.3%; Filipino, 19.0%; Vietnamese, 18.8%; Chinese, 15.3%; Korean, 12.9%; Japanese, 9.7%) compared with Hispanic (13.3%) and NH White (7.0%) females.[43]
  - The proportion of pregnancies complicated by gestational diabetes varied by geography, with the highest rate in South Dakota (9.2%) and the lowest rate in the District of Columbia (3.4%) after standardization for age and race/ethnicity (Chart 11-3).

Risk Factors

- In an individual participant data meta-analysis of 265 270 births from 39 cohorts in Europe, North America, and Australia, higher prepregnancy BMI (OR per 1-kg/m^2 higher BMI, 1.12 [95% CI, 1.12–1.13]) and higher GWG (OR per 1-SD higher GWG, 1.14 [95% CI, 1.10–1.18]) were each associated with higher risks of gestational diabetes.[4] Approximately 42.8% of gestational diabetes cases were estimated as attributable to prepregnancy overweight (OR, 2.22 [95% CI, 2.06–2.40]) or obesity (OR, 4.59 [95% CI, 4.22–4.99]).
- Among 782 nulliparous females in the early second trimester with objectively measured sleep for 5 to 7 nights, short sleep duration (<7 hours per night average; present in 27.9%) and late sleep midpoint (>5 AM average; present in 18.9%) were significantly associated with risk for gestational diabetes (aOR, 2.06 [95% CI, 1.01–4.19] and 2.37 [95% CI, 1.13–4.97], respectively) independently of age, race/ethnicity, employment schedule, BMI, and snoring.[44]
- In a meta-analysis of 29 studies, polycystic ovary syndrome was associated with higher risk of gestational diabetes (RR, 2.78 [95% CI, 2.27–3.40]).[17]

Genetics/Family History

- Many of the genetic risk factors for type 2 diabetes overlap with those for gestational diabetes (See Chapter 10 for genetics/family history of MetS and type 2 diabetes). For example, in a cohort of 283 Danish women with a history of gestational diabetes and 2446 middle-aged control subjects with normal glucose tolerance, common type 2 diabetes risk variants rs7903146 in *TCF7L2* (OR, 1.44 [95% CI, 1.19–1.74]; *P*=0.00017), rs7756992 in *CDKAL1* (OR, 1.22 [95% CI, 1.00–1.49]; *P*=0.049), and rs7501939 in *TCF2* (OR, 1.22 [95% CI, 1.01–1.48]; *P*=0.039) were associated with gestational diabetes.[45] In another case-control study of 2636 women with gestational diabetes and 6086 women without gestational diabetes from the NHS II and the Danish National Birthday Cohort, a weighted GRS of 8 variants previously associated with diabetes was associated with gestational diabetes (OR for highest GRS quartile compared with lowest, 1.53 [95% CI 1.34–1.74]).[46]
- A GWAS of gestational diabetes in a discovery cohort of 468 Korean women with gestational diabetes and 1242 women without diabetes with validation in a second cohort of 931 cases and 783 controls also identified 2 known type 2 diabetes loci (a variant in *CDKAL1*: OR, 1.52; $P=6.7\times10^{-16}$; and a variant near *MTNR1B*: OR, 1.45, $P=2.5\times10^{-13}$ in joint analyses).[47]

Prevention

- In a population-based cohort study of 1333 females enrolled in the CARDIA study, higher prepregnancy fitness objectively measured with a treadmill test was associated with a 21% lower risk (95% CI, 0.65–0.96) of gestational diabetes (per 1-SD increment or 2.3 METs).[48]

Complications: Maternal CVD

- In a systematic review that pooled 8 cohort studies, the odds of CVD in females with gestational diabetes was 68% higher (95% CI, 1.11–2.52) compared with females without gestational diabetes.[36]
- On the basis of data from females recruited and enrolled in a population-based cohort study, CARDIA, among females who reported a history of gestational diabetes compared with those who did not have gestational diabetes and had at least 1 live birth, rates of incident diabetes (incidence rate, 18.0 [95% CI, 13.3–22.8] versus 5.1 [95% CI, 4.2–6.0]), NAFLD (OR, 2.29 [95% CI, 1.23–4.27]; *P*=0.01),[49] and adverse cardiac structure and function were higher in >20 years of follow-up.[50]

Complications: Offspring Morbidity and Mortality

- Among 2 432 000 live-born children without congenital HD in the Danish national health registries during 1977 to 2016, in utero exposure to gestational diabetes was associated with higher risk for CVD during up to 40 years of follow-up (aOR, 1.19 [95% CI, 1.07–1.32]).[51] Findings were similar when a sibship design was used (ie, comparing exposed with unexposed siblings) and when controlling for maternal prepregnancy BMI and paternal diabetes status.
- In the multinational HAPO Follow-Up Study of 4832 children 10 to 14 years of age, in utero exposure to gestational diabetes, independently of maternal BMI during pregnancy, was associated with higher odds of obesity (aOR, 1.58 [95% CI, 1.24–2.01]; risk difference, 5.0% [95% CI, 2.0%–8.0%]) and excess adiposity (body fat percentage >85th percentile; aOR, 1.35 [95% CI, 1.08–1.68]; risk difference, 4.2% [95% CI, 0.9%–7.4%]) at 10 to 14 years of age.[52] Gestational diabetes exposure was also associated with greater odds for impaired glucose tolerance at 10 to 14 years of age, independently of maternal BMI, child BMI, and family history of diabetes (aOR, 1.96 [95% CI, 1.41–2.73]).[53]

Preterm Birth

Incidence, Prevalence, and Secular Trends (See Chart 11-4)

- The proportion of PTBs has also increased in the United States. In 2016, these accounted for 9.9% of all births. A similar proportion of PTBs (10.0%) was reported in 2018 of a total of 3 791 712 live births (or a birth rate of 11.6 per 1000 population).[7,54]
  - PTB rates were higher among NH Black females (14.1%) compared with NH White (9.1%) and Hispanic (9.7%) females in 2018 (Chart 11-4).[54]

Risk Factors

- Among 9470 nulliparous pregnant females (60.4% NH White, 13.8% NH Black, 16.7% Hispanic, 4.0% Asian, 5.0% other), preterm delivery occurred in 8.1% of NH White females, 12.3% of NH Black females (OR versus NH White females, 1.60 [95% CI, 1.32–1.93]), 8.1% of Hispanic females (OR, 1.00 [95% CI, 0.82–1.23]), and 6.3% of Asian females (OR, 0.77 [95% CI, 0.51–1.18]).[14] The higher risk among NH Black females was partly attenuated by adjustment for age, BMI, smoking, and medical comorbidities (aOR, 1.31 [95% CI, 1.06–1.63]) and, separately, for perceived social support (aOR, 1.35 [95% CI, 1.06–1.72]), although risk remained elevated. The OR for the association of low perceived social support (lowest quartile of support) with preterm delivery was 1.21 (95% CI, 1.01–1.44).
- Among 1482 nulliparous low-risk females at <20 weeks' gestation (who received placebo in a trial of low-dose aspirin to prevent preeclampsia), risks for indicated (but not spontaneous) preterm delivery were elevated even with mild stage 1 hypertension (SBP 130–135 mm Hg or DBP 80–85 mm Hg; 4.2% versus 1.1%, RR, 3.79 [95% CI, 1.28–11.20]; adjusted for age, race, and prepregnancy BMI: RR, 3.98 [95% CI, 1.36–11.70]).[55]
- In a meta-analysis of 6 studies, objectively measured SDB (OSA) was associated with higher risk of preterm delivery, with an aOR of 1.6 (95% CI, 1.2–2.2).[56] Short sleep duration and poor sleep quality were also associated with preterm delivery, with specific definitions and corresponding ORs varying between studies.[56]

Genetics/Family History

- Heritability estimates for birth weight and length of gestational length range from 25% to 40%.[57] In a study of 244 000 Swedish births, fetal genetic factors explained 13.1% (95% CI, 6.8–19.4) of variation in gestational age at delivery, and maternal genetic factors explained 20.6% (95% CI, 18.1–23.2).[58]
- A GWAS of gestational duration PTB analyzed a discovery set of 43 568 women of European ancestry and found that variants at the *EBF1*, *EEFSEC*, *AGTR2*, *WNT4*, *ADCY5*, and *RAP2C* loci were associated with gestational duration and variants at the *EBF1*, *EEFSEC*, and *AGTR2* loci were associated with PTB.[59] These genes have previously established roles in uterine development, maternal nutrition, and vascular control. Another GWAS, this one in 84 689 infants, found a locus on chromosome 2q13, which includes several IL-1 family member genes, associated with gestational duration.[60]

Complications: Maternal CVD

- In a meta-analysis of 14 studies, females with a history of PTB (<37 weeks' gestation) had a 63% (95% intrinsic CI, 1.39–1.93) higher risk of CVD compared with females with no history of PTB.[36]
- Among 1049 Black and White females in the CARDIA study, 272 (26%) had a pregnancy with a PTB (<37 weeks). Females with PTB were more likely to have an increasing trajectory of SBP and CAC (39% versus 12%) over 25 years of follow-up.[61]
- Among 57 904 females in the NHS II with at least 1 live birth, PTB was associated with increased risk of hypertension (HR, 1.11 [95% CI, 1.06–1.17]), type 2 diabetes (HR, 1.17 [95% CI, 1.03–1.33]), and hyperlipidemia (HR, 1.07 [95% CI, 1.03–1.11]).[62]

Complications: Offspring Morbidity and Mortality

- Among 4296 814 singleton live births in Sweden during 1973 to 2015 with up to 45 years of follow-up, gestational age at birth was inversely associated with mortality at 0 to 45 years of age, with an aHR of 0.78 (95% CI, 0.78–0.78) per 1-week-longer gestation.[63] Relative to full-term birth (39–41 weeks), preterm birth (<37 weeks) and early-term birth (37–38 weeks) were associated with mortality (aHR, 5.01 [95% CI, 4.88–5.15] and 1.34 [95% CI, 1.30–1.37], respectively), and earlier gestations were associated with even higher risks (eg, <28 weeks; aHR, 66.14 [95% CI, 63.09–69.34]). The HRs for mortality were highest in infancy (aHR for preterm, 17.15 [95% CI, 16.50–17.82]) and weakened at subsequent age intervals but remained significantly elevated through 30 to 45 years of age (aHR for preterm, 1.28 [95% CI, 1.14–1.43]).
- Among 2141 709 live-born singletons in the Swedish Birth Registry from 1973 to 1994 followed up through 2015 (maximum, 43 years of age), gestational age at birth was inversely associated with risk for premature CHD (aHR at 30–43 years of age versus full-term [39–41 weeks] births: for preterm [<37 weeks], 1.53 [95% CI, 1.20–1.94]; for early-term [37–38 weeks], 1.19 [95% CI, 1.01–1.40]).[64] Cosibling analyses supported an association that was independent of familial shared genetic and environmental factors.
- Among 1306 943 individuals without congenital malformations born in Sweden from 1983 to 1995 and followed up through 2010, birth before 32 weeks' gestation was associated with higher risk for premature cerebrovascular disease from 15 to 27 years of age (aHR, 1.89 [95% CI, 1.01–3.54] among 955 total cases of cerebrovascular disease).[65]

SGA Delivery

Incidence, Prevalence, and Secular Trends (See Chart 11-5)

- The percentage of low-birth-weight (defined as delivered at <2500 g) deliveries was 8.3% for 2017 to 2018, which has increased slightly since 2014 (8.0%). Prevalence of low birth weight by race is shown in Chart 11-5.[66]

Risk Factors

- Among 9470 nulliparous pregnant females (60.4% NH White, 13.8% NH Black, 16.7% Hispanic, 4.0% Asian, 5.0% other), NH White females were least likely to experience SGA delivery (8.6%), whereas higher rates were seen among Hispanic females (11.7%; OR, 1.41 [95% CI, 1.18–1.69]), Asian females (16.4%; OR, 2.08 [95% CI, 1.56–2.77]), and NH Black females (17.2%; OR, 2.21 [95% CI, 1.86–2.62]).[14] These differences remained essentially unchanged after adjustment for age, BMI, smoking, medical comorbidities, or psychosocial burden (including depression, anxiety, experienced racism, perceived stress, social support, or resilience), although lower social support was independently associated with SGA delivery (OR, 1.20 [95% CI, 1.03–1.40] for lowest quartile of perceived social support compared with upper 3 quartiles).
- Among 1482 nulliparous low-risk females at <20 weeks' gestation (who received placebo in a trial of low-dose aspirin to prevent preeclampsia), risks for SGA delivery were elevated even for mild stage 1 hypertension (SBP 130–135 or DBP 80–85 mm Hg; 10.2% versus 5.6%, adjusted for age, race, and prepregnancy BMI: RR, 2.16 [95% CI, 1.12–4.16]) by the 2017 AHA/ACC hypertension guidelines.[55]
- In a population-based cohort of 157 446 nonhypertensive females with single births at term, DBP of 80 to 89 mm Hg (versus <80 mm Hg) at 36 weeks was associated with increased risk of SGA (aOR, 1.69 [95% CI, 1.51–1.90]).[67] In addition, risk of SGA was higher by 2.0% (95% CI, 1.5%–2.8%) per 1–mm Hg rise in DBP from early (first prenatal visit, <20 weeks) to late (36 weeks) pregnancy.
- In an individual participant data meta-analysis of 265 270 births from 39 cohorts in Europe, North America, and Australia, prepregnancy underweight BMI (BMI <18.5 kg/m^2; OR, 1.67 [95% CI, 1.58–1.76]) was associated with higher risks for SGA delivery.[4] Females with underweight prepregnancy BMI and low GWG had the highest odds for SGA delivery (3.12 [95% CI, 2.75–3.54]), but risks were elevated when GWG was low even for normal weight (1.81 [95% CI, 1.73–1.89]) and overweight (1.23 [95% CI, 1.14–1.33]) females (but not females with obesity).

Complications: Maternal CVD

- In a meta-analysis examining 4 studies that defined low birth weight (<2500 g at term), females with a history of a low-birth-weight infant had no difference in risk for CVD (OR, 1.29 [95% intrinsic CI, 0.91–1.83]). Across 7 studies (3 of which defined SGA as 1–2 SD from the mean and 4 defined it as <10th percentile of weight for gestational age), a trend was observed of higher risk of CVD, but a pooled estimate was not possible because of the heterogeneity of studies.[36]
- In data from 11 110 females in the prospectively collected Vasterbotten Intervention Program and population-based registries in Sweden, low birth weight was associated with 10-year risk of CVD (HR, 1.95 [95% CI, 1.38–2.75]) at 50 years of age. However, this association did not persist by 60 years of age, and the history of low birth weight

did not improve risk reclassification for CVD in prediction models.[68]

Complications: Offspring Morbidity and Mortality

- In meta-analyses of associations between birth weight and adult mortality outcomes, birth weight was inversely associated with risks for all-cause mortality (aHR, 0.94 [95% CI, 0.92–0.97] per 1-kg higher birth weight among 394 062 participants) and CVD mortality (aHR, 0.88 [95% CI, 0.85–0.91] among 325 982 participants) but directly associated with risk for cancer mortality (aHR, 1.09 [95% CI, 1.05–1.13] among 277 623 participants).[69]
- A 2018 meta-analysis examined associations between birth weight and adult cardiometabolic outcomes. For adult type 2 diabetes, among 49 studies with 4 053 367 participants, the association was J shaped, with pooled HRs of 0.78 (95% CI, 0.70–0.87) per 1-kg higher birth weight, 1.45 (95% CI, 1.33–1.59) for <2.5 kg (versus >2.5 kg), 0.94 (95% CI, 0.87–1.01) for >4.0 kg (versus <4.0 kg), and 1.08 (95% CI, 0.95–1.23) for >4.5 kg (versus <4.5 kg). For CVD, among 33 studies with 5 949 477 participants, the association was also J shaped, with pooled HRs of 0.84 (95% CI, 0.81–0.86) per 1-kg higher birth weight, 1.30 (95% CI, 1.01–1.67) for <2.5 kg, 0.99 (95% CI, 0.90–1.10) for >4.0 kg, and 1.28 (95% CI, 1.10–1.50) for >4.5 kg. For hypertension, among 53 studies with 4 335 149 participants, the association was inverse, with pooled HRs of 0.77 (95% CI, 0.68–0.88) per 1-kg higher birth weight, 1.30 (95% CI, 1.16–1.46) for <2.5 kg, 0.88 (95% CI, 0.81–0.95) for >4.0 kg, and 1.05 (95% CI, 0.93–1.19) for >4.5 kg.[70]

Pregnancy Loss

Incidence, Prevalence, and Secular Trends (See Charts 11-6 and 11-7)

- Between 2014 and 2016, stillbirth or late fetal death (at ≥28 weeks' gestation) was unchanged (2.88 in 2016 versus 2.83 in 2014 per 1000 live births and fetal deaths) (Chart 11-6).[71]
  - Perinatal mortality rates (late fetal deaths at ≥28 weeks' gestation and early neonatal death at <7 days of age) were highest for females ≥40 years of age (9.86 per 1000 live births and fetal deaths) and lowest among females 30 to 34 years of age (5.37 per 1000 live births and fetal deaths) in 2016.
  - Perinatal mortality rates (late fetal deaths at ≥28 weeks' gestation and early neonatal death at <7 days of age) were highest among NH Black females (10.66 per 1000 live births and fetal deaths) compared with Hispanic (5.35 per 1000 live births and fetal deaths) and NH White (4.98 per 1000 live births and fetal deaths) females in 2016.
  - Geographic disparities are observed in perinatal mortality rates, with the highest rate in Alabama and Mississippi (8.32 per 1000 live births and fetal deaths) and the lowest rate in Wyoming (4.33 per 1000 live births and fetal deaths) in 2016.
  - This followed an overall trend similar to total fetal deaths between 2014 and 2016 (Chart 11-7).

Risk Factors

- From 2008 to 2010, 51 080 stillbirth deliveries occurred at a rate of 4.08 per 1000 live births in the United States, with a higher risk of stillbirth in NH Black females (OR, 2.12 [95% CI, 2.07–2.17]) or females >35 years of age (OR, 1.40 [95% CI, 1.37–144]) compared with females without stillbirth.
- Preexisting diabetes (OR, 4.02 [95% CI, 3.84–4.20]) or hypertension (OR, 2.56 [95% CI, 2.46–2.66]) was more common in females who experienced stillbirth compared with females without stillbirth.[72]
- According to a systematic review and meta-analysis in high-income countries that identified 96 population-based studies, the highest-ranking modifiable risk factor was maternal overweight and obesity status (PAR ranging from 8%–18% across 5 countries). In addition, advanced maternal age (>35 years of age; PAR, 7%–11%), smoking (4%–7%), SGA (23%), and placental abruption (15%) were important contributors.[73]
- Antiphospholipid syndrome was associated with higher risk for pregnancy loss (RR, 2.42 [95% CI, 1.46–4.01] for loss at <10 weeks; RR, 1.33 [95% CI, 1.00–1.76] for loss at ≥10 weeks) in a meta-analysis of 212 184 females (including 770 with antiphospholipid syndrome) from 8 studies.[74]

Genetics/Family History

- Genetic factors related to recurrent pregnancy loss can be attributable to maternal or fetal genetic factors. Maternal genetic thrombophilias are a risk factor for recurrent pregnancy loss and include FVL, prothrombin gene mutation, and deficiencies in protein C, protein S, and antithrombin III.
- Fetal genetic factors also play a role in recurrent pregnancy loss. Fetal aneuploidy is common in first trimester spontaneous miscarriages but is also seen in recurrent pregnancy loss, increasing with maternal age (in 1 study accounting for 78% of miscarriages in women ≥35 years of age with recurrent pregnancy loss versus 70% in women with nonrecurrent pregnancy loss).[75]

- Fetal single-gene disorders may also play a role in recurrent pregnancy loss; for example, 1 study found that 3.3% of stillbirths carried mutations in LQTS genes compared with a prevalence of <0.05% in the general population.[76] α-Thalassemia and X-linked diseases are single-gene disorders that can also lead to recurrent pregnancy loss.

Complications: Maternal CVD

- Data from the NHS II identified higher rates of type 2 diabetes (HR, 1.20 [95% CI, 1.07–1.34]), hypertension (HR, 1.05 [95% CI, 1.00–1.11]), and hyperlipidemia (HR, 1.06 [95% CI, 1.02–1.10]) with early miscarriage (<12 weeks) with similar findings for late miscarriage (12–19 weeks). Rates of type 2 diabetes (HR, 1.45 [95% CI, 1.13–1.87]) and hypertension (HR, 1.15 [95% CI, 1.01–1.30]) were higher in females with a history of stillbirth delivery.[77]
- In 79 121 postmenopausal females from the WHI, ≈35% experienced a history of pregnancy loss. This was associated with higher adjusted risk of incident CVD (HR, 1.11 [95% CI, 1.06–1.16]) over a mean follow-up of 16 years. Females with a history of pregnancy loss also had higher levels of CVD risk factors (BMI, hypertension, and diabetes).[78]

Health Care Utilization

- In 2016, there were 313 530 hospital discharges for HDP, 128 240 for preexisting diabetes and gestational diabetes, 362 955 for PTB, and 78 820 for SGA/low birth weight.
- In 2016, there were 73 485 visits to the ED for HDP, 19 903 for preexisting diabetes and gestational diabetes, 101 047 for PTB, and 5985 for SGA/low birth weight.
- According to a systematic review and meta-analysis that included 52 articles, late-preterm infants born at 34 to 36 weeks' gestation compared with term infants had a higher aOR of all-cause admissions in the neonatal period (OR, 2.34 [95% CI, 1.19–4.61]) and through adolescence (OR, 1.09 [95% CI, 1.05–1.13]).[79]

Cost

- Pregnancy and postpartum care accounted for $71.3 billion ($64.9–$77.7 billion) in total health care spending in 2016. Complications related to HDP and PTB were estimated to account for $5.5 billion ($4.8–$6.3 billion) and $28.2 billion (21.8–37.6 billion), respectively.[80]

Global Burden (See Charts 11-8 and 11-9)

- According to WHO data from 2013, an estimated 20 million low-birth-weight infants globally are born every year.[81]
- Data from the WHO Global Survey on Maternal and Perinatal Health (23 countries) and 22 birth cohort studies were used to estimate prevalence of preterm-SGA (defined as <10th percentile from the 1991 US national reference population) and demonstrated significant geographic heterogeneity globally with higher rates of SGA infants in low- and middle-income countries that were concentrated in South Asia.[82]
- In an analysis of data from the WHO Global Survey for Maternal and Perinatal Health (conducted in African, Latin American, and Asian countries), severe anemia (hemoglobin <7 g/dL) at the time of admission for delivery was associated with higher risks for gestational hypertension (4.6% versus 2.7%; aOR among nulliparous females, 1.56 [95% CI, 0.94–2.58] and multiparous females, 1.73 [95% CI, 1.25–2.39]) and preeclampsia/eclampsia (12.6% versus 4.0%; aOR among nulliparous females, 3.74 [95% CI, 2.90–4.81] and multiparous females, 3.45 [95% CI, 2.79–4.25]).[83] Sickle cell disease was associated with higher risk for gestational hypertension (7.2% versus 2.1%; aOR among nulliparous females, 2.41 [95% CI, 1.42–4.10] and multiparous females, 3.26 [95% CI, 2.32–4.58]) but not preeclampsia/eclampsia (4.2% versus 4.5%; *P*=0.629). No significant associations were found between thalassemia and HDPs.
- Globally, 2.5 million (uncertainty range, 2.4–3.0 million) third-trimester stillbirths (defined as ≥28 weeks or late fetal deaths) occurred annually with a PAF of 6.7% for maternal age >35 years, 8.2% for malaria, 14% for prolonged pregnancy (>42 weeks gestation), and 10% for lifestyle factors and obesity.[84]
- Based on data from 204 countries in the 2019 GBD study, the global incidence of maternal hypertensive disorders is shown in Chart 11-8. The incidence of maternal hypertensive disorders is estimated to be 18.0 million (15.2–21.1 million) with an average rate of 926.9 (782.6–1082.9) per 100 000 female population 15 to 49 years of age. Geographic variations exist, with the highest rates in parts of sub-Saharan Africa.
- Based on data from the 2019 GBD study, global incidence of neonatal PTBs is shown in Chart 11-9. The incidence of neonatal PTBs is estimated to be 15.2 million (15.1–15.3 million) with an average rate of 11 243 (11 165–11 319) per 100 000 at birth. There is wide geographic heterogeneity, with the highest rates in the Caribbean, South Asia, and some countries of North Africa and the Middle East.

Table 11-1. Unadjusted Prevalence of Preexisting Diabetes and Gestational Diabetes Among Women With a Live Birth by Selected Maternal Characteristics, United States, 2016

Characteristic*	No.†	Preexisting diabetes, %	Gestational diabetes, %
Total	3 942 094	0.9	6.0
Age group, y			
<20	211 827	0.4	1.9
20–24	803 153	0.5	3.3
25–29	1 148 057	0.7	5.1
30–34	1 110 010	1.0	7.0
35–39	546 995	1.4	9.6
≥40	122 052	2.1	12.8
Race and Hispanic origin‡			
NH White	2 054 437	0.7	5.3
NH Black	558 044	1.2	4.8
NH Asian	254 326	0.9	11.1
Hispanic	917 822	1.0	6.6
American Indian/Alaska Native	31 375	2.1	9.2
Native Hawaiian/Pacific Islander	9337	1.8	8.4
>1 Race	80 836	0.9	5.8
Prepregnancy BMI§			
Underweight	134 392	0.3	2.9
Normal weight	1 699 751	0.4	3.6
Overweight	997 977	0.8	6.1
Obesity class 1	548 092	1.3	8.8
Obesity class 2	266 105	2.0	11.2
Obesity class 3	187 689	3.2	13.9

BMI indicates body mass index; and NH, non-Hispanic.

*Statistically significant ($P<0.05$) differences in the distribution of preexisting diabetes and gestational diabetes (or no diabetic conditions) were observed by all maternal characteristics.

†The number of women within a characteristic group (eg, age group) might not sum to the total number of women because of missing information.

‡Race and Hispanic origin are reported separately on the birth certificate. Women reporting Hispanic origin were categorized as Hispanic regardless of their race. Categories represent single-race reporting (ie, mothers reported only 1 race); mothers reporting >1 race were categorized as >1 race.

§Prepregnancy BMI classified as underweight (BMI <18.5 kg/m^2), normal weight (BMI, 18.5–24.9 kg/m^2), overweight (BMI, 25.0–29.9 kg/m^2), obesity class 1 (BMI, 30.0–34.9 kg/m^2), obesity class 2 (BMI, 35.0–39.9 kg/m^2), and obesity class 3 (BMI ≥40.0 kg/m^2).

Source: Data derived from Deputy et al,[42] Table 1.

Pre-Pregnancy Body Mass Index Category	Gestational Weight Gain Category		
	Low (≤ 1.1 SD)	Medium (-1.0 to 0.9 SD)	High (≥1.0 SD)
Underweight	1.09 (0.94 – 1.26)	1.04 (0.96 – 1.12)	1.13 (0.98 – 1.30)
Normal weight	1.04 (1.01 – 1.08)	Referent	1.10 (1.06 – 1.14)
Overweight	1.23 (1.16 – 1.32)	1.38 (1.33 – 1.43)	1.63 (1.54– 1.73)
Obese	1.70 (1.56 – 1.85)	2.06 (1.96 – 2.16)	2.51 (2.31 – 2.74)

Chart 11-1. Adjusted odds ratios for any adverse pregnancy outcome (APO), by prepregnancy body mass index (BMI) and gestational weight gain (GWG) categories.
Estimates are based on a meta-analysis of individual participant data from 265 270 females from 39 European, North American, and Oceanic cohort studies. APOs include hypertensive disorder of pregnancy (gestational hypertension or preeclampsia), gestational diabetes, preterm birth (<37 weeks' gestation), small (birth weight <10th percentile) or large (birthweight >90th percentile) size for sex, and gestational age at birth. Prepregnancy BMI categories are as follows: underweight, <18.5 kg/m^2; normal weight, 18.5 to 24.9 kg/m^2; overweight, 25.0 to 29.9 kg/m^2; and obesity, ≥30 kg/m^2. GWG values corresponding to the SD cutoffs were not provided by the source, but the median gestational weight gain was 14.0 kg (95% range, 3.9–27.0 kg).
Source: Data derived from Santos et al.[4]

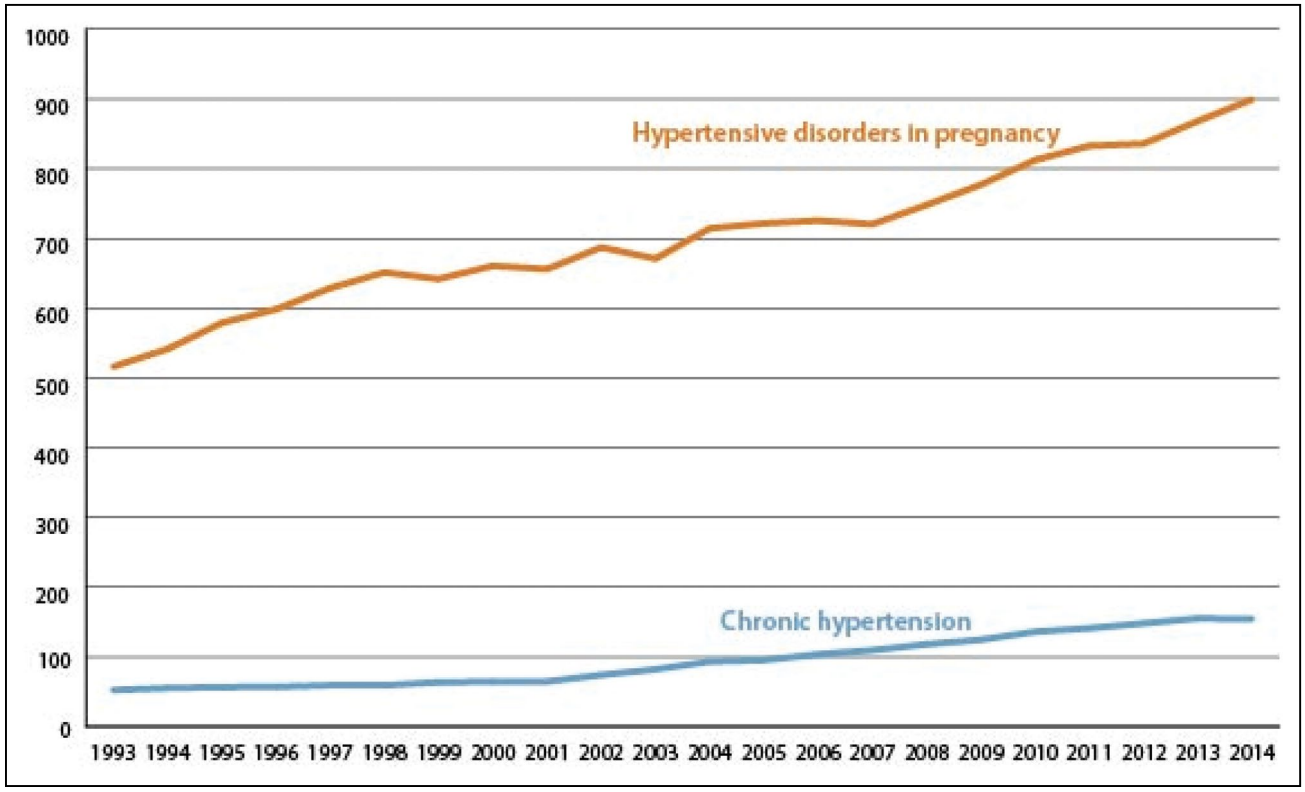

Chart 11-2. Trends in the rates of hypertensive disorders per 10 000 delivery hospitalizations, United States, 1993 to 2014.
Source: Reprinted from Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion.[85]

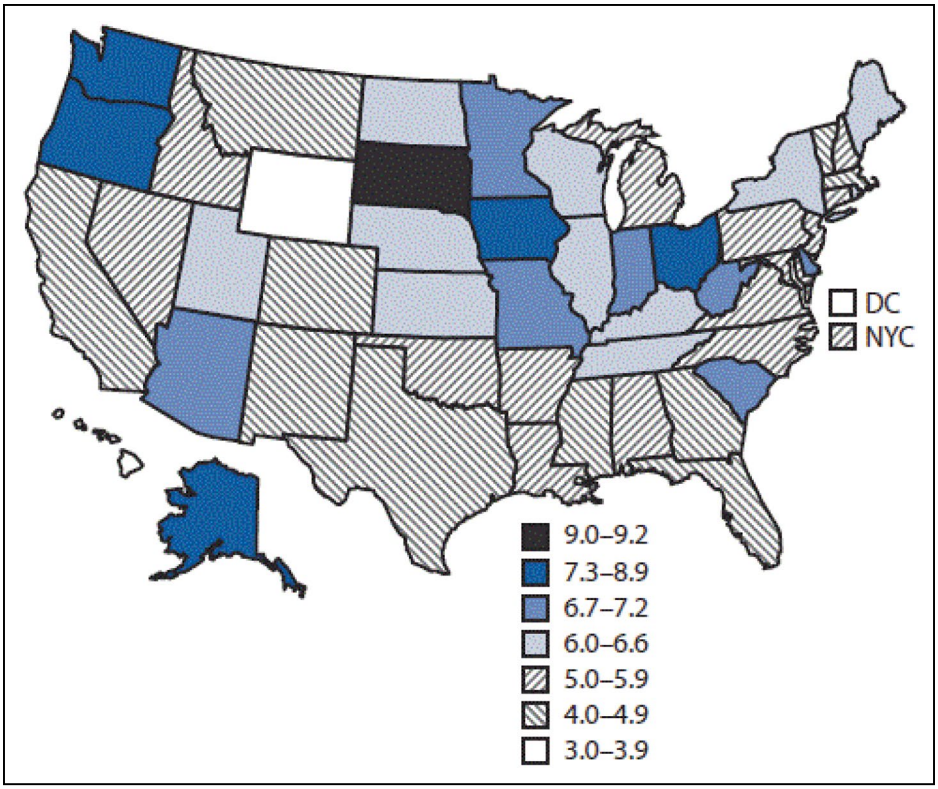

Chart 11-3. Standardized* prevalence of gestational diabetes among women who had a live birth by state, United States, 2016.
NYC indicates New York City.
*Standardized to age and race/ethnicity distribution of US resident mothers delivering in 2012.
Source: Reprinted from Deputy et al.[42]

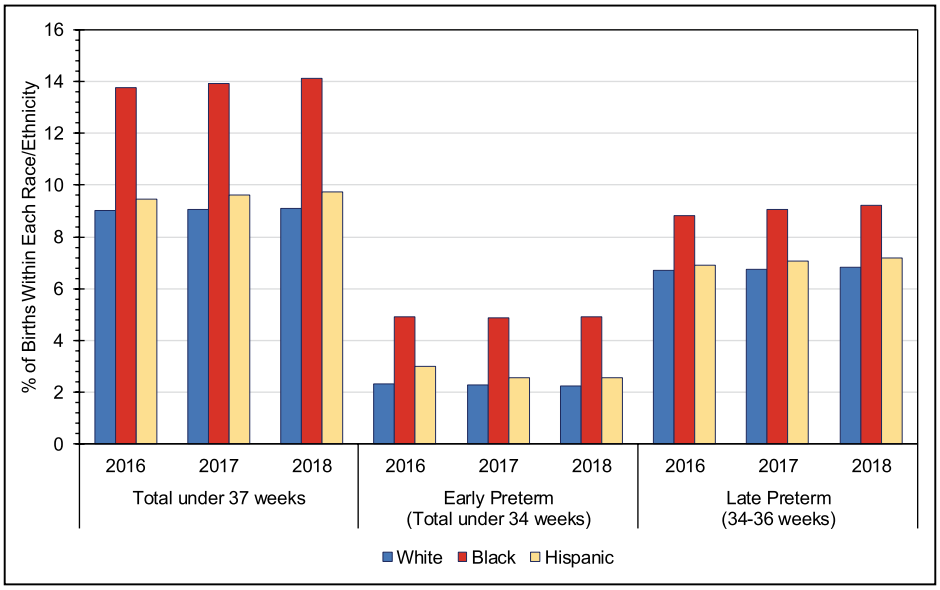

Chart 11-4. Trends in the rates of preterm birth by gestational age (weeks) in the United States by maternal race/ethnicity, 2016 to 2018.
Source: Data derived from Martin et al.[66]

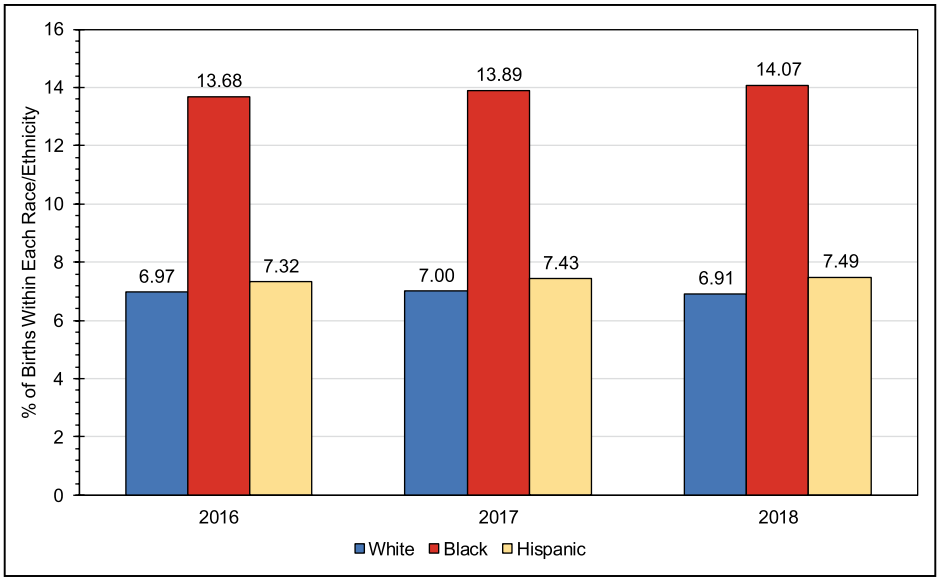

Chart 11-5. Trends in the rates of low-birth-weight infants (<2500 g) in the United States by race/ethnicity of mother, 2016 to 2018.
Source: Data derived from Martin et al.[66]

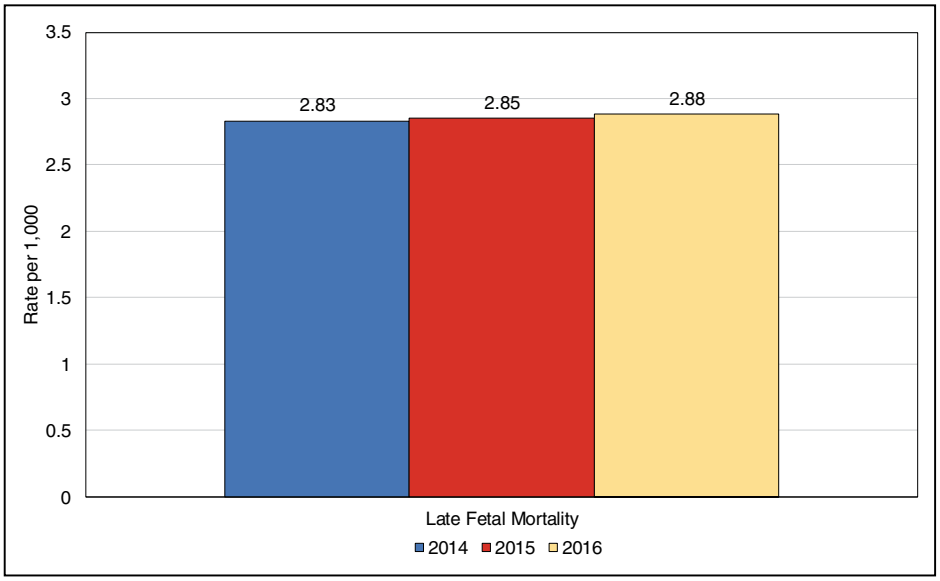

Chart 11-6. Late fetal mortality rates, United States, 2014 to 2016.
Late fetal mortality rate is the number of fetal deaths at ≥28 weeks of gestation per 1000 live births and fetal deaths at ≥28 weeks of gestation.
Source: Data derived from Gregory et al.[71]

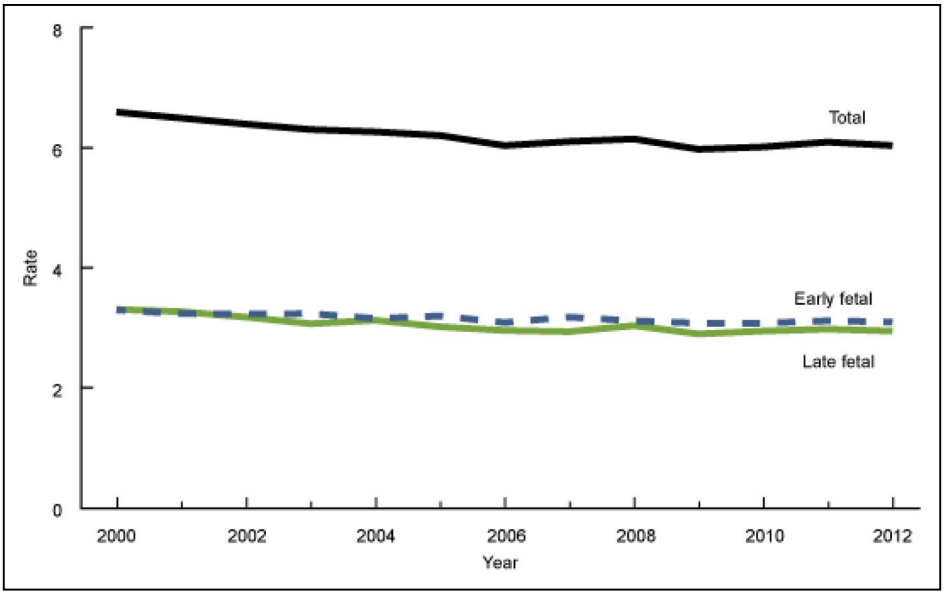

Chart 11-7. Total, early, and late fetal mortality rates, United States, 2000 to 2012.
Total fetal mortality rate is the number of fetal deaths at ≥20 weeks of gestation per 1000 live births and fetal deaths. Early fetal mortality rate is the number of fetal deaths at 20 to 27 weeks per 1000 live births and fetal deaths at 20 to 27 weeks. Late fetal mortality rate is the number of fetal deaths at ≥28 weeks of gestation per 1000 live births and fetal deaths at ≥28 weeks of gestation.
Source: Reprinted from Gregory et al.[86]

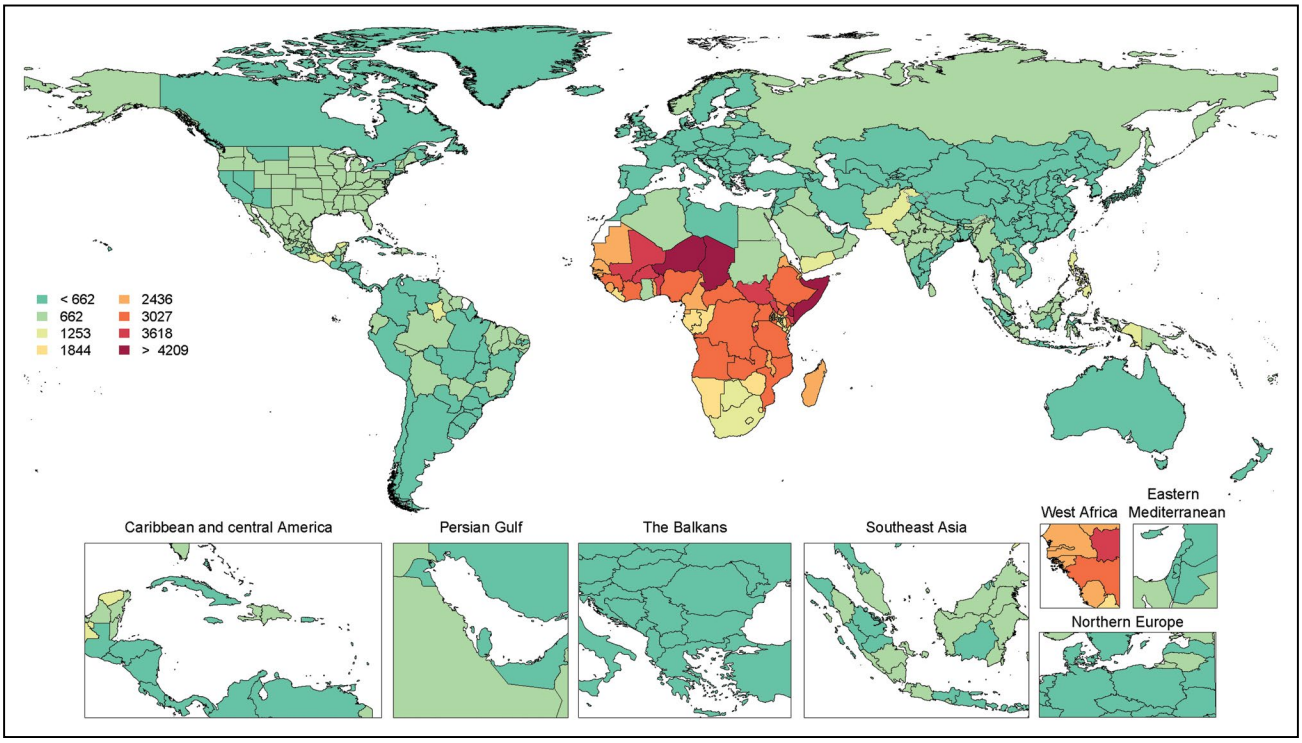

Chart 11-8. Incidence rate (cases per 100 000 population) of maternal hypertensive disorders in females 15 to 49 years of age, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[87] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[88]

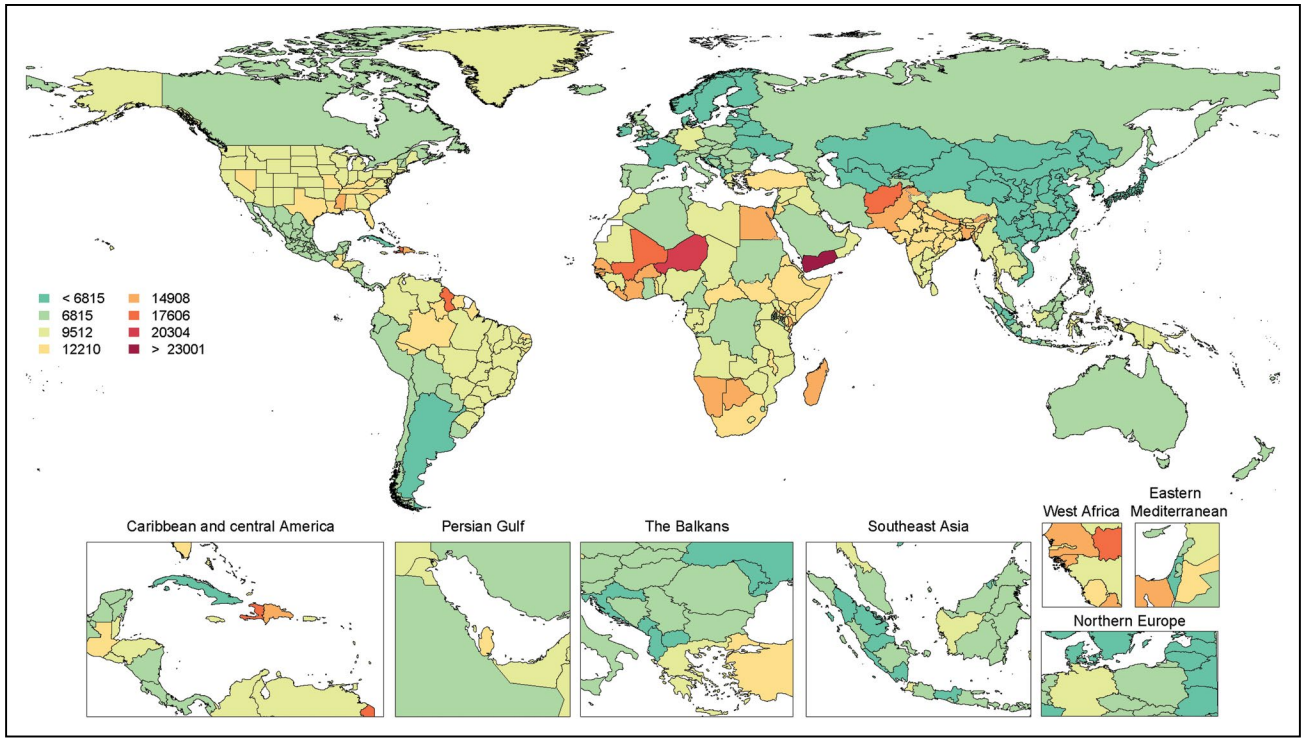

Chart 11-9. Incidence rate at birth (per 100 000 population) of neonatal preterm birth, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[87] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[88]

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12. KIDNEY DISEASE

ICD-10 N18.0. See Charts 12-1 through 12-10

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Definition (See Chart 12-1)

CKD, defined as reduced eGFR (<60 mL·min^{-1}·1.73 m^{-2}), excess urinary albumin excretion (urine ACR ≥30 mg/g), 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.[1,2]

- eGFR is usually determined from the serum creatinine level with equations that account for age, sex, and race.

Abbreviations Used in Chapter 12

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACR	albumin-to-creatinine ratio
AF	atrial fibrillation
Af Am	African American
AHA	American Heart Association
AHEI	Alternative Healthy Eating Index
aHR	adjusted hazard ratio
AI/AN	American Indian or Alaska Native
AMI	acute myocardial infarction
aOR	adjusted odds ratio
ARIC	Atherosclerosis Risk in Communities study
ASCVD	atherosclerotic cardiovascular 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
CARES	Cardiac Arrest Registry to Enhance Survival
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval

(*Continued*)

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Abbreviations Used in Chapter 12 Continued

CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMS	Centers for Medicare & Medicaid Services
CPR	cardiopulmonary resuscitation
CVA	cerebrovascular accident
CVD	cardiovascular disease
DALY	disability-adjusted life-year
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
EMS	emergency medical services
ESRD	end-stage renal disease
FHS	Framingham Heart Study
GBD	Global Burden of Disease Study
GFR	glomerular filtration rate
GWAS	genome-wide association study
HBP	high blood pressure
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
HEI	Healthy Eating Index
HF	heart failure
HR	hazard ratio
HTN	hypertension
ICD-10	*International Classification of Diseases, 10th Revision*
IHD	ischemic heart disease
IL	interleukin
JHS	Jackson Heart Study
KDIGO	Kidney Disease: Improving Global Outcomes
MACE	major adverse cardiovascular events
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
MR	mitral regurgitation
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NIS	National (Nationwide) Inpatient Sample
OR	odds ratio
OSA	obstructive sleep apnea
PAD	peripheral arterial/artery disease
PCI	percutaneous coronary intervention
PE	pulmonary embolism
PH	pulmonary hypertension
PI	Pacific Islander
RR	relative risk
SCA	sudden cardiac arrest
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
TNF	tumor necrosis factor
TVT	Transcatheter Valve Therapy
uACR	urine albumin-to-creatinine ratio
UI	uncertainty interval
USRDS	United States Renal Data System
VA	ventricular arrhythmia
VHD	valvular heart disease
VTE	venous thromboembolism
WC	waist circumference

- The spot (random) urine ACR is recommended as a measure of urine albumin excretion.
- CKD is characterized by eGFR category (G1–G5) and albuminuria category (A1–A3), as well as cause of CKD (Chart 12-1).[3,4]
- ESRD is defined as severe CKD requiring long-term kidney replacement therapy such as hemodialysis (in center or home), peritoneal dialysis, or kidney transplantation.[4] Individuals with ESRD are an extremely high-risk population for cardiovascular morbidity and mortality.

Prevalence (See Charts 12-1 through 12-3)

- Using data from NHANES 2013 to 2016, the USRDS has estimated the prevalence of CKD by eGFR and albuminuria categories as shown in Chart 12-1. The overall prevalence of CKD (eGFR <60 mL·min^{-1}·1.73 m^{-2} or ACR ≥30 mg/g; shown in yellow, orange, and red in Chart 12-1) in 2013 to 2016 was 14.8%.[2]
- The prevalence of CKD increases substantially with age, as follows[2]:
  - 6.3% for those 20 to 39 years of age
  - 10.4% for those 40 to 59 years of age
  - 32.2% for those ≥60 years of age
- According to NHANES 2001 to 2016, the prevalence of ACR ≥30 mg/g was higher for NH Black adults (12.6%) than NH White adults (9.6%), whereas eGFR <60 mL·min^{-1}·1.73 m^{-2} was lower among NH Black adults (5.8%) than NH White adults (8.2%).[2]
- At the end of 2017, the unadjusted prevalence of ESRD estimated from cases reported to the CMS in the United States was 2204 per million, with a total of 746 557 prevalent cases across the country.[2]
- The prevalence of ESRD varies regionally across the United States. Although prevalent cases of peritoneal dialysis have increased over time, hemodialysis continues to be the modality of choice for those starting dialysis (Chart 12-2).
- ESRD prevalence is highest in Native Hawaiian/Pacific Islander people compared with other races, and prevalence is higher among Hispanic people than among NH people (Chart 12-3).

Incidence (See Chart 12-3)

- For US adults 30 to 49, 50 to 64, and ≥65 years of age 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.[5]
- The incidence of ESRD is higher among Black individuals than White individuals (Chart 12-3),[2] 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.[6]

Secular Trends (See Chart 12-3)

- According to NHANES data, the prevalence of CKD (eGFR, 15–59 mL·min^{-1}·1.73 m^{-2}) increased slowly from the 1990s to the early 2000s because of an aging population and higher prevalence of risk factors, but the prevalence plateaued from 2004 to 2012.[7]
- Among Medicare beneficiaries, the prevalence of CKD (based on coded diagnosis) increased from 2.5% in 2000 to 14.5% in 2017. In particular, the prevalence of CKD increased with age from 10.5% at 65 to 74 years of age to 23.9% at 85 years of age, with males and Black adults having higher prevalence than females and White adults, respectively.[1]
- The prevalence of ESRD increased across most racial/ethnic groups from 2000 to 2016 primarily because of improved survival, whereas the incidence rate appeared to stabilize or decrease slightly (Chart 12-3).[2]
- A simulation model reported that the incidence of ESRD in the United States is projected to increase 11% to 18% through 2030 given changes in demographics, clinical characteristics, and lifestyle factors and improvements in kidney replacement therapy.[8]

Risk Factors (See Charts 12-4 and 12-5)

- Many traditional CVD risk factors are also risk factors for CKD, including older age, male sex, hypertension, diabetes, smoking, and family history of CVD (Chart 12-4). In NHANES 2013 to 2016, the prevalence of CKD was 31% in adults ≥20 years of age with HBP and 37% in adults with diabetes. Among adults with obesity (BMI >30 kg/m^2), nearly 17% had CKD.[2]
- In a pooled analysis of >5.5 million adults, higher BMI, WC, and waist-to-height ratio were independently associated with eGFR decline and death in individuals who had normal or reduced levels of eGFR.[9]
- OSA increased the risk of CKD independently of BMI and other traditional risk factors, and this association was apparent among those with treated OSA (HR, 2.79 [95% CI, 2.48–3.13]) and untreated OSA (HR, 2.27 [95% CI, 2.19–2.36]).[10]

- Cardiovascular fitness and healthy lifestyles are associated with decreased risk and progression of CKD.[11–13] For example, having more of the Life's Simple 7 ideal health factors was associated with progressively lower risk of incident CKD in the ARIC study (Chart 12-5).
- In the ARIC study, higher scores for HEI (HR per 1 SD, 0.94 [95% CI, 0.90–0.98]), AHEI (HR per 1 SD, 0.93 [95% CI, 0.89–0.96]), and alternate Mediterranean diet (HR per 1 SD, 0.93 [95% CI, 0.89–0.97]) were associated with a lower risk of incident CKD during a median follow-up of 24 years.[14]
- In a meta-analysis of 23 studies, preeclampsia increased the risk of ESRD (RR, 4.90 [95% CI, 3.56–6.74]) and CKD (RR, 2.11 [95% CI, 1.72–2.59]).[15]

Social Determinants of CKD

- Zip code–level poverty was associated with an increased risk of ESRD (RR, 1.24 [95% CI, 1.22–1.25]) after accounting for age, sex, and race/ethnicity, and this association was stronger in 2005 to 2010 than 1995 to 2004.[16]
- A meta-analysis of 43 studies reported that lower SES, particularly income, was associated with a higher prevalence of CKD and faster progression to ESRD.[17] This association was observed in higher- versus lower- or middle-income countries and was more pronounced in the United States relative to Europe.
- In the HCHS/SOL, lower language acculturation was associated with CKD among older adults (>65 years of age); however, among those with CKD, acculturation measures were not associated with hypertension or diabetes control.[18]

Genetics/Family History

- It is estimated that ≈30% of early-onset CKD is caused by single-gene mutations, and several hundred loci have been implicated in monogenic CKD.[19,20]
- GWASs in >1 million individuals have revealed >260 candidate loci for CKD phenotypes, including eGFR and serum urate.[21–24]
- Racial differences in CKD prevalence might be partially attributable to differences in ancestry and genetic risk. The *APOL1* gene has been well studied as a kidney disease locus in individuals of African ancestry.[25] 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.[26]
- Although certain variants of *APOL1* increase risk, this explains only a portion of the racial disparity in ESRD risk.[25] For example, eGFR decline was faster even for Black adults with low-risk *APOL1* status (0 or 1 allele) than for White adults in CARDIA; this difference was attenuated by adjustment for SES and traditional risk factors.[27]
- In a large, 2-stage individual-participant data meta-analysis, *APOL1* kidney-risk variants were not associated with incident CVD or death independently of kidney measures.[28]

Awareness, Treatment, and Control

- In NHANES 2013 to 2016, CKD awareness was particularly low, ranging from 2% to 5% for adults with early-stage CKD to 57% for those with more advanced CKD (eGFR, 15–29 mL·min^{-1}·1.73 m^{-2}).[2]
- Among patients with CKD with hypertension, intensive BP <130 mm Hg versus standard BP <140 mm Hg decreased the risk of all-cause mortality (HR, 0.79 [95% CI, 0.63–1.00]) in a pooled analysis of 4 randomized clinical trials.[29]

Complications

- In an analysis of GBD 2002 to 2016 data, DALYs attributable to CKD increased by 52.6%, and death attributable to CKD increased by 58.3%. The burden was most pronounced in the southern United States, with much of the increase in CKD DALYs attributable to increased metabolic risks, aging of the population, and population growth. Age-standardized CKD DALY rates increased by 18.6% over the same time period.[30]

Cost

- In 2017, Medicare spent >$84 billion caring for people with CKD and $36 billion for people with ESRD, which is 23% of all Medicare fee-for-service spending.[2]
- In 2015, admissions for CVD accounted for 27% of all inpatient spending for patients with ESRD.[2]
- In SHARP, a study of patients in Europe, North America, and Australasia, nonfatal major cardiovascular events were associated with £6133 (95% CI, 5608–6658) higher costs for patients with ESRD on dialysis and £4350 (95% CI, 3819–4880) higher costs for other patients with CKD in the year of the event (compared with years before the event).[31]
- 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).[32]

Global Burden of Kidney Disease (See Charts 12-6 and 12-7)

- The GBD 2019 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 369 diseases and injuries in 204 countries and territories.[33]
  - In 2019, the total estimated prevalence of CKD was 697 million people (95% UI, 650–741 million), a 25% increase since 2010.
  - Age-standardized prevalence of CKD is highest in Central Latin America, Southeast Asia, North Africa and the Middle East, and Eastern Europe (Chart 12-6).
  - Central Latin America had the highest age-standardized mortality rates attributable to CKD in 2019 (Chart 12-7).

Kidney Disease and CVD

CKD and CVD Outcomes

- The association of reduced eGFR with CVD risk is generally similar across age, race, and sex subgroups,[34] although albuminuria tends to be a stronger risk factor for females than for males and for older (>65 years of age) versus younger people.[35]
- The addition of eGFR or albuminuria improves CVD prediction beyond traditional risk factors used in risk equations.[35]
- A meta-analysis of 21 cohort studies of 27 465 individuals with CKD found that nontraditional risk factors such as serum albumin, phosphate, urate, and hemoglobin are associated with CVD risk in this population.[36] In the Chronic Renal Insufficiency Cohort of 2399 participants without a history of CVD at baseline, a composite inflammation score (IL-6, TNF-α, fibrinogen, and serum albumin) was associated with increased CVD risk (ie, MI, PAD, stroke, or death) (standardized HR, 1.47 [95% CI, 1.32–1.65]).[37]
- In a randomized clinical trial of adults with PAD, CKD increased the risk of MACEs (HR, 1.45 [95% CI, 1.30–1.63]) but not major amputation (HR, 0.92 [95% CI, 0.66–1.28]).[38]
- In a post hoc analysis of hypertension patients in SPRINT, albuminuria increased stroke risk overall (HR, 2.24 [95% CI, 1.55–3.23]), with this association being present for those in the standard BP treatment arm (HR, 2.71 [95% CI, 1.61–4.55]) but not the intensive BP treatment arm (HR, 0.93 [95% CI, 0.48–1.78]).[39]

Prevalence of CVD Among People With CKD (See Charts 12-8 and 12-9)

- 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 12-8 and 12-9).
- Nearly two-thirds (64.5%) of patients with CKD ≥66 years of age have CVD compared with approximately one-third (32.4%) of patients without CKD in this age group.[2]
- The prevalence of CVD in patients with ESRD differs by treatment modality. Approximately 71% of patients with ESRD on hemodialysis have any CVD, whereas 58% of patients on peritoneal dialysis and 41% of patients receiving transplantation have any CVD (Chart 12-9).

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.[40]
- Both eGFR and albuminuria appear to predict HF events more strongly than CHD or stroke events.[35]
- In a study of adults with CKD 50 to 79 years of age, 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.[41]
- In a meta-analysis of patients with CKD, the prevalence of PH was 23% and increased the risk of CVD (RR, 1.67 [95% CI, 1.07–2.60]) and mortality (RR, 1.44 [95% CI, 1.17–1.76]).[42]
- Females with CKD appear to have higher risk of incident PAD than males with CKD, particularly at younger ages.[43]
- A patient-level pooled analysis of randomized trials explored the effect of CKD on prognosis for females who undergo PCI.[44] Creatinine clearance <45 mL/min was an independent risk factor for 3-year MACEs (aHR, 1.56) and all-cause mortality (aHR, 2.67).
- Despite higher overall event rates than NH White people, NH Black people 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.[45] However, the risk of HF associated with CKD might be greater for Black people and Hispanic people than for White people.[40]
- Clinically significant bradyarrhythmias appear to be more common than ventricular arrhythmias among patients on hemodialysis and are highest in the immediate hours before dialysis sessions.[46]

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,[47,48] although observational data from large registries can provide insight into the risks and benefits in this population.

- According to NHANES data, the percentage of adults taking statins increased from 17.6% in 1999 to 2002 to 35.7% in 2011 to 2014 among those with CKD. However, there was no difference in statin use for those with versus without CKD (RR, 1.01 [95% CI, 0.96–1.08]).[49]
- Among veterans with diabetes and CKD, the proportion receiving an ACE inhibitor/angiotensin receptor blocker was 66% (95% CI, 62%–69%) in 2013 to 2014.[50,51]
- In NHANES 1999 to 2014, 34.9% of adults with CKD used an ACE inhibitor/angiotensin receptor blocker. The use of ACE inhibitors/angiotensin receptor blockers increased in the early 2000s among adults with CKD but plateaued subsequently.[50]
- Rates of stress testing among Medicare beneficiaries declined from 2008 to 2012, but rates were 5% to 15% higher for those with CKD and ESRD than for those without CKD.[52]
- In a study of >12 000 people undergoing hemodialysis in the USRDS who had AF, only 15% initiated warfarin therapy within 30 days, and 70% discontinued use within 1 year.[53]
- 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]).[54]
- In a study of 17 910 patients undergoing angiography for stable IHD in Alberta, Canada, those with ESRD (OR, 0.52 [95% CI, 0.35–0.79]) or mild to moderate CKD (OR, 0.80 [95% CI, 0.71–0.89]) were less likely to be revascularized for angiographically significant (>70%) coronary stenoses compared with those without CKD.[55]
- For patients undergoing TAVR in the United Kingdom, eGFR <45 mL·min^{-1}·1.73 m^{-2} was associated with higher odds of in-hospital (aOR, 1.45 [95% CI, 1.03–2.05]) and longer-term (aOR, 1.36 [95% CI, 1.17–1.58]) mortality compared with higher eGFR.[56] 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 (aOR, 2.21 [95% CI, 1.81–2.69]).[57]
- For patients with eGFR <60 but >15 mL·min^{-1}·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.[58]
- Among patients being treated with hemodialysis who were 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.[59] Among patients who underwent lower-extremity bypass surgery in the USRDS 2006 to 2011, females with ESRD were less likely than males with ESRD to receive an autogenous vein graft. Among those who received a prosthetic graft, acute graft failure was higher for females.[60]
- In a pooled analysis of patients with stable IHD, diabetes, and CKD from 3 clinical trials, CABG plus optimal medical therapy was associated with lower risk of subsequent revascularization (HR, 0.25 [95% CI, 0.15–0.41]) and MACEs (HR, 0.77 [95% CI, 0.55–1.06]) compared with PCI plus optimal medical therapy.[61]
- A randomized clinical trial comparing an initial invasive strategy (coronary angiography and revascularization added to medical therapy) with an initial conservative strategy (medical therapy alone and angiography if medical therapy fails) among those with advanced kidney disease (eGFR <30 mL·min^{-1}·1.73 m^{-2} or receiving dialysis) and moderate or severe myocardial ischemia reported similar rates of death or nonfatal MI (estimated 3-year event rate, 36.4% versus 36.7%; aHR, 1.01 [95% CI, 0.79–1.29]).[62]

Cardiovascular Hospitalization and Mortality Attributable to CVD Among People With CKD (See Chart 12-10)

- CVD is a leading cause of death for people with CKD. Mortality risk depends not only on eGFR but also on category of albuminuria. The adjusted RR of all-cause mortality and cardiovascular mortality is highest in those with eGFR of 15 to 30 mL·min^{-1}·1.73 m^{-2} and those with ACR >300 mg/g.
- For patients with severe valvular HD, CKD is a particularly strong risk factor for mortality. In the Duke University Echocardiography Database (1999–2013), 5-year survival was substantially lower for patients with CKD than for patients without CKD (42% versus 67% for severe aortic stenosis and 37% versus 65% for severe MR, CKD versus non-CKD, respectively).[63]
- Data from CARES and the CMS dialysis facility database indicate that dialysis staff initiated CPR in 81.4% of events and applied defibrillators before EMS arrival in 52.3%. Staff-initiated CPR was

associated with a 3-fold increase in the odds of hospital discharge and better neurological status at the time of discharge.[64]

- Data from the prospective Chronic Renal Insufficiency Cohort demonstrated that the crude rate of HF admissions was 5.8 per 100 person-years. The rates of both HF hospitalizations and rehospitalization were even higher across categories of lower eGFR and higher urine ACR (Chart 12-10).[65]
- 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.
  - Cystatin C levels predicted ASCVD, HF, all-cause mortality, and cardiovascular death in the FHS after accounting for clinical cardiovascular risk factors.[66]
  - Cystatin C–based eGFR was a stronger predictor of HF than creatinine-based eGFR among patients with CKD in the Chronic Renal Insufficiency Cohort study.[67]
  - The stronger associations observed with outcomes (relative to creatinine or creatinine-based eGFR) might be explained in part by non-GFR determinants of cystatin C such as chronic inflammation.[68]

FOOTNOTE

Disclosure: A portion of the data reported has been supplied by the USRDS.[1,2] 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			Total
				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	54.9	4.2	0.5	**59.6**
	G2	Mildly decreased	60-89	30.2	2.9	0.3	**33.5**
	G3a	Mildly to moderately decreased	45-59	3.6	0.8	0.3	**4.7**
	G3b	Moderately to severely decreased	30-44	1.0	0.4	0.2	**1.7**
	G4	Severely decreased	15-29	0.13	0.10	0.15	**0.37**
	G5	Kidney failure	< 15	0.01	0.04	0.09	**0.13**
			Total	**89.9**	**8.5**	**1.6**	**100**

Chart 12-1. Percentage of NHANES participants within the KDIGO 2012 prognosis of chronic kidney disease by GFR and albuminuria categories, United States, 2013 to 2016.

Green=low risk; yellow=moderately high risk; orange=high risk; red=very high risk.

GFR indicates glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; and NHANES, National Health and Nutrition Examination Survey.

Source: Reprinted from 2018 United States Renal Data System Annual Data Report, volume 1, Table 1.1,[2] using NHANES 2013 to 2016.

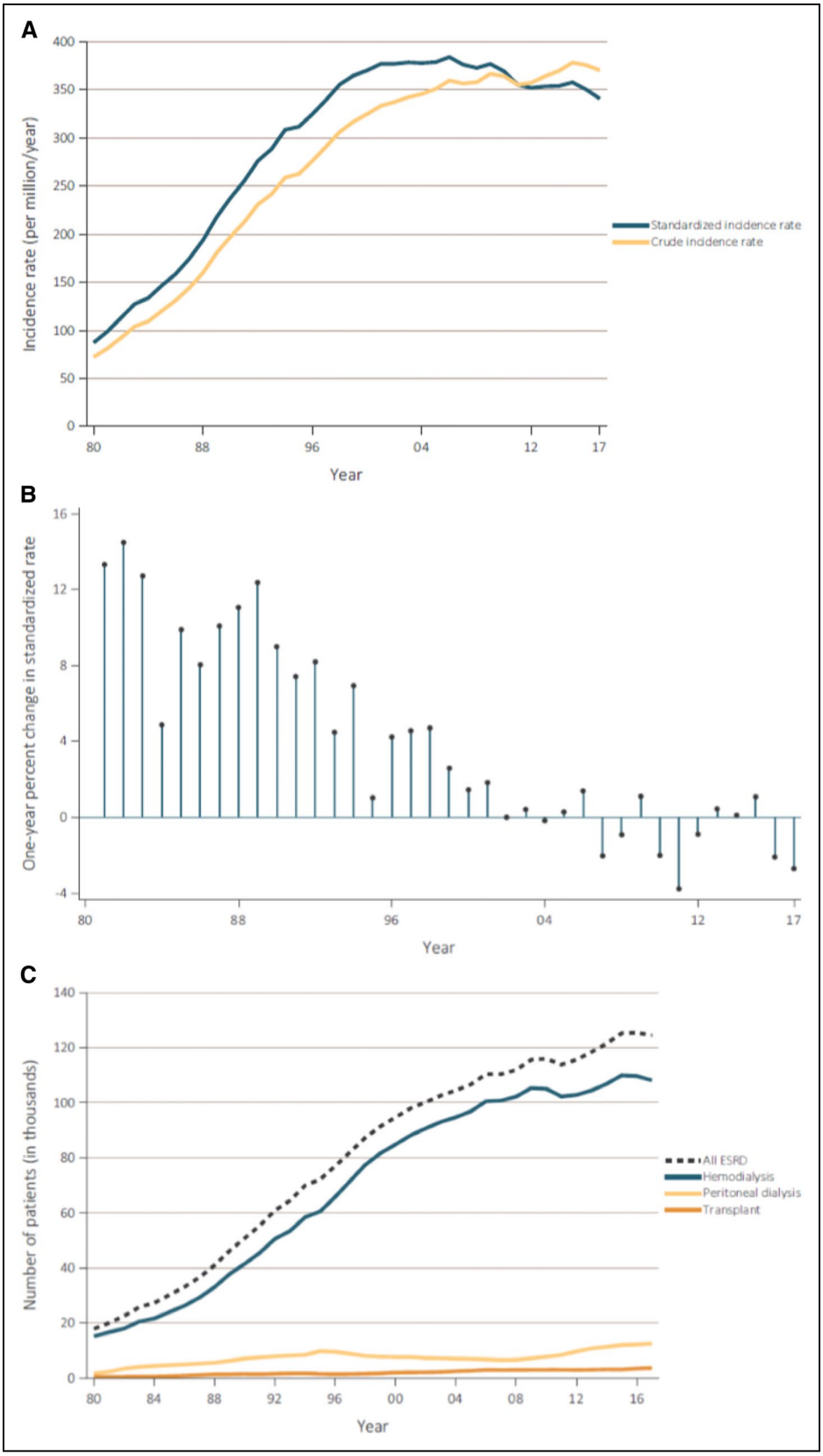

Chart 12-2. Temporal trends in the number of ESRD incident cases, United States, 1980 to 2017, and trends in the annual number of ESRD incident cases by modality, United States, 1980 to 2017.

A, Incidence rate per million per year, 1980 to 2017. **B**, One-year percentage change in standardized incidence rate, 1980 to 2017. **C**, ESRD incident cases by modality, 1980 to 2017.

ESRD indicates end-stage renal disease.

Source: Reprinted from 2019 United States Renal Data System Annual Data Report, Figures 9 and 10.[1]

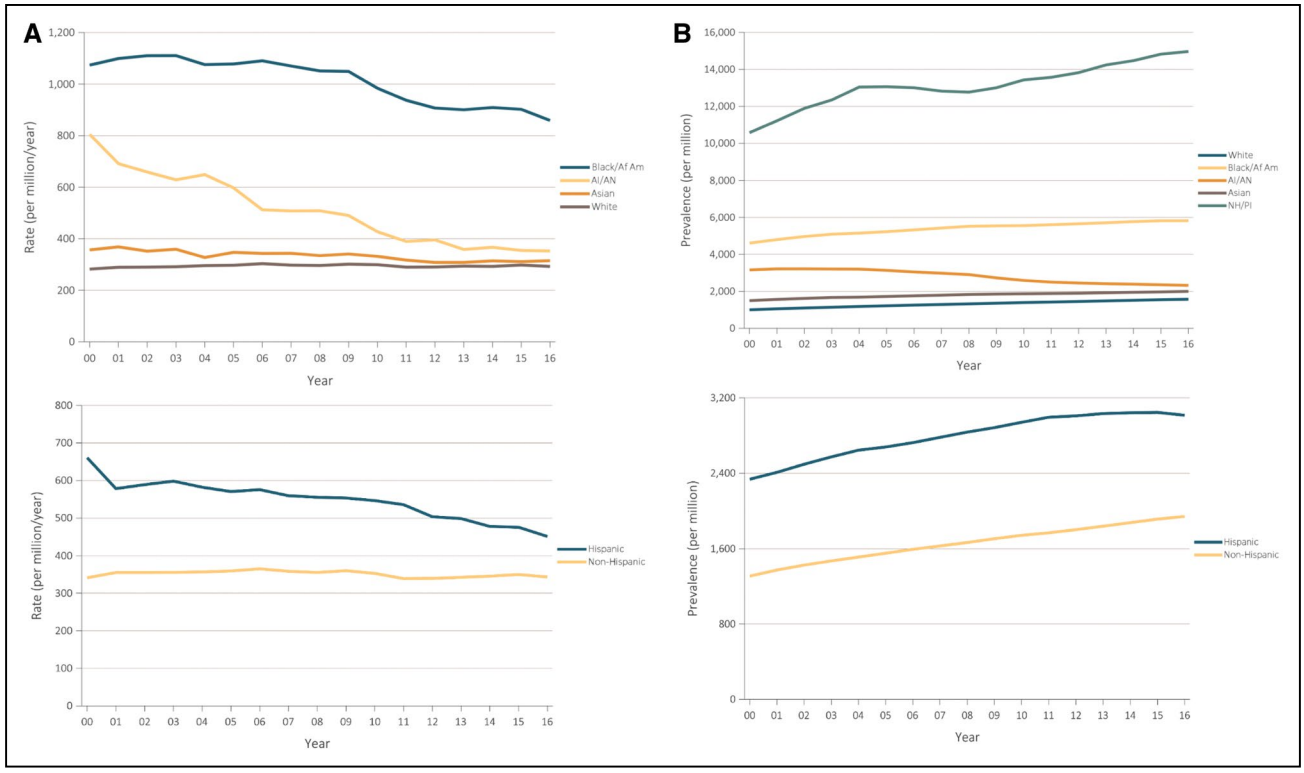

Chart 12-3. Temporal trends in end-stage renal disease by race and Hispanic ethnicity, United States, 2000 to 2016.
A, Standardized* incidence rate (per million). **B**, Standardized* prevalence of end-stage renal disease.
Af Am indicates African American; AI/AN, American Indian or Alaska Native; NH, non-Hispanic; and PI, Pacific Islander.
*Standardized for age and sex; the ethnicity analysis is further adjusted for race. The standard population was the US population in 2011.
Source: Reprinted from 2018 United States Renal Data System Annual Data Report, volume 2, Figures 1.5 to 1.6 and 1.12 to 1.13.[2]

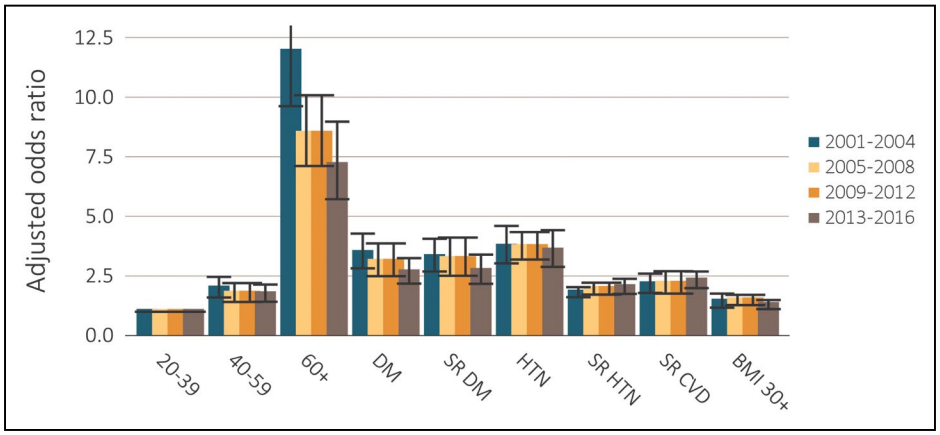

Chart 12-4. Adjusted odds ratios of chronic kidney disease (CKD) in NHANES participants by risk factor, United States, 2001 to 2016.
CKD was defined as presence of estimated glomerular filtration rate (eGFR) <60 m·min^{-1}·1.73 m^{-2}, urine albumin-to-creatinine ratio (ACR) ≥30 mg/g, and either eGFR <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 CKD-EPI equation. Whisker lines indicate 95% CIs.
BMI indicates body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; NHANES, National Health and Nutrition Examination Survey; and SR, self-report.
Source: Reprinted from 2018 United States Renal Data System Annual Data Report, volume 1, Figure 1.6,[2] using NHANES 2001 to 2004, 2005 to 2008, 2009 to 2012, and 2013 to 2016.

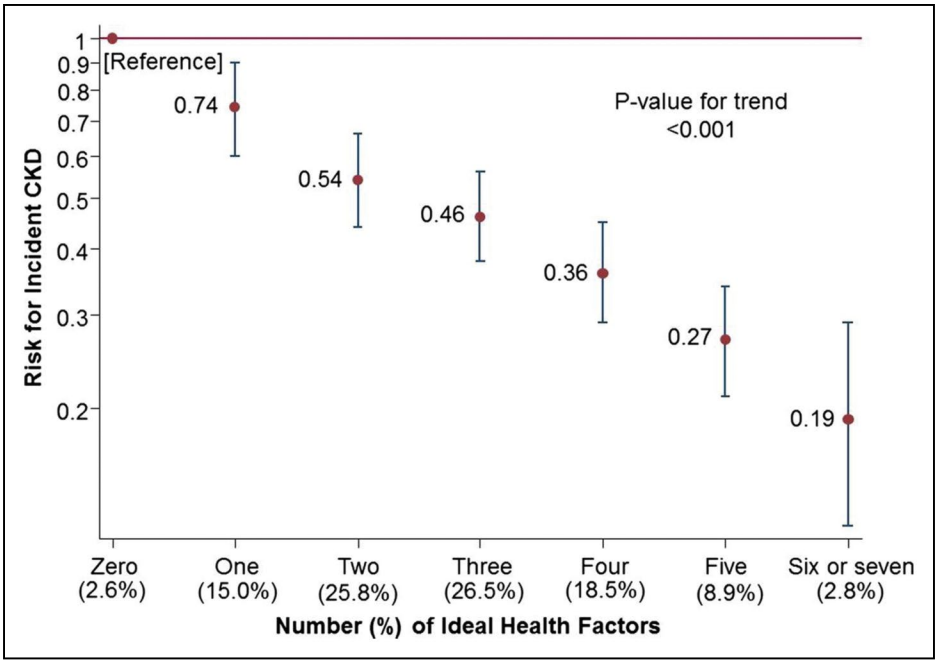

Chart 12-5. Relationship of the AHA's Life's Simple 7 health factors and risk of incident CKD.
Hazard ratio adjusted for age, sex, race, and baseline estimated glomerular filtration rate. Error bars represent the 95% CI.
AHA indicates American Heart Association; and CKD, chronic kidney disease.
Source: Reprinted from Rebholz et al.[13] Copyright © 2016, The Authors. Published on behalf of the American Heart Association, Inc., by Wiley Blackwell. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

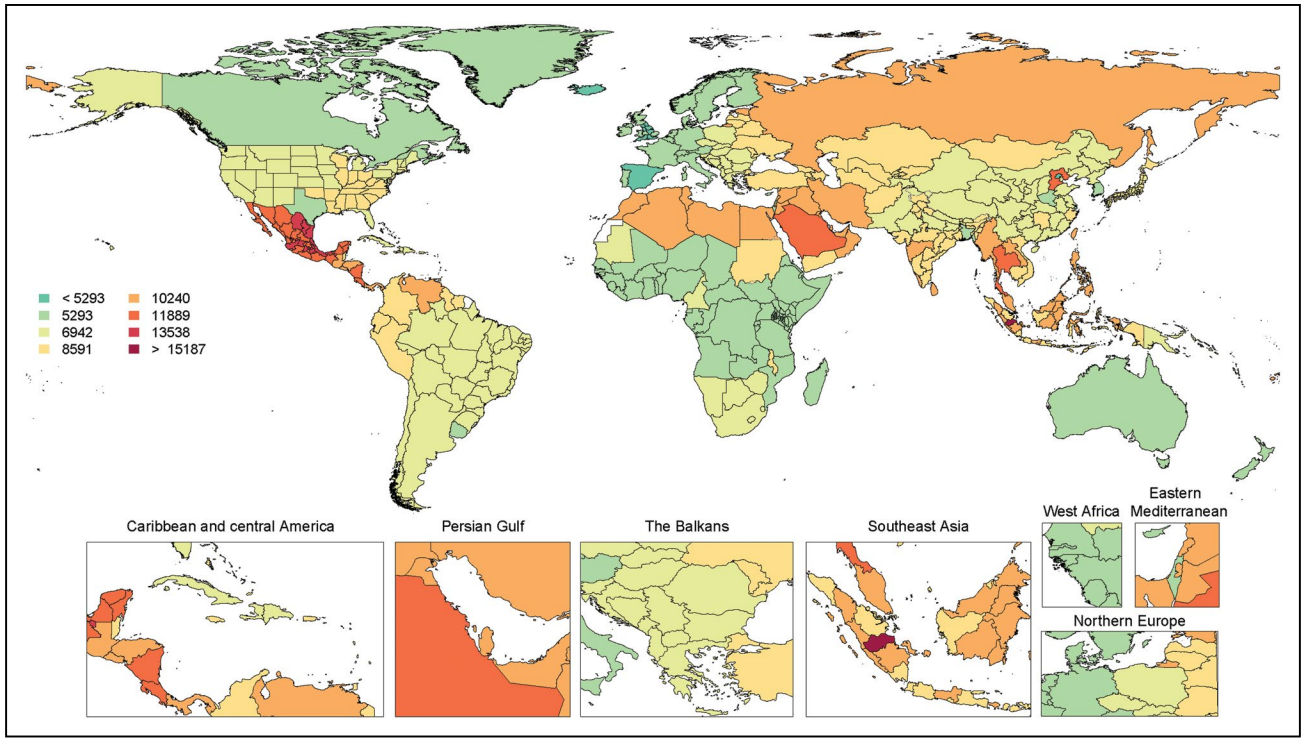

Chart 12-6. Age-standardized global prevalence rates for chronic kidney disease per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[33] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[69]

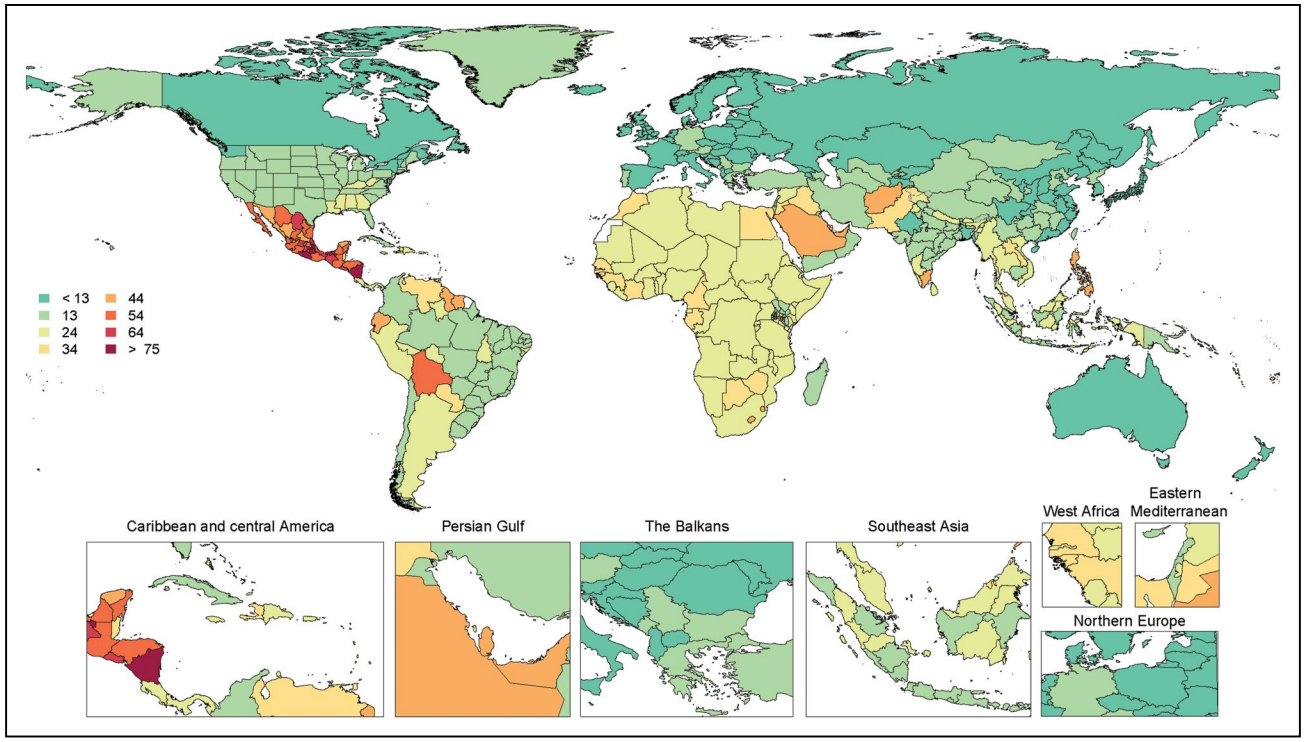

Chart 12-7. Age-standardized global mortality rates for chronic kidney disease per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[33] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[69]

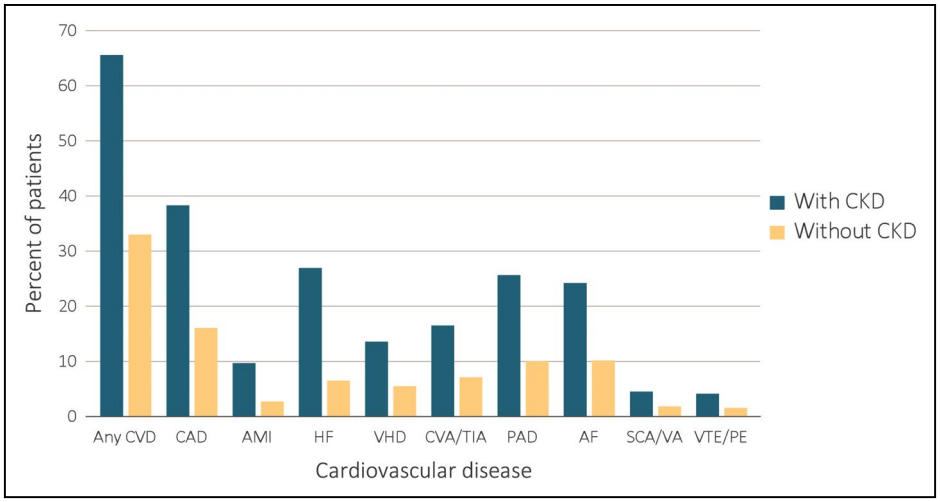

Chart 12-8. Prevalence of CVD in US patients with or without CKD, 2016.
Special analyses, Medicare 5% sample.
AF indicates atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CKD, chronic kidney disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; HF, heart failure; PAD, peripheral arterial disease; PE, pulmonary embolism; SCA, sudden cardiac arrest; TIA, transient ischemic attack; VA, ventricular arrhythmia; VHD, valvular heart disease; and VTE, venous thromboembolism.
Source: Reprinted from 2018 United States Renal Data System Annual Data Report, volume 1, Figure 4.1.[2]

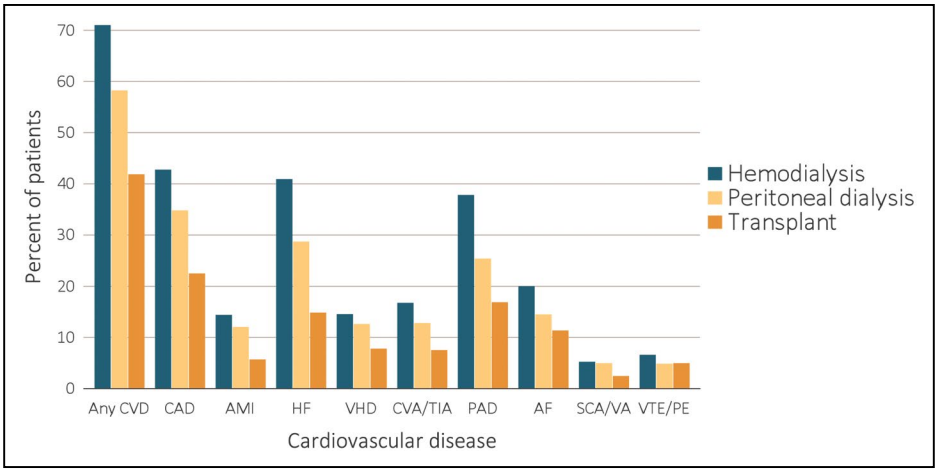

Chart 12-9. Prevalence of CVD in US patients with end-stage renal disease (ESRD) by treatment modality, 2016.
Point prevalent hemodialysis, peritoneal dialysis, and transplant patients ≥22 years of age who were continuously enrolled in Medicare Parts A and B, and with Medicare as primary payer from January 1, 2016, to December 31, 2016, and for whom the ESRD service date was at least 90 days before January 1, 2016.
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; VA, ventricular arrhythmia; VHD, valvular heart disease; and VTE, venous thromboembolism.
Source: Reprinted from 2018 United States Renal Data System Annual Data Report, volume 2, Figure 8.1.[2]

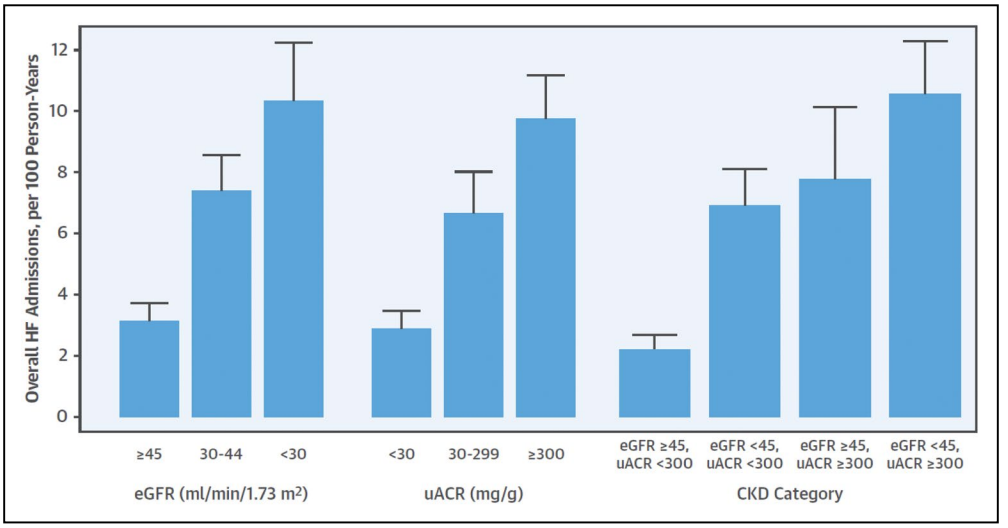

Chart 12-10. US heart failure hospitalization rates among those with CKD based on eGFR and albuminuria.
Unadjusted rates of HF admissions across by level of kidney function among participants with CKD.
CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; and uACR, urine albumin-to-creatinine ratio.
Source: Reprinted from Bansal et al,[65] Central Illustration, with permission from the American College of Cardiology Foundation. Copyright © 2019, by the American College of Cardiology Foundation.

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13. SLEEP

See Charts 13-1 through 13-4

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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 13-1 and 13-2)

- The American Academy of Sleep Medicine and the Sleep Research Society recommend that adults obtain ≥7 hours of sleep per night to promote optimal health.[1]

Abbreviations Used in Chapter 13

ACS	acute coronary syndrome
AF	atrial fibrillation
AHI	apnea-hypopnea index
AMI	acute myocardial infarction
BMI	body mass index
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CAD	coronary artery disease
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CI	confidence interval
CPAP	continuous positive airway pressure
CVD	cardiovascular disease
DBP	diastolic blood pressure
HF	heart failure
HR	hazard ratio
JHS	Jackson Heart Study
MACE	major adverse cardiovascular events
MI	myocardial infarction
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey

(*Continued*)

Abbreviations Used in Chapter 13 Continued

NHIS	National Health Interview Survey
NSTEMI	non–ST-segment–elevation myocardial infarction
OR	odds ratio
OSA	obstructive sleep apnea
PA	physical activity
PCI	percutaneous coronary intervention
RCT	randomized controlled trial
RR	relative risk
SAGE	Study on Global Ageing and Adult Health
SAVE	Sleep Apnea Cardiovascular Endpoints
SBP	systolic blood pressure
SD	standard deviation
SNP	single-nucleotide polymorphism
STEMI	ST-segment–elevation myocardial infarction
TIA	transient ischemic attack
UA	unstable angina
WHO	World Health Organization

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

- The CDC used 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.[2]
- Analysis of 2018 BRFSS data indicated that the proportion of adults reporting inadequate sleep (<7 hours) was 35.4%. Older people (>65 years) were less likely to report sleeping <7 hours, and younger males (<45 years) were more likely to report sleeping <7 hours (Chart 13-1).[3]
- 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]
- Prevalence of OSA varies by sex. On the basis of data from the Wisconsin Cohort Study, OSA prevalence estimates among subjects 30 to 70 years of age in the United States in 2007 to 2010 were 33.9% among males and 17.4% among females for AHI ≥5 events per hour (mild to severe OSA). Prevalence estimates of moderate to severe OSA (AHI ≥15 events per hour) 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 13.2% in females for mild to severe OSA.[5]
- A systematic review estimated the prevalence of OSA in cerebrovascular disease in 3242 patients who had cerebral infarction, TIA, ischemic stroke, or hemorrhagic stroke and found that the pooled prevalence of OSA (defined as AHI >10 events per hour) was 62% (95% CI, 55%–69%) and the

pooled prevalence of severe OSA (AHI >30 events per hour) was 30% (95% CI, 23%–37%).[6]

- The 2018 BRFSS asked respondents, "Over the last 2 weeks, how many days have you had trouble falling asleep or staying asleep or sleeping too much?" Results showed that 54% responded zero (never), 23% responded 1 to 6 days, and 22% responded 7 to 14 days. Females were more likely to report having sleep problems on 7 to 14 of the past 14 days than males at all ages (Chart 13-2) (unpublished tabulation using BRFSS[3]).
- The prevalence of restless legs syndrome among patients with CAD was estimated in a sample of 326 consecutive patients who were hospitalized to undergo percutaneous coronary revascularization for CAD in Japan. Restless legs syndrome was identified in a face-to-face interview with a trained physician among 26 patients (8.0%).[7]

Children/Adolescents

- The American Academy of Sleep Medicine and Sleep Research Society have published guidelines for pediatric populations: Infants 4 to 12 months of age should sleep 12 to 16 h/d; children 1 to 2 years of age should sleep 11 to 14 h/d; children 3 to 5 years of age should sleep 10 to 13 h/d; children 6 to 12 years of age should sleep 9 to 12 h/d; and adolescents 13 to 18 years of age should sleep 8 to 10 h/d.[8]
- National poll data indicated that 63.3% (95% CI, 57.7%–68.5%) of children 6 to 11 years of age and 56.7% (95% CI, 50.9%–62.4%) of children 12 to 17 years of age obtained sufficient sleep, whereas 47.2% (95% CI, 41.5%–52.9%) of children 6 to 11 years of age and 38.5% (95% CI, 33.0%–44.2%) of children 12 to 17 years of age had excellent sleep quality.[9]

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% (95% CI, 66.8%–68.7%) for adults 18 to 24 years of age, 62.1% (95% CI, 61.3%–62.9%) for adults 25 to 34 years of age, 61.7% (95% CI, 60.9%–62.5%) for adults 35 to 44 years of age, 62.7% (95% CI, 62.2–63.1%) adults 45 to 64 years of age, and 73.7% (95% CI, 73.2%–74.2%) for adults ≥65 years of age.[2]

Risk Factors

- On the basis of data from NHANES, risk factors for short sleep duration include smoking (OR, 0.63 [95% CI, 0.51–0.79] for ex-smokers; OR, 0.68 [95% CI, 0.53–0.85] for never smokers versus 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 kg/m^2 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).[10]
- According to data from NHANES, characteristics associated with trouble sleeping include not being married (OR, 1.16 [95% CI, 1.01–1.36] for 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 kg/m^2 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).[10]
- Predictors of moderate to severe OSA (AHI ≥15 events per hour) among a sample of 852 Black people were male sex (OR, 2.67 [95% CI, 1.87–3.80]), larger BMI (OR, 2.06 per SD [95% CI, 1.71–2.47]), larger neck circumference (OR, 1.55 per SD [95% CI, 1.18–2.05]), and habitual snoring (OR, 1.94 [95% CI, 1.37–2.75]).[11]
- National data indicate that the following characteristics are associated with increased risk of incident diagnosed insomnia: >45 years of age (HR, 1.69 [95% CI, 1.40–2.03] for 45–64 years of age; HR, 2.11 [95% CI, 1.63–2.73] for ≥65 years of age) versus 18 to 44 years of age, 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; 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.[12] 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.[12]
- Among a random sample of 1936 Sicilian males and females ≥18 years of age, those who adhered to a Mediterranean diet were more likely to report better subjective sleep quality. Compared with those in the lowest quartile for adherence, the OR for having adequate sleep quality was 1.48 (95% CI, 1.15–1.90) for the second quartile, 1.85 (95% CI, 1.43–2.39) for the third quartile, and 1.82 (95% CI, 1.32–2.52) for the fourth quartile in adjusted models.[13]

Social Determinants

Race/Ethnicity and Sleep (See Charts 13-3 and 13-4)

- Data from the CDC indicated that in 2014 the age-adjusted prevalence of healthy sleep duration was lower among Native Hawaiian/Pacific Islander people (53.7%), NH Black people (54.2%), multiracial NH people (53.6%), and American Indian/Alaska Native people (59.6%) compared with NH White people (66.8%), Hispanic people (65.5%), and Asian people (62.5%).[2]
- The Chicago Area Sleep Study (n=495) used wrist activity monitoring and showed an adjusted mean sleep duration of 6.7 hours for Black individuals, 6.8 hours for Asian individuals, 6.9 hours for Hispanic/Latino individuals, and 7.5 hours for White individuals.[14] This study also observed lower sleep quality in Black and Hispanic/Latino individuals compared with White individuals.
- In the 2018 BRFSS, NH Black people had the highest percentage of respondents reporting sleeping <7 hours per night (45.4%), whereas NH White people had the lowest percentage (33.2%) of respondents reporting sleeping <7 hours (Chart 13-3).
- In the 2018 BRFSS, NH American Indian/Alaska Native people had the highest percentage of respondents indicating sleep problems ≥7 of 14 days (54.8%), whereas NH Black people and Hispanic people had the lowest percentages (14.9% and 15.2%, respectively) (Chart 13-4).
- In a sample of Black people from the JHS, the prevalence of moderate to severe OSA (AHI ≥15 events per hour) was 23.6%.[11]

Other Social Determinants of Sleep

- In addition to race/ethnicity, social characteristics associated with short sleep duration include lower education (OR, 1.47 [95% CI, 1.19–1.78] for less than high school versus greater than high school), not being married (OR, 1.43 [95% CI, 1.25–1.67] for not married versus married), and poverty (OR, 1.54 [95% CI, 1.27–1.85] for poverty/income ratio <1 versus ≥2).[10]
- Among Native Hawaiian and Pacific Islander people from the NHIS, low neighborhood social cohesion was associated with increased odds of short sleep duration (OR, 1.53 [95% CI, 1.10–2.13]). Neighborhood social cohesion was not associated with trouble falling or staying asleep or feeling well rested.[15]
- Data from the WHO's longitudinal SAGE from 6 countries (Mexico, Ghana, South Africa, India, China, and Russia) collected in 2007 to 2010 indicated that participants who felt safe in their neighborhoods were less likely to report short sleep in Ghana (OR, 0.44 [95% CI, 0.33–0.58]) and China (OR, 0.72 [95% CI, 0.60–0.87]). Neighborhood safety was also associated with reduced likelihood of insomnia in China (OR, 0.22 [95% CI, 0.13–0.37]), Ghana (OR, 0.52 [95% CI, 0.37–0.71]), Russia (OR, 0.59 [95% CI, 0.43–0.81]), and India (OR, 0.73 [95% CI, 0.62–0.87]).[16]

Family History and Genetics

- Genetic factors may influence sleep either directly by controlling sleep disorders or indirectly through modulation of risk factors such as obesity. In a study of >120 000 individuals, >50 genetic loci were identified as contributing to the interaction between sleep duration and blood lipid profiles.[17]
- Heritability of sleep behaviors varies but is estimated to be ≈40%.[18] Genetic studies have identified variants associated with OSA.[19,20] Data suggest genetic control of interindividual variability in circadian rhythms, with variants in clock genes such as *CRY1* and *CRY2* being of particular interest.[21,22] Several variants have been found to be associated with chronotype, insomnia, and sleep duration in the UK Biobank, with evidence for shared genetics between insomnia and cardiometabolic traits.[23-25]
- A case-control study examined circadian gene polymorphisms in patients with type 2 diabetes who had an MI (n=231 cases) and those who did not (n=426 controls). Eight genetic variants in 3 circadian rhythm–regulating genes (*ARNTL*, *CLOCK*, and *PER2*) were genotyped. In an adjusted logistic regression model, the *ARNTL* SNP rs12363415 was associated with history of MI (OR for GG+AG versus AA, 7.37 [95% CI, 4.15–13.08]).[26]

Awareness, Treatment, and Control

- 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 patients than in untreated patients.[27]
- An RCT enrolled people 45 to 75 years of age with moderate to severe OSA without excessive daytime sleepiness and who also had coronary or cerebrovascular disease to compare CPAP plus usual care with usual care alone.[28] 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, or TIA.
- A retrospective chart review of 75 pediatric patients (7–17 years of age) referred to a sleep clinic for snoring compared 6-month change in BP between 3 groups (25 patients in each): snorers without OSA

(AHI <1 event per hour), with OSA but no treatment (AHI >1 event per hour), and with OSA with CPAP treatment. SBP was higher at baseline in the 2 OSA groups ($P<0.05$) but decreased in the CPAP-treated group over 6 months (median change, −5 mm Hg [25th–75th percentile, −19 to 0 mm Hg]), whereas SBP increased in the untreated OSA group (median change, 4 mm Hg [25th–75th percentile: 0–10 mm Hg]). DBP did not differ between groups at baseline, nor did the 6-month change in DBP differ between groups.[29]

- The SAVE study was a multicenter, randomized trial of CPAP plus standard care versus standard care alone in adults with a history of cardiac or cerebrovascular events and moderate to severe OSA without excessive daytime sleepiness. A post hoc analysis examined whether weight change over an average of 3.78 years differed between the CPAP group (n=1248) and the control group (n=1235). Investigators found that weight change was similar in the 2 groups for both males (adjusted change, −0.14 kg [95% CI, −0.37 to 0.09]) and females (adjusted change, 0.07 kg [95% CI, −0.40 to 0.54]). When the analysis was restricted to those who used CPAP for at least 4 hours per night (n=516), male CPAP users gained more weight compared with propensity-matched controls (adjusted change, 0.38 kg [95% CI, 0.04–0.73]), but no significant differences were observed in females (adjusted change, −0.22 kg [95% CI, −0.97 to 0.53]).[30]

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.[31]
- A prospective cohort study found that the association between sleep duration and mortality varied with age.[32] Among adults <65 years of age, both short sleep duration (≤5 hours per night) and long sleep duration (≥8 hours per night) were associated with increased mortality risk (HR, 1.37 [95% CI, 1.09–1.71]; 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 2005 to 2008 indicated that long sleep duration (>8 hours per night) was associated with an increased risk of all-cause mortality overall (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.[10] No statistically significant associations were observed between short sleep (<7 hours per night) and all-cause mortality.
- A meta-analysis of 137 prospective cohort studies with a total of 5 134 036 participants found that long sleep duration (cutoff varied by study) was associated with increased mortality risk (RR, 1.39 [95% CI, 1.31–1.47]).[33]
- 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]).[27]
- A study among males and females 21 to 75 years of age 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.[34]

Complications

- A meta-analysis examined sleep duration and total CVD (26 articles), CHD (22 articles), and stroke (16 articles).[31] 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 with 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 study in Spain estimated sleep duration using wrist actigraphy and measured atherosclerotic plaque burden using 3-dimensional vascular ultrasound in 3804 adults between 40 and 54 years of age without a history of CVD or OSA. In fully adjusted models, sleeping <6 hours per night was significantly associated with a higher noncoronary plaque burden compared with those sleeping 7 to 8 hours a night (OR, 1.27 [95% CI, 1.06–1.52]), whereas those sleeping 6 to 7 hours a night (OR, 1.10 [95% CI, 0.94–1.30]) or >8 hours a night (OR, 1.31 [95% CI, 0.92–1.85]) did not differ from those sleeping 7 to 8 hours a night.[35]
- 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 (n=1850), which used in-home polysomnography to characterize sleep, 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]).[36]

- In the Jackson Heart Sleep Study among 664 Black adults with hypertension (average 65 years of age), the associations between OSA and BP control or resistant hypertension were examined. In fully adjusted models, uncontrolled hypertension was not associated with either moderate to severe OSA or nocturnal hypoxemia. However, resistant hypertension was associated with moderate or severe OSA (OR, 2.04 [95% CI, 1.14–3.67]) and nocturnal hypoxemia (OR, 1.25 [95% CI, 1.01–1.55] per SD of percent sleep time <90% oxyhemoglobin saturation).[37]
- A prospective study examined 744 adults without hypertension or severe OSA at baseline and found that mild to moderate OSA (AHI, 5–29.9 events per hour) was significantly associated with incident hypertension over an average of 9.2 years of follow-up (HR, 2.94 [95% CI, 1.96–4.41]) in adjusted models. This association also varied by age; mild to moderate OSA was significantly associated with incident hypertension in those ≤60 years of age (HR, 3.62 [95% CI, 2.34–5.60]) but not in adults >60 years of age (HR, 1.36 [95% CI, 0.50–3.72]).[38]
- 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]).[39]
- A prospective observational study enrolled patients with suspected metabolic disorders and possible OSA and examined incident major adverse cardiovascular and cerebrovascular events. A significant elevated risk of major adverse cardiovascular and cerebrovascular events was observed for patients with moderate OSA (HR, 3.85 [95% CI, 1.07–13.88] versus no OSA) and severe OSA (HR, 3.54 [95% CI, 1.03–12.22] versus no OSA). Using CPAP for ≥4 hours per night ≥5 d/wk was not significantly associated with major adverse cardiovascular and cerebrovascular events (HR, 1.44 [95% CI, 0.80–2.59] versus less frequent or no CPAP use).[40]
- A meta-analysis analyzed data from 9 cohort studies with 2755 participants that described the association between OSA and MACEs after PCI with stenting and found that OSA was associated with a significantly increased risk of MACEs (pooled RR, 1.96 [95% CI, 1.36–2.81]).[41]
- 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 is highest among those with severe OSA: 18.3% for no OSA, 35.4% for mild OSA, 33.9% for moderate OSA, and 41.6% for severe OSA.[42]
- Central sleep apnea was associated with increased odds of incident AF (OR, 3.00 [95% CI, 1.40–6.44] for central apnea index ≥5 versus <5), but OSA was not associated with incident AF.[43]
- A prospective observational study in Spain enrolled consecutive patients ≥65 years of age referred to a sleep clinic for suspicion of OSA. Patients were grouped as no or mild OSA (AHI ≤15 events per hour), untreated moderate OSA (AHI, 15–29.9 events per hour and CPAP not prescribed or noncompliant), untreated severe OSA (AHI ≥30 events per hour and no or noncompliant CPAP), and CPAP-treated (AHI ≥15 events per hour and CPAP compliance ≥4 h/d). Patients were followed up for ≈71 to 72 months. Compared with the patients with AHI <15 events per hour, the fully adjusted HRs for the incidence of stroke were 1.76 (95% CI, 0.62–4.97), 3.42 (95% CI, 1.37–8.52), and 1.02 (95% CI, 0.41–2.56) for the untreated moderate OSA, untreated severe OSA, and the CPAP-treated groups, respectively (n=859). Incident CHD did not differ significantly between the group with no to mild OSA and the other OSA groups: The fully adjusted HRs for the incidence of stroke were 1.83 (95% CI, 0.68–4.9), 2.05 (95% CI, 0.65–6.47), and 1.07 (95% CI, 0.34–3.30) for the untreated moderate OSA group, the untreated severe OSA group, and the CPAP-treated group, respectively (n=794).[44]
- A prospective study in China enrolled 804 consecutive patients admitted for ACS and who had a sleep study. In fully adjusted models, OSA (AHI ≥15 events per hour) was not associated with incidence of major adverse cardiovascular and cerebrovascular events (HR, 1.55 [95% CI, 0.94–2.57]). Analyses stratified by follow-up time (<1 year, ≥1 year) observed no significant association between OSA and major adverse cardiovascular and cerebrovascular events with <1 year follow-up (HR, 1.18, [95% CI, 0.67–2.09]), but in the group with ≥1 year of follow-up time, OSA was significantly associated with incident major adverse cardiovascular and cerebrovascular events in fully adjusted models (HR, 3.87 [95% CI, 1.20–12.46]).[45]

Costs

- Analysis of direct and indirect costs related to inadequate sleep in Australia suggested that the approximate cost for a population the size of the United States would be more than $585 billion for the 2016 to 2017 financial year.[46]

Global Burden

- An analysis of the global prevalence and burden of OSA estimated that 936 million (95% CI, 903–970 million) males and females 30 to 69 years of age have mild to severe OSA (AHI ≥5 events per hour) and 425 million (95% CI, 399–450 million) have moderate to severe OSA (AHI ≥15 events per hour) globally. The prevalence was highest in China, followed by the United States, Brazil, and India.[47]

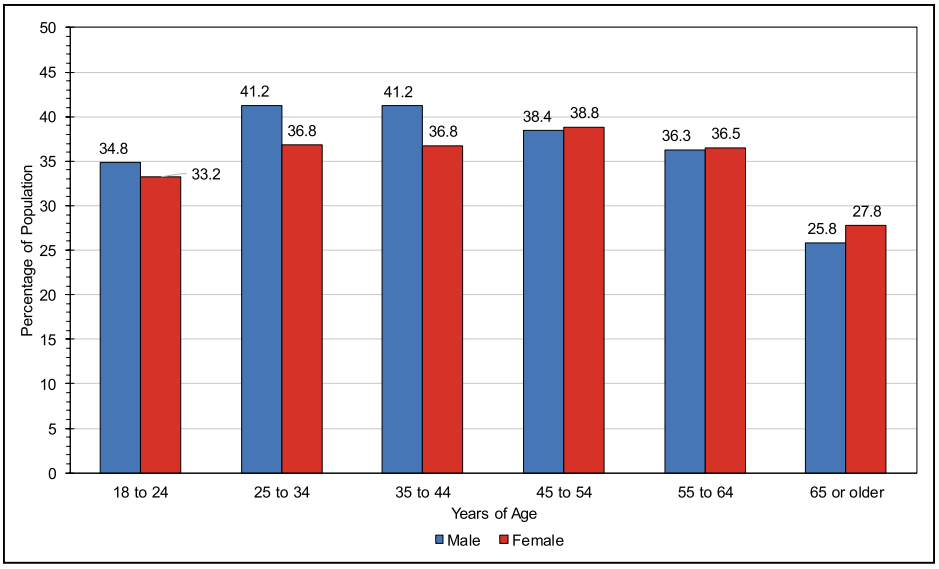

Chart 13-1. Prevalence of reporting sleep duration <7 hours per night in US adults by sex and age, 2018.
Percentages are adjusted for complex sampling design, including primary sampling units, strata, and sampling weights. Survey question was, "On average, how many hours of sleep do you get in a 24-hour period?"
Source: Unpublished tabulation using Behavioral Risk Factor Surveillance Survey, 2018.[3]

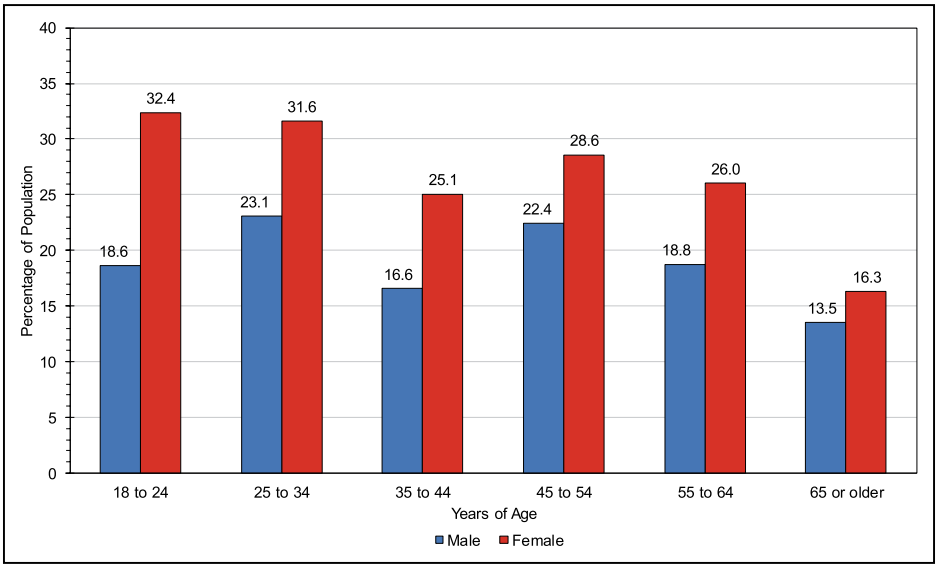

Chart 13-2. Prevalence of reporting sleep problems ≥7 of 14 days in US adults by sex and age, 2018.
Percentages are adjusted for complex sampling design, including primary sampling units, strata, and sampling weights. Survey question was, "Over the last 2 weeks, how many days have you had trouble falling asleep or staying asleep or sleeping too much?"
Source: Unpublished tabulation using Behavioral Risk Factor Surveillance Survey, 2018.[3]

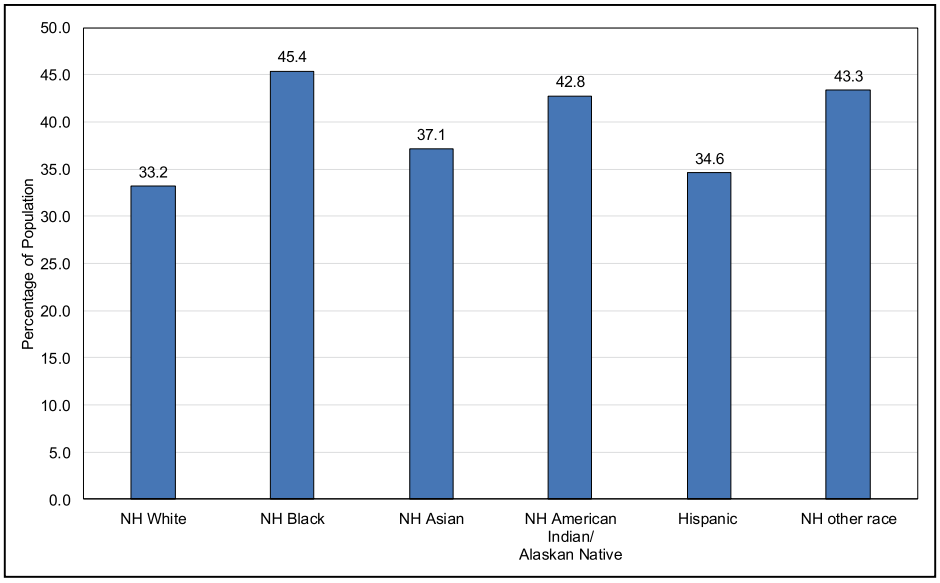

Chart 13-3. Prevalence of reporting sleep duration <7 hours per night in US adults by race, 2018.
Percentages are adjusted for complex sampling design, including primary sampling units, strata, and sampling weights. Survey question was, "On average, how many hours of sleep do you get in a 24-hour period?"
NH indicates non-Hispanic.
Source: Unpublished tabulation using Behavioral Risk Factor Surveillance Survey, 2018.[3]

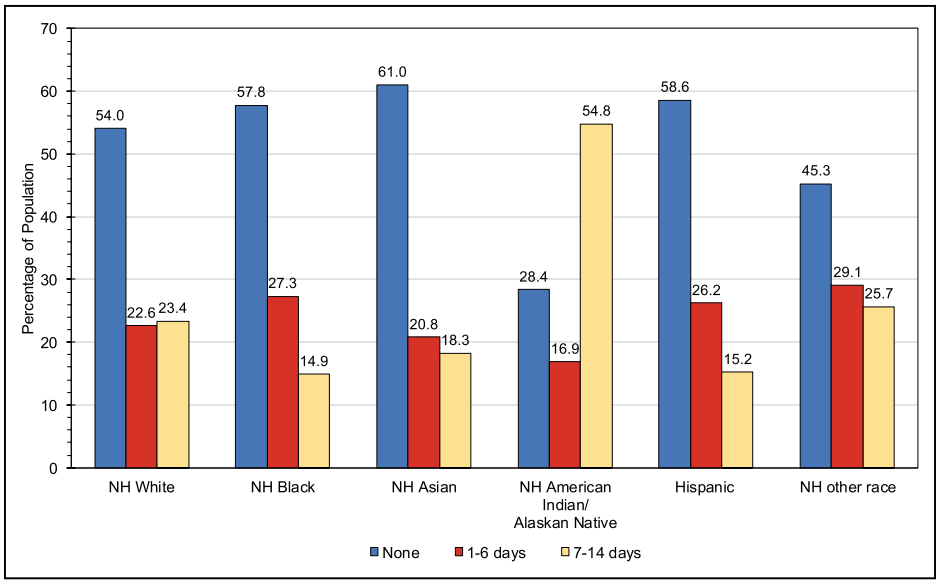

Chart 13-4. Prevalence of sleep problems in the past 2 weeks in US adults by race, 2018.
Percentages are age adjusted for complex sampling design, including primary sampling units, strata, and sampling weights. Survey question was, "Over the last 2 weeks, how many days have you had trouble falling asleep or staying asleep or sleeping too much?"
NH indicates non-Hispanic.
Source: Unpublished tabulation using Behavioral Risk Factor Surveillance Survey, 2018.[3]

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14. TOTAL CARDIOVASCULAR DISEASES

ICD-9 390 to 459; ICD-10 I00 to I99. See Tables 14-1 and 14-2 and Charts 14-1 through 14-20

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Prevalence (See Table 14-1 and Chart 14-1)

- On the basis of NHANES 2015 to 2018 data,[1] the prevalence of CVD (comprising CHD, HF, stroke, and hypertension) in adults ≥20 years of age is 49.2% overall (126.9 million in 2018) and increases with age in both males and females. CVD prevalence excluding hypertension (CHD, HF, and stroke only) is 9.3% overall (26.1 million in 2018) (Table 14-1). Chart 14-1 presents the prevalence breakdown of CVD by age and sex, with and without hypertension in the CVD definition.
- On the basis of the 2018 NHIS[2]:
  - The age-adjusted prevalence of all types of HD (CHD, angina, heart attack, or any other heart condition or disease; excludes hypertension) was 11.2%; the corresponding age-adjusted prevalences of HD among racial/ethnic groups in which only 1 race was reported were 11.5% among White people, 10.0% among Black people, 8.2% among Hispanic/Latino people, 7.7% among Asian people, and 14.6% among American Indian or Alaska Native people.
  - The age-adjusted prevalence of HD, CHD, hypertension, and stroke was higher in males (12.6%, 7.4%, 26.1%, and 3.1%, respectively) than females (10.1%, 4.1%, 23.5%, and 2.6%, respectively).

Abbreviations Used in Chapter 14

ACC	American College of Cardiology
AF	atrial fibrillation
AHA	American Heart Association
aHR	adjusted hazard ratio
ARIC	Atherosclerosis Risk in Communities study
ASCVD	atherosclerotic cardiovascular disease
ATP III	Adult Treatment Panel III
BMI	body mass index
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CLRD	chronic lower respiratory disease
CRP	C-reactive protein
CVD	cardiovascular disease
CVH	cardiovascular health
DBP	diastolic blood pressure
DCM	dilated cardiomyopathy
ED	emergency department
FHS	Framingham Heart Study
FRS	Framingham Risk Score
GBD	Global Burden of Disease Study
GWAS	genome-wide association study
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HBP	high blood pressure
HCM	hypertrophic cardiomyopathy

(*Continued*)

Abbreviations Used in Chapter 14 Continued

HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HDL-C	high-density lipoprotein cholesterol
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
IL	interleukin
IMPACT	International Model for Policy Analysis of Agricultural Commodities and Trade
JHS	Jackson Heart Study
MEPS	Medical Expenditure Panel Survey
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
NAMCS	National Ambulatory Medical Care Survey
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
NHS	Nurses' Health Study
NVSS	National Vital Statistics System
OR	odds ratio
PA	physical activity
PAD	peripheral artery disease
PWV	pulse-wave velocity
RCT	randomized controlled trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
TC	total cholesterol
TNF	tumor necrosis factor
UI	uncertainty interval

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

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— Unemployed individuals who had previously worked had higher age-adjusted prevalence of HD (13.9%), CHD (7.7%), hypertension (30.5%), and stroke (4.7%) than individuals who either were employed (9.5%, 4.0%, 21.8%, and 1.6%, respectively) or were not employed and had never worked (10.2%, 6.7%, 24.6%, and 3.2%, respectively).

- According to data from the 2011 BRFSS and NVSS, there are significant state-level variations in poor CVH in the United States that are explained in part by individual and state-level factors such as policies, food, and PA environments.[3] For example, a 1-SD increase in the density of farmer's markets within the state was associated with an OR for poor CVH of 0.91 (95% CI, 0.85–0.98). A 1-SD increase in the density of convenience stores within the state was associated with an OR for poor CVH of 1.09 (95% CI, 1.01–1.17). Louisiana had the highest age-adjusted prevalence of poor CVH (17.2%), and Colorado had the lowest adjusted prevalence of poor CVH (6.0%). The mean age-adjusted prevalence of poor CVH across states was 10.4%.

Incidence

- In a meta-analysis of CVD incidence among 32 studies of Asian populations free of CVD at baseline and with >10 years of follow-up, the incidence of fatal CVD was 3.68 (95% CI, 2.84–4.53) events per 1000 person-years.[4]

Lifetime Risk and Cumulative Incidence

- According to data from 7 cohort studies in the United States of Black and White males and females (ARIC, CHS, CARDIA, FHS, FHS Offspring Cohort Study, JHS, and MESA; n=19630) followed up from 1960 to 2015, the risk for CVD (MI or stroke) from 55 to 85 years of age varied from 15.3% in females with fasting glucose <5.0 mmol/L (90 mg/dL) at baseline to 38.6% in females with fasting glucose ≥7.0 mmol/L (126 mg/dL) or taking diabetes medication at baseline. In males, the risk varied from 21.5% in those with fasting glucose of 5.0 to 5.5 mmol/L (90 – 99 mg/dL) at baseline to 47.7% in those with fasting glucose ≥7.0 mmol/L or taking diabetes medication at baseline.[5]

Secular Trends

- According to data from NHANES using 35416 participants, BMI increased more in females (from mean of 28.1 kg/m^2 in 2001–2004 to 29.6 kg/m^2 in 2013–2016) than males (from mean of 27.9 to 29.0 kg/m^2). TC decreased more in males (from mean of 201 mg/dL in 2001–2004 to mean of 188 mg/dL in 2013–2016) than females (from mean of 203 to 294 mg/dL). Secular trends in SBP, smoking status, HDL-C, and HbA_{1c} were not statistically significantly different between males and females.[6]
- From 2000 to 2012 in a cohort study of 9012 people living with HIV in British Columbia, Canada, and free from CVD at baseline, the adjusted incidence rate of CVD per 1000 person-years remained relatively stable from 9.11 (95% CI, 5.87–14.13) in 2000 to 10.01 (95% CI, 7.55–13.27) in 2012.[7]

Risk Factors

- 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.[8]
- People living with HIV are more likely to experience CVD before 60 years of age 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 diabetes (67% for males, 57% for females).[9]
- Patients living with type 1 diabetes are at increased risk of early CVD. In participants in the Pittsburgh Epidemiology of Diabetes Complications Study with type 1 diabetes who were 40 to 44 years of age at baseline, mean absolute 10-year CVD risk was 14.8% with an event rate of 1478 (95% CI, 1003–2100) events per 100000 person-years. Mean absolute 10-year CVD risk was 6.3% in those 30 to 39 years of age, with an event rate of 628 (95% CI, 379–984) events per 100000 person-years.[10]
- Highest quintile versus lowest quintile of neighborhood-level socioeconomic deprivation was associated with 1.43 (95% CI, 1.07–1.92) greater odds of CVD mortality in older males in Britain independently of individual social class or risk factors.[11] Similar findings have been reported among older adults in the United States.[12]
- Air pollution, as defined by increased ambient exposure to particulate matter (particles with median aerodynamic diameter <2.5 μm), is associated with elevated blood glucose, poor endothelial function, incident CVD events, and all-cause mortality and accounts in part for the racial differences in all-cause mortality and incident CVD.[13]

- In a meta-analysis of sex differences in the association between diabetes and CVD mortality (49 studies representing 5 162 654 participants), the pooled and adjusted ratio for females versus males of the RR of diabetes was 1.30 (95% CI, 1.13–1.49).[14]
- Among 58 782 participants in the Japan Collaborative Cohort study who completed a baseline daily dietary survey and were recruited from 1988 to 1990 and whose follow-up ended between 1999 and 2008, depending on the geographic region in which they lived, the aHR for the highest quintile (2.49–4.61) of the daily dietary inflammation index, an index based on food and beverage consumption associated with levels of IL-1, IL-4, IL-6, IL-10, TNF-α, and CRP, compared with the lowest quintile (–5.80 to –0.33) for CVD mortality was 1.30 (95% CI, 1.13–1.49). The study sample for analysis excluded 22 941 participants who did not complete the dietary survey.[15]
- Among 5638 females 63 to 97 years of age enrolled between 2012 and 2014 in the Objective Physical Activity and Cardiovascular Health study and without CVD at baseline, the aHR for any incident CVD event (MI, revascularization, hospitalized angina, HF, stroke, or death resulting from any CVD) in those with the highest daily mean sedentary time (≥11 h/d) versus the lowest daily mean sedentary time (≤≈9 h/d) was 1.62 (95% CI, 1.21–2.17).[16]

Risk Prediction

- In a meta-analysis of studies assessing the performance of the FRS, ATP III score, and the Pooled Cohort Equation score for predicting 10-year risk of CVD, the pooled ratio of observed number of CVD events within 10 years versus the expected number of events varied in score/sex strata from 0.58 (95% CI, 0.43–0.73) for the FRS in males to 0.79 (95% CI, 0.60–0.97) for the ATP III score in females. In other words, these equations overestimated the number of events over 10 years by as little as 3% and as much as 57%, depending on sex and equation.[17]

Borderline Risk Factors/Subclinical/Unrecognized Disease

- Among 2119 participants in the Framingham Offspring Cohort study, the aHR for CVD events among those with concurrent high central pulse pressure and high carotid-femoral PWV versus those with concurrent low central pulse pressure and low carotid-femoral PWV was 1.52 (95% CI, 1.10–2.11).[18]

Genetics and Family History

- Genetic contributors to IHD are well documented. Since the first GWAS identified the now most consistently replicated genetic marker for CHD and MI in European-derived populations, on chromosome 9p21.3,[19] many additional CHD loci have been identified. A large-scale GWAS of CAD in >60 000 cases and >123 000 controls identified 2213 genetic variants as genome-wide significantly associated with CAD, grouping in 44 loci across the genome.[20] More recent GWASs have identified at least 13 additional loci across the genome, implicating pathways in blood vessel morphogenesis, lipid metabolism, nitric oxide signaling, and inflammation.[21]
- Ischemic stroke is a heritable disease. The largest multiethnic GWAS of stroke conducted to date reports 32 genetic loci, including 22 not previously reported.[22] 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.
- Atherosclerotic PAD is heritable. A large-scale GWAS in >31 000 PAD cases and >211 000 controls from the Million Veterans Program and >5000 PAD cases and >389 000 controls from the UK Biobank identified 19 PAD loci, 18 of which were novel, and included loci associated with atherosclerotic disease in addition to loci specific for PAD.[23]
- 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.[23a] In a GWAS of >47 000 cases and >930 000 controls, 11 HF loci were identified, all of which have known relationships to other CVD traits.[24] In a sample of >1 million individuals, >100 AF loci were identified.[25] Given the heterogeneous multifactorial nature of common HF, identification of causal genetic loci remains a challenge.

Prevention (See Chapter 2 for more detailed statistics on healthy lifestyle and low risk factor levels.)

- During >5 million person-years of follow-up combined in the NHS 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.[26]
- In young adults 18 to 30 years of age 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 55 years of age).[27]

- In the United States, higher whole grain consumption was associated with lower CVD mortality independently 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.[28]
- In the Shandong-Ministry of Health Action on Sodium and Hypertension survey of individuals 25 to 69 years of age living in Shandong, China, during 2011, the number of CVD deaths attributable to high sodium intake, mediated through high SBP, was estimated to be 16 100 (95% UI, 11 000–22 600) deaths. This number was estimated to be 19.9% (95% UI, 13.7%–25.0%) of all CVD deaths. It was estimated that 8500 (95% UI, 6000–10 800) CVD deaths would be prevented if overall sodium consumption was decreased by 30%. UIs were generated from the 2.5th and 97.5th percentile estimates from 1000 Monte Carlo simulations.[29]
- By combining estimates from NHANES, REGARDS, and RCTs for BP-lowering treatments, it was estimated that achieving the 2017 ACC/AHA BP goals could prevent 3.0 million (uncertainty range, 1.1–5.1 million) CVD events (CHD, stroke, and HF) compared with current BP levels, but achieving the 2017 ACC/AHA BP goals could also increase serious adverse events by 3.3 million (uncertainty range, 2.2–4.4 million).[30] The uncertainty ranges reflect using the lower and upper bounds of the 95% CIs of both treatment effect estimates and the CVD event rates estimated from REGARDS.
- Among 134 480 participants in the Shanghai Men's Health Study (conducted from 2002–2014) and the Shanghai Women's Health Study (conducted from 1997–2014), the aHR for CVD mortality in the highest versus lowest quintiles of dietary vitamin B_6 intake was 0.73 (95% CI, 0.63–0.85) in males and 0.80 (95% CI, 0.70–0.92) in females.[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 Supplemental Nutrition Assistance Program 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]

Awareness, Treatment, and Control

- According to data from NHANES among 35 416 participants in 2013 to 2016, the prevalence of controlled BP (SBP <130 mm Hg and DBP <80 mm Hg) among participants with hypertension was 30% in females and 22% in males; the prevalence of controlled diabetes (HbA_{1c} <6.5%) among participants with diabetes was 30% in females and 20% in males; and the prevalence of controlled dyslipidemia (TC <240 mg/dL) among participants with dyslipidemia was 51% in females and 63% in males.[6]

Mortality
(See Table 14-2 and Charts 14-2 through 14-17)
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 chronic lower respiratory disease; G30 for Alzheimer disease; E10 to E14 for diabetes; and V01 to X59 and Y85 to Y86 for accidents.

- Deaths attributable to diseases of the heart (Chart 14-2) and CVD (Chart 14-3) in the United States increased steadily during the 1900s to the 1980s and declined into the 2010s.
- CHD (42.1%) is the leading cause of CVD death in the United States, followed by stroke (17.0%), HBP (11.0%), HF (9.6%), diseases of the arteries (2.9%), and other minor CVD causes combined (17.4%) (Chart 14-4).
- The age-adjusted death rate attributable to CVD decreased from 252.2 per 100 000 population in 2008 to 217.1 per 100 000 in 2018, which amounts to a 13.9% decrease (unpublished NHLBI tabulation using CDC WONDER[33]).
- There was a decrease in life expectancy disparity between White and Black males. In 1980, the disparity in life expectancy between the 2 groups was 7 years; however, in 2016, when the life expectancies were 76.4 and 72 years, respectively, the disparity was only 4 years.[34]
- On the basis of these national CVD mortality data, the Million Hearts 2022 Initiative focuses on preventing a combined 1 million heart attacks, strokes, and other cardiovascular events[35]:
  - In 2016, >1000 deaths caused by heart attack, stroke, or other cardiovascular events occurred daily.
  - 2.2 million hospitalizations and 415 480 deaths occurred in 2016.
  - In addition, 35% of the life-changing cardiovascular events occurred in adults 35 to 64

years of age. This age group accounted for 775 000 hospitalization and 73 000 deaths attributable to cardiovascular events.
  - The mortality rate in NH Black people was 211.6 per 100 000, which was the highest compared with all other racial and ethnic groups.
  - There is remarkable geographic variation in the life-changing cardiovascular events, with the highest rates being evident in the Southeast and Midwest regions of the United States.
  - The lowest CVD event rates (comprising deaths, hospitalizations, and ED visits) were in Utah (805.7), Wyoming (828.9), and Vermont (840.6), whereas the highest were noted in Washington, DC (2048.2), Tennessee (1551.6), and Kentucky (1510.3).
- On the basis of 2018 mortality data (unpublished NHLBI tabulation using the NVSS[36]):
  - CVD currently claims more lives each year than cancer and chronic lung disease combined. In 2018, 365 744 people died of CHD, the most common type of HD.
  - In 2018, 2 839 205 resident deaths were registered in the United States, which exceeds the 2017 figure by 25 702 deaths. Ten leading causes accounted for 73.8% of all registered deaths. The 10 leading causes of death in 2018 were the same as in 2017; these include HD (No. 1), cancer (No. 2), unintentional injuries (No. 3), chronic lower respiratory diseases (No. 4), stroke (No. 5), Alzheimer disease (No. 6), diabetes (No. 7), influenza and pneumonia (No. 8), kidney disease (No. 9), and suicide (No. 10). From 2017 to 2018, 6 of the 10 leading causes of death had a decrease in age-adjusted death rates. The age-adjusted rate decreased 0.8% for HD, 2.2% for cancer, 2.8% for unintentional injuries, 2.9% for chronic lower respiratory disease, 1.3% for stroke, and 1.6% for Alzheimer disease. The age-adjusted death rates increased 4.2% for influenza and pneumonia and 1.4% for suicide but did not change appreciably for diabetes or kidney disease.[37]
- HD accounted for 655 381 of the total 868 662 CVD deaths in 2018 (unpublished NHLBI tabulation using NVSS[36]).
- The number of CVD deaths for both sexes and by age category is shown in Chart 14-5 and is split into males in Chart 14-6 and females in Chart 14-7.
- The percentages of total deaths caused by CVD and other leading causes by race/ethnicity are presented in Charts 14-8 through 14-11.
- The number of CVD deaths for all males and females in the United States declined from 1980 to 2010 but increased in recent years (Chart 14-12). The difference in age-adjusted death rates for HD also narrowed among US racial and ethnic groups between 1999 and 2018. Nonetheless, there was a decrease in the rate of decline in the overall age-adjusted HD death rate in recent years, and differences in death rates persisted among major US racial/ethnic groups. In 1999, there were 337.4 deaths per 100 000 people among NH Black people compared with 156.5 among NH Asian people or Pacific Islander people. In 2018, the death rates per 100 000 people for these 2 groups were 209.3 and 85.2, respectively, thus preserving the >2-fold difference in death rates observed in 1999 (unpublished NHLBI tabulation using CDC WONDER[33]).
- The age-adjusted death rates per 100 000 population for CVD, CHD, and stroke differ by US state (Chart 14-13 and Table 14-2) and globally (Charts 14-14 through 14-17).
- CVD death rates also vary among US counties. In 2014, the ratio between counties at the 90th and 10th percentiles 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).[38] A region of higher CVD mortality extends from southeastern Oklahoma along the Mississippi River Valley to eastern Kentucky.[38]

Complications

- Among 392 participants in the National Health and Aging Trends Study who were at least 65 years of age and functionally independent at baseline, 23.8% of those with CVD at baseline experience rapid functional decline compared with 16.2% of those without CVD at baseline. The Short Physical Performance Battery was used to assess physical function.[39]

Health Care Use: Hospital Discharges/ Ambulatory Care Visits (See Table 14-1 and Chart 14-18)

- In the decade between 2005 and 2015, 2 trends were observed in overall access to CVD care attributable to cost. In the first half of this interval (2005–2010), there was increased difficulty with accessing medical care because of cost, whereas in the second half (2010–2015), the difficulty decreased. In 2015, poor access because of cost affected 1 in every 10 adults in the United States, and regional differences were

observed, with the greatest difficulties reported in the South.[34]

- From 2006 to 2016, the number of inpatient discharges from short-stay hospitals with CVD as the principal diagnosis decreased from 5 899 000 to 4 840 000 (Table 14-1). Readers comparing data across years should note that beginning October 1, 2015, a transition was made from *ICD-9* to *ICD-10*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years. CVD principal diagnosis discharges in 2016 comprised 2 629 000 males and 2 211 000 females (unpublished NHLBI tabulation using HCUP,[40] 2016).
- From 1993 to 2016, 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 14-18).
- In 2016, there were 72 128 000 physician office visits with a primary diagnosis of CVD (unpublished NHLBI tabulation using NAMCS,[41] 2016). In 2016, there were 4 774 000 ED visits with a primary diagnosis of CVD (unpublished NHLBI tabulation using NHAMCS,[42] 2016).
- In 2014, an estimated 7 971 000 inpatient cardiovascular operations and procedures were performed in the United States (unpublished NHLBI tabulation of HCUP[40]).

Cost (See Chapter 27 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 health care expenditures were associated with disability care and totaled $397.8 billion.[43] The estimated direct and indirect cost of CVD for 2016 to 2017 was $363.4 billion (MEPS,[44] unpublished NHLBI tabulation).

Global Burden (See Charts 14-14 through 14-17 and Charts 14-19 and 14-20)

- Death rates for CVD, CHD, stroke, and all CVD in selected countries in 2017 to 2018 are presented in Charts 14-14 through 14-17.
- In 2019, ≈18.6 million (95% UI, 17.1–19.7 million) deaths were attributed to CVD globally, which amounted to an increase of 17.1% (95% UI, 11.4%–22.9%) from 2010. The age-adjusted death rate per 100 000 population was 239.8 (95% UI, 219.4–254.9), which represents a decrease of 11.1% (95% UI, −15.3% to −7.0%) from 2010. Overall, the crude prevalence of CVD was 523.2 million cases (95% UI, 497.1–550.2 million) in 2019, an increase of 26.6% (95% UI, 26.0%–27.1%) compared with 2010. However, the age-adjusted prevalence rate was 6431.6 (95% UI, 6110.0–6759.8) per 100 000, an increase of 0.6% (95% UI, 0.3% to 1.0%) from 2010.[45]
- The GBD 2019 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 369 diseases and injuries in 204 countries and territories. CVD mortality and prevalence vary widely among world regions[45]:
  - The highest mortality rates attributable to CVD were in Eastern Europe and Central Asia (Chart 14-19).
  - CVD prevalence is highest in North Africa and the Middle East, Central Asia, and high-income North America (Chart 14-20).
- CVD represents 37% of deaths of individuals <70 years of age that are attributable to noncommunicable diseases.[46]
- In 2016, ≈17.9 million people died of CVD, thus making it the predominant cause of death globally.[46]

Table 14-1. CVDs in the United States

Population group	Total CVD prevalence,* 2015–2018: age ≥20 y	Prevalence, 2015–2018: age ≥20 y†	Mortality, 2018: all ages‡	Hospital discharges, 2016: all ages	Cost, 2016–2017
Both sexes	126 900 000 (49.2%)	26 100 000 (9.3%)	868 662	4 840 000	$363.4 Billion
Males	66 100 000 (54.1%)	13 700 000 (10.4%)	448 498 (51.6%)§	2 629 000	$228.6 Billion
Females	60 800 000 (44.4%)	12 400 000 (8.4%)	420 164 (48.4%)§	2 211 000	$134.8 Billion
NH White males	53.6%	10.4%	344 013	…	…
NH White females	42.1%	7.8%	326 069	…	…
NH Black males	60.1%	11.0%	56 945	…	…
NH Black females	58.8%	11.5%	53 641	…	…
Hispanic males	52.3%	8.7%	30 584	…	…
Hispanic females	42.7%	8.1%	25 983	…	…
NH Asian males	52.0%	6.8%	12 596	…	…
NH Asian females	42.5%	4.2%	11 421‖	…	…
NH American Indian/ Alaska Native	…	…	4642	…	…

CVD indicates cardiovascular disease; ellipses (…), data not available; and NH, non-Hispanic.

*Total CVD prevalence includes coronary heart disease, heart failure, stroke, and hypertension. CVD prevalence rates do not include peripheral artery disease (PAD) because the ankle brachial index measurement used to ascertain PAD was discontinued after the National Health and Nutrition Examination Survey (NHANES) 2003 to 2004 cycle.

†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 CVD mortality that is attributable to males vs females.

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

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES, 2015 to 2018.[1] Percentages for racial/ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2018 US population estimates. Mortality: Unpublished NHLBI tabulation using National Vital Statistics System.[36] 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 Asian people includes Pacific Islander people. Hospital discharges: Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project.[40] Cost: Unpublished NHLBI tabulation using Medical Expenditure Panel Survey,[44] average annual 2016 to 2017 (direct costs) and mortality data from 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).

Table 14-2. Age-Adjusted Death Rates per 100 000 Population for CVD, CHD, and Stroke, by State, 2016 to 2018

State	CVD			CHD			Stroke		
	Rank	Death rate	% Change, 2006–2008 to 2016–2018	Rank	Death rate	% Change, 2006–2008 to 2016–2018	Rank	Death rate	% Change, 2006–2008 to 2016–2018
Alabama	51	293.3	−11.1	20	84.7	−27.6	51	51.0	−11.4
Alaska	8	188.2	−13.3	8	71.7	−17.9	31	38.0	−18.2
Arizona	7	187.4	−15.3	25	87.2	−28.2	9	30.5	−14.5
Arkansas	49	284.0	−9.3	52	135.6	−14.4	45	43.6	−25.5
California	18	198.0	−20.6	23	86.1	−34.7	27	37.2	−14.9
Colorado	3	174.0	−15.7	2	63.7	−31.6	19	35.3	−8.8
Connecticut	6	183.5	−16.3	11	76.1	−25.4	3	27.1	−19.7
Delaware	31	218.0	−13.4	31	92.0	−31.8	47	44.8	11.1
District of Columbia	42	252.4	−21.6	45	110.1	−40.3	25	36.5	−6.6
Florida	20	198.9	−14.1	27	90.8	−28.9	34	38.6	6.1
Georgia	38	238.8	−16.3	9	73.5	−28.5	46	43.7	−15.3
Hawaii	5	176.2	−14.5	5	66.3	−20.1	24	36.4	−14.1
Idaho	27	210.0	−8.1	16	82.9	−20.4	29	37.3	−19.2

(*Continued*)

Table 14-2. Continued

State	CVD			CHD			Stroke		
	Rank	Death rate	% Change, 2006–2008 to 2016–2018	Rank	Death rate	% Change, 2006–2008 to 2016–2018	Rank	Death rate	% Change, 2006–2008 to 2016–2018
Illinois	32	218.6	–16.7	18	83.7	–35.2	30	38.0	–15.2
Indiana	39	239.6	–13.9	39	100.8	–23.5	36	39.7	–16.6
Iowa	29	215.3	–12.2	40	102.3	–26.3	14	32.7	–24.5
Kansas	33	219.8	–13.0	28	91.1	–15.6	28	37.3	–21.4
Kentucky	45	255.5	–15.2	42	103.9	–28.1	39	40.5	–18.8
Louisiana	48	274.0	–11.8	34	96.9	–28.1	50	46.7	–8.8
Maine	13	195.6	–13.9	13	77.9	–28.3	18	35.2	–13.6
Maryland	34	220.8	–15.5	30	91.9	–33.8	38	40.0	–6.2
Massachusetts	4	174.6	–20.8	6	68.7	–34.7	4	27.2	–25.8
Michigan	43	253.6	–12.0	47	114.9	–25.1	35	39.4	–11.0
Minnesota	2	165.6	–11.2	1	60.6	–20.4	12	32.4	–15.9
Mississippi	52	302.6	–15.5	43	104.5	–28.0	52	51.1	–7.9
Missouri	40	246.9	–15.3	44	105.2	–31.1	37	40.0	–19.6
Montana	24	205.9	–8.6	26	87.2	–10.2	13	32.7	–19.0
Nebraska	14	197.1	–14.2	10	74.4	–18.4	11	32.0	–25.8
Nevada	44	254.1	–7.7	46	112.5	1.4	22	36.2	–11.0
New Hampshire	11	192.5	–14.6	15	81.7	–29.3	5	28.0	–19.8
New Jersey	26	207.3	–16.2	29	91.3	–32.3	8	30.1	–14.1
New Mexico	15	197.3	–12.1	36	99.4	–12.4	16	34.0	–14.2
New York	30	215.7	–22.2	48	118.0	–33.9	1	24.8	–14.9
North Carolina	28	214.4	–18.5	19	84.7	–31.3	44	42.4	–17.9
North Dakota	12	193.2	–15.2	17	82.9	–32.7	17	34.1	–18.0
Ohio	41	247.6	–10.7	41	102.4	–29.8	43	42.0	–7.5
Oklahoma	50	290.8	–11.4	50	126.6	–27.4	42	41.8	–24.5
Oregon	10	189.3	–14.4	3	63.8	–32.5	33	38.5	–15.0
Pennsylvania	36	226.2	–14.5	33	96.8	–26.9	23	36.2	–16.1
Puerto Rico	1	155.4	–23.8	7	69.3	–27.8	2	25.0	–40.0
Rhode Island	16	197.3	–20.3	37	99.8	–37.1	6	28.1	–14.5
South Carolina	37	233.2	–14.8	21	85.3	–26.8	49	45.3	–16.3
South Dakota	25	206.3	–10.4	38	100.7	–22.9	20	35.4	–13.9
Tennessee	47	263.8	–14.0	49	121.9	–26.8	48	44.8	–18.7
Texas	35	225.1	–15.6	32	94.6	–27.1	41	41.2	–18.3
Utah	19	198.7	–7.0	4	65.4	–16.3	26	37.1	–6.8
Vermont	21	200.1	–10.1	35	98.8	–17.4	7	29.2	–23.5
Virginia	22	204.0	–18.8	12	77.1	–30.4	32	38.2	–18.3
Washington	9	188.5	–17.8	14	78.3	–31.5	21	35.6	–16.5
West Virginia	46	256.6	–16.7	51	127.5	–18.9	40	40.7	–16.6
Wisconsin	23	205.5	–12.5	24	87.1	–21.0	15	33.4	–21.3
Wyoming	17	197.4	–18.2	22	85.9	–18.3	10	30.8	–29.6
Total United States		218.6	–15.8		92.7	–29.3		37.3	–14.1

Rates are most current data available as of March 2020. 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: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System data.[36]

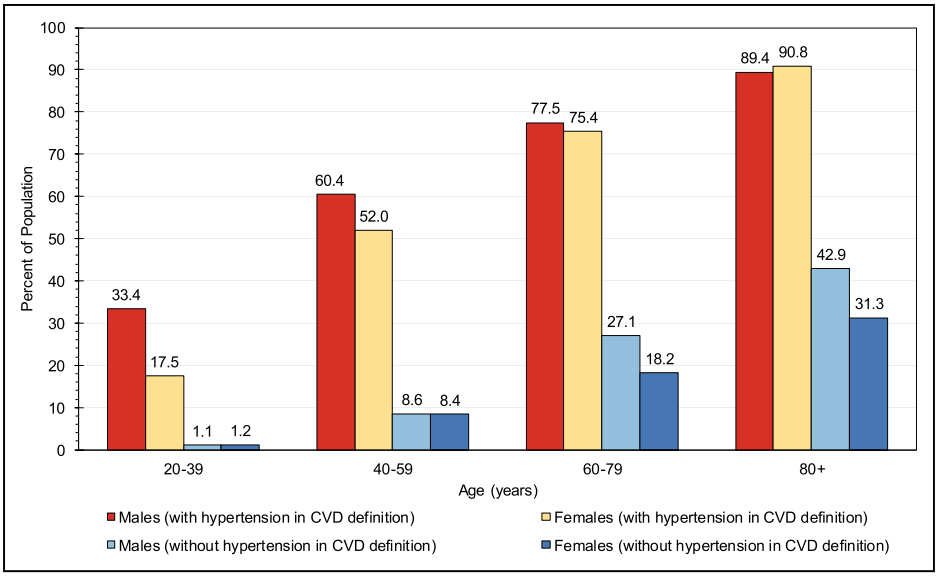

Chart 14-1. Prevalence of CVD in US adults ≥20 years of age by age and sex (NHANES, 2015–2018).
These data include coronary heart disease, heart failure, stroke, and with and without hypertension.
CVD indicates cardiovascular disease; and NHANES, National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2015 to 2018.[1]

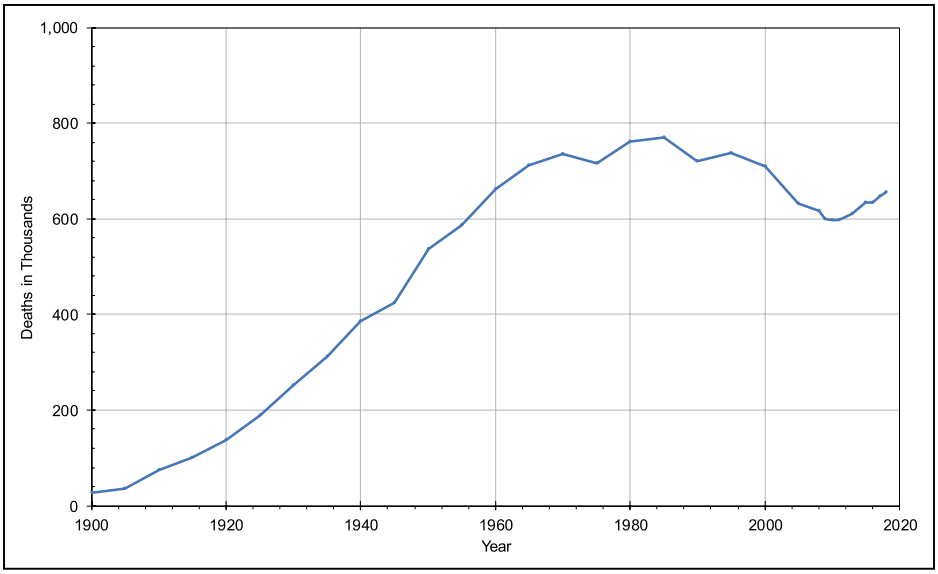

Chart 14-2. Deaths attributable to diseases of the heart, United States, 1900 to 2018.
See Glossary (Chapter 29) for an explanation of diseases of the heart. In the years 1900 to 1920, the *International Classification of Diseases* codes were 77 to 80; for 1925, 87 to 90; for 1930 to 1945, 90 to 95; 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 2018, I00 to I09, I11, I13, and I20 to I51. Before 1933, data are for a death registration area, 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: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.[36]

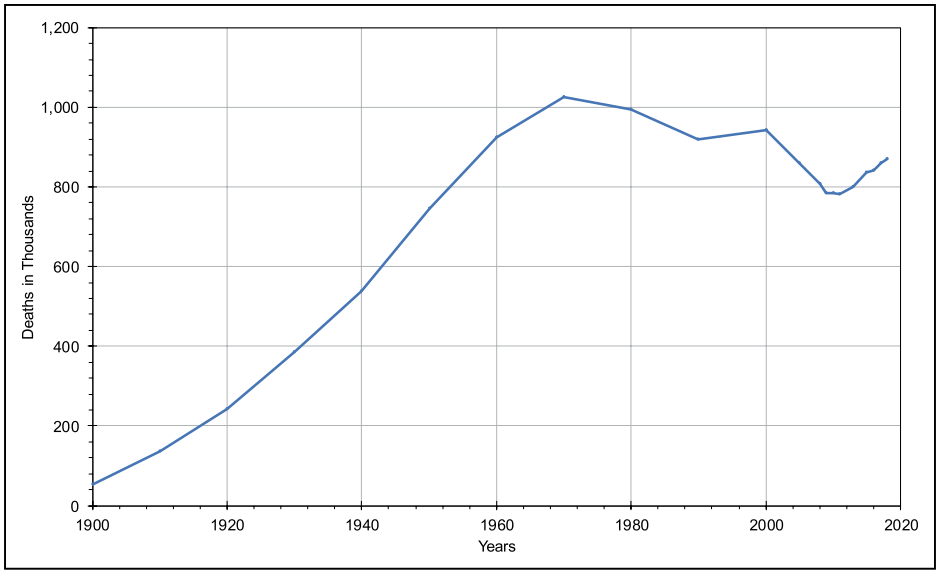

Chart 14-3. Deaths attributable to cardiovascular disease (CVD), United States, 1900 to 2018.
CVD (*International Classification of Diseases, 10th Revision* codes I00–I99) does not include congenital heart disease. Before 1933, data are for a death registration area, not the entire United States.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.[36]

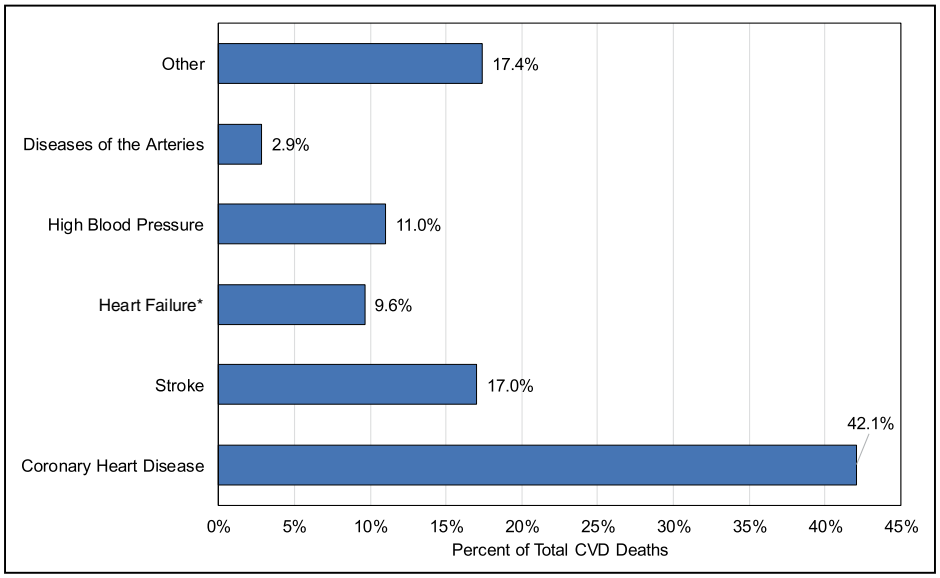

Chart 14-4. Percentage breakdown of deaths attributable to CVD, United States, 2018.
Total may not add to 100 because of rounding. Coronary heart disease includes *International Classification of Diseases, 10th Revision* (*ICD-10)* codes I20 to I25; stroke, I60 to I69; heart failure (HF), I50; high blood pressure, I10 to I13 and I15; diseases of the arteries, I70 to I78; and other, all remaining *ICD-I0* I categories. CVD indicates cardiovascular disease.
*Not a true underlying cause. HF appeared among the multiple causes of death on 42% of death certificates on which CVD is listed as the underlying cause.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System, 2018.[36]

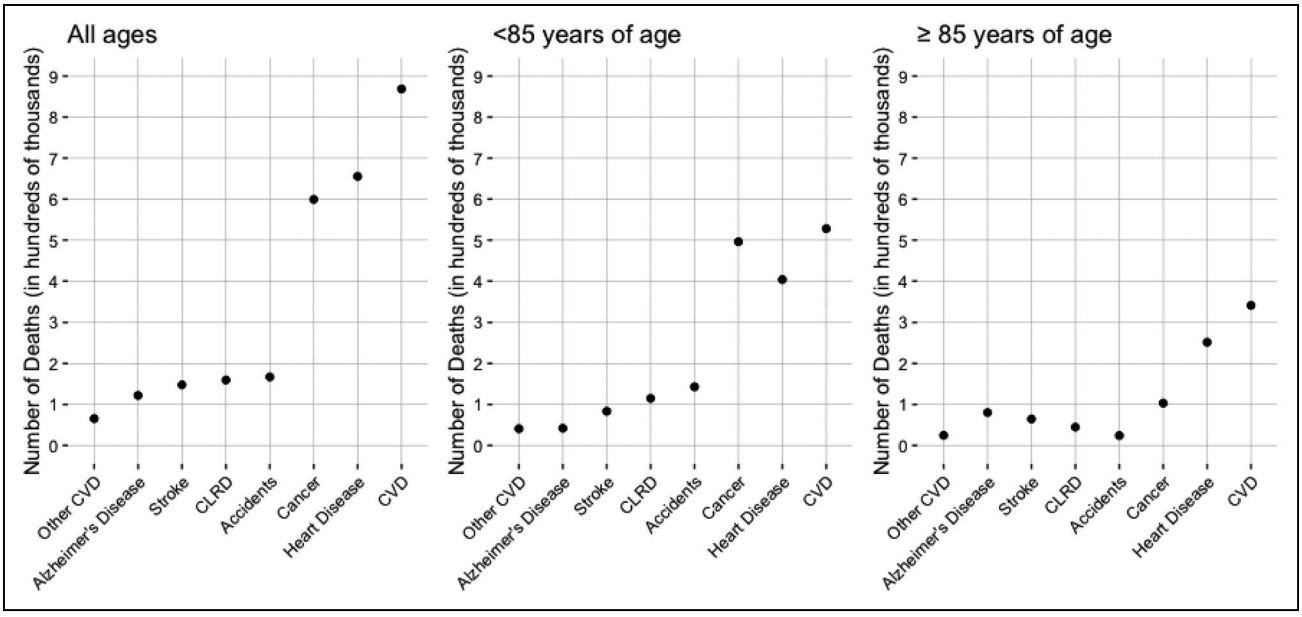

Chart 14-5. CVD and other major causes of death: all ages, <85 years of age, and ≥85 years of age, United States, 2018.
Deaths among both sexes. Deaths with age not stated are not included in the totals. Accidents includes *International Classification of Diseases, 10th Revision* codes V01 to X59, Y85, and Y86; Alzheimer disease, G30; CLRD, J40 to J47; cancer, C00 to C97; other CVD, I10, I12, I15, and I70 to I99; stroke, I60 to I69; and heart disease, I00 to I09, I11, I13, and I20 to I51.
CLRD indicates chronic lower respiratory disease; and CVD, cardiovascular disease.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System, 2018.[36]

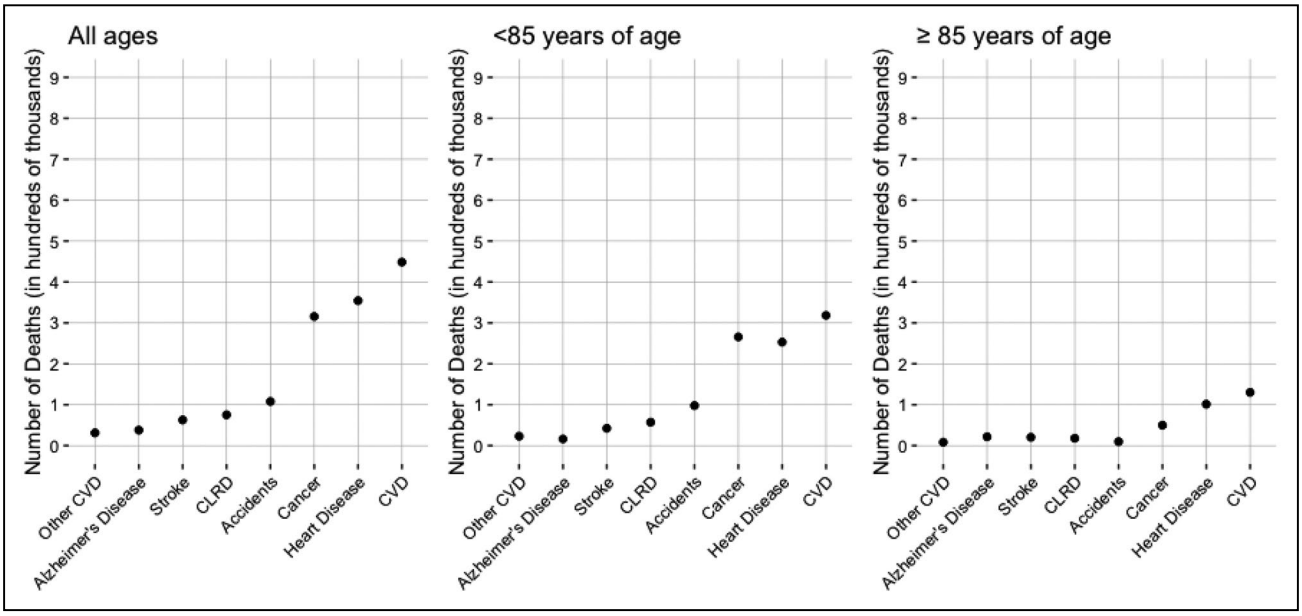

Chart 14-6. CVD and other major causes of death in US males: all ages, <85 years of age, and ≥85 years of age, 2018.
Accidents includes *International Classification of Diseases, 10th Revision* codes V01 to X59, Y85, and Y86; Alzheimer disease, G30; CLRD, J40 to J47; cancer, C00 to C97; other CVD, I10, I12, I15, and I70 to I99; stroke, I60 to I69; and heart disease, I00 to I09, I11, I13, and I20 to I51.
CLRD indicates chronic lower respiratory disease; and CVD, cardiovascular disease.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System, 2018.[36]

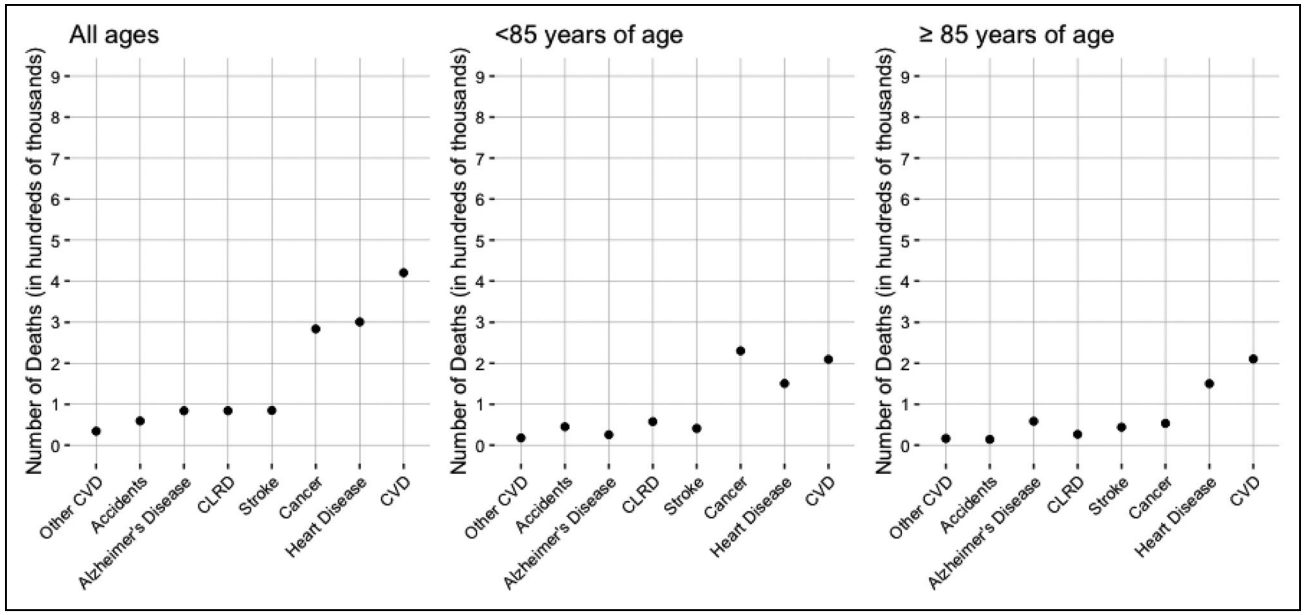

Chart 14-7. CVD and other major causes of death in US females: all ages, <85 years of age, and ≥85 years of age, 2018.
Accidents includes *International Classification of Diseases, 10th Revision* codes V01 to X59, Y85, and Y86; Alzheimer disease, G30; CLRD, J40 to J47; cancer, C00 to C97; other CVD, I10, I12, I15, and I70 to I99; stroke, I60 to I69; and heart disease, I00 to I09, I11, I13, and I20 to I51.
CLRD indicates chronic lower respiratory disease; and CVD, cardiovascular disease.
Source: Unpublished National Heart, Lung, and Blood Institute using National Vital Statistics System, 2018.[36]

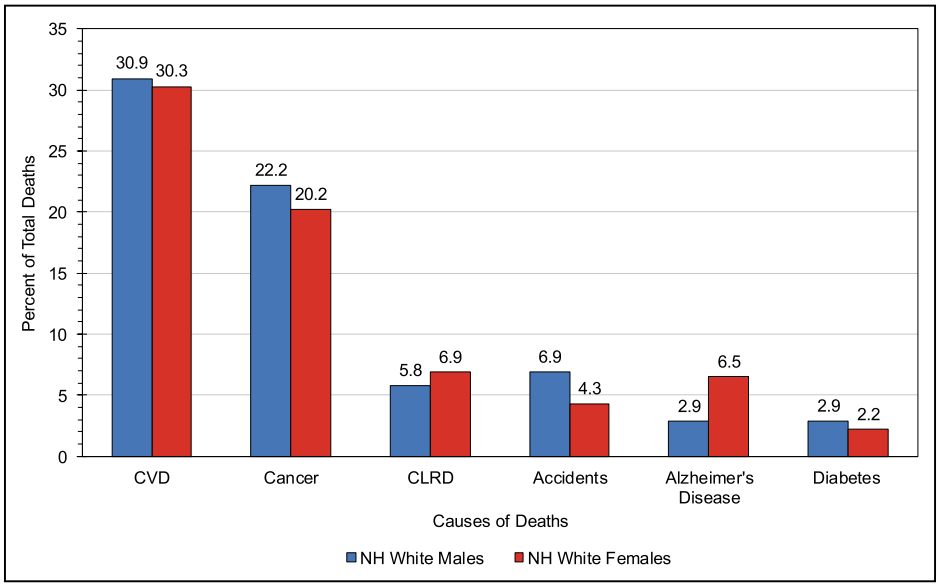

Chart 14-8. CVD and other major causes of death for NH White males and females, United States, 2018.
Diseases included CVD (*International Classification of Diseases, 10th Revision* codes I00–I99); cancer (C00–C97); CLRD (J40–J47); accidents (V01–X59 andY85–Y86); Alzheimer disease (G30); and diabetes (E10–E14).
CLRD indicates chronic lower respiratory disease; CVD, cardiovascular disease; and NH, non-Hispanic.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System, 2018.[36]

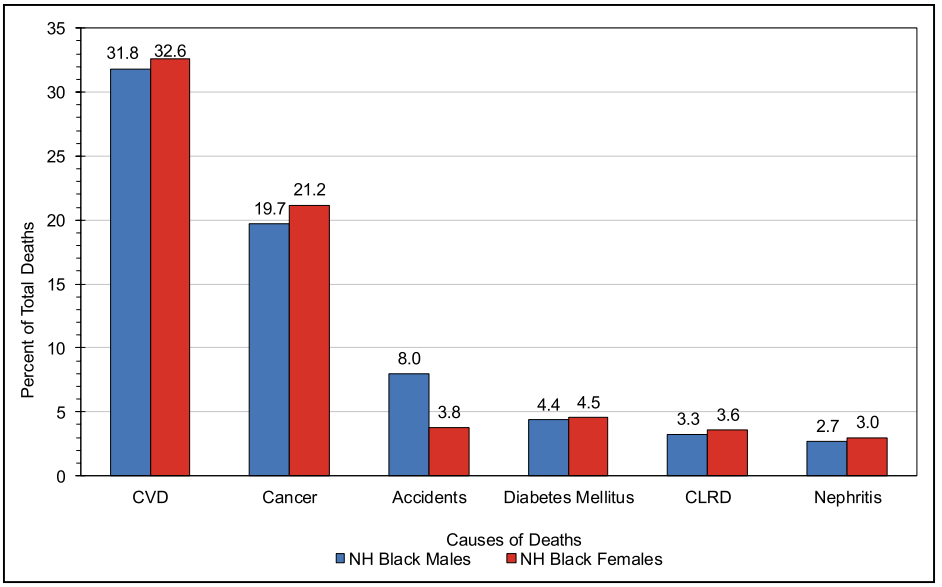

Chart 14-9. CVD and other major causes of death for NH Black males and females, United States, 2018.
Diseases included CVD (*International Classification of Diseases, 10th Revision* codes I00–I99); cancer (C00–C97); CLRD (J40–J47); accidents (V01–X59, Y85, and Y86); assault (homicide) (U01 and U02, X85–Y09, Y87.1); and diabetes (E10–E14).
CLRD indicates chronic lower respiratory disease; CVD, cardiovascular disease; and NH, non-Hispanic.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System, 2018.[36]

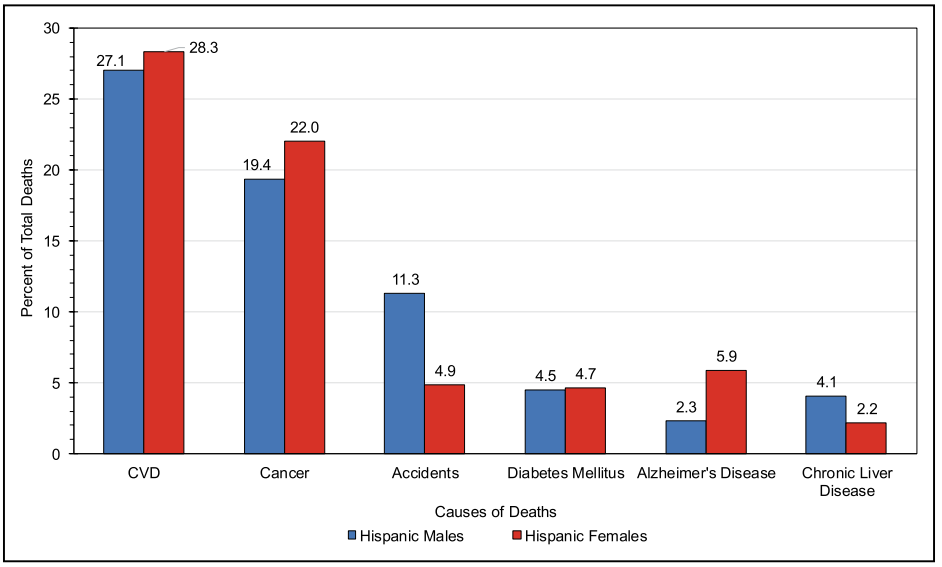

Chart 14-10. CVD and other major causes of death for Hispanic or Latino males and females, United States, 2018.
Number of deaths shown may be lower than actual because of underreporting in this population. Diseases included CVD (*International Classification of Diseases, 10th Revision* codes I00–I99); cancer (C00–C97); accidents (V01–X59 and Y85–Y86); diabetes (E10–E14); Alzheimer disease (G30); and chronic liver disease (K70, K73, and K74).
CVD indicates cardiovascular disease.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System, 2018.[36]

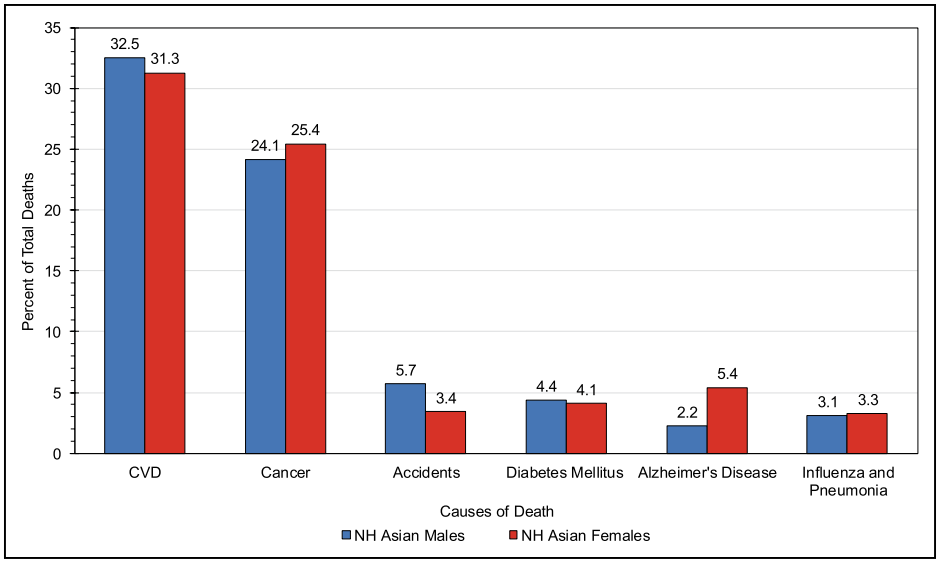

Chart 14-11. CVD and other major causes of death for NH Asian or Pacific Islander males and females, United States, 2018.
"Asian or Pacific Islander" is a heterogeneous category that includes people at high CVD risk (eg, South Asian people) and people at low CVD risk (eg, Japanese people). More specific 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, Y85, and Y86); diabetes (E10–E14); Alzheimer disease (G30); and influenza and pneumonia (J09–J18).
CVD indicates cardiovascular disease; and NH, non-Hispanic.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System, 2018.[36]

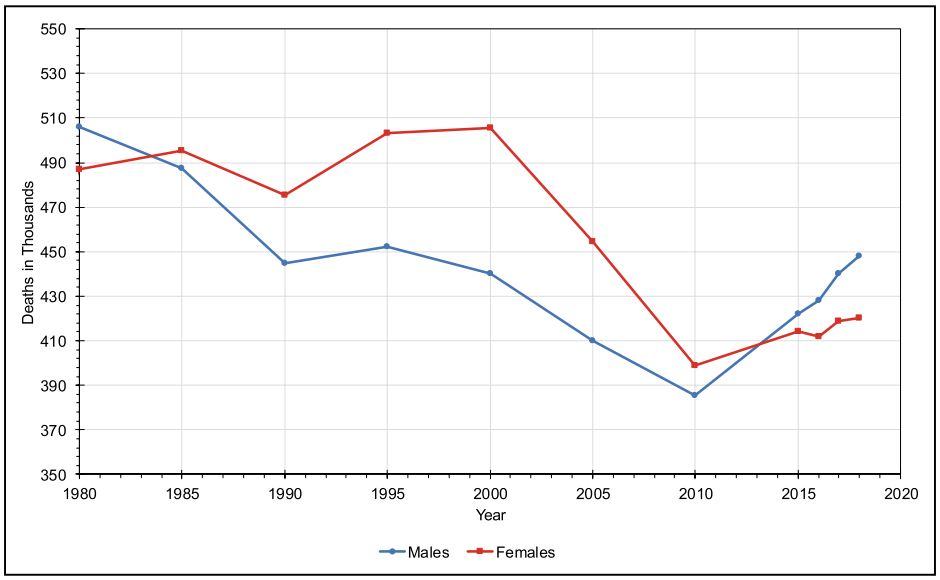

Chart 14-12. Cardiovascular disease (CVD) mortality trends for US males and females, 1980 to 2018.
CVD excludes congenital cardiovascular defects (*International Classification of Diseases, 10th Revision* [*ICD-10*] codes I00–I99). The overall comparability for CVD between the *International Classification of Diseases, 9th Revision* (1979–1998) and *ICD-10* (1999–2015) is 0.9962. No comparability ratios were applied.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.[36]

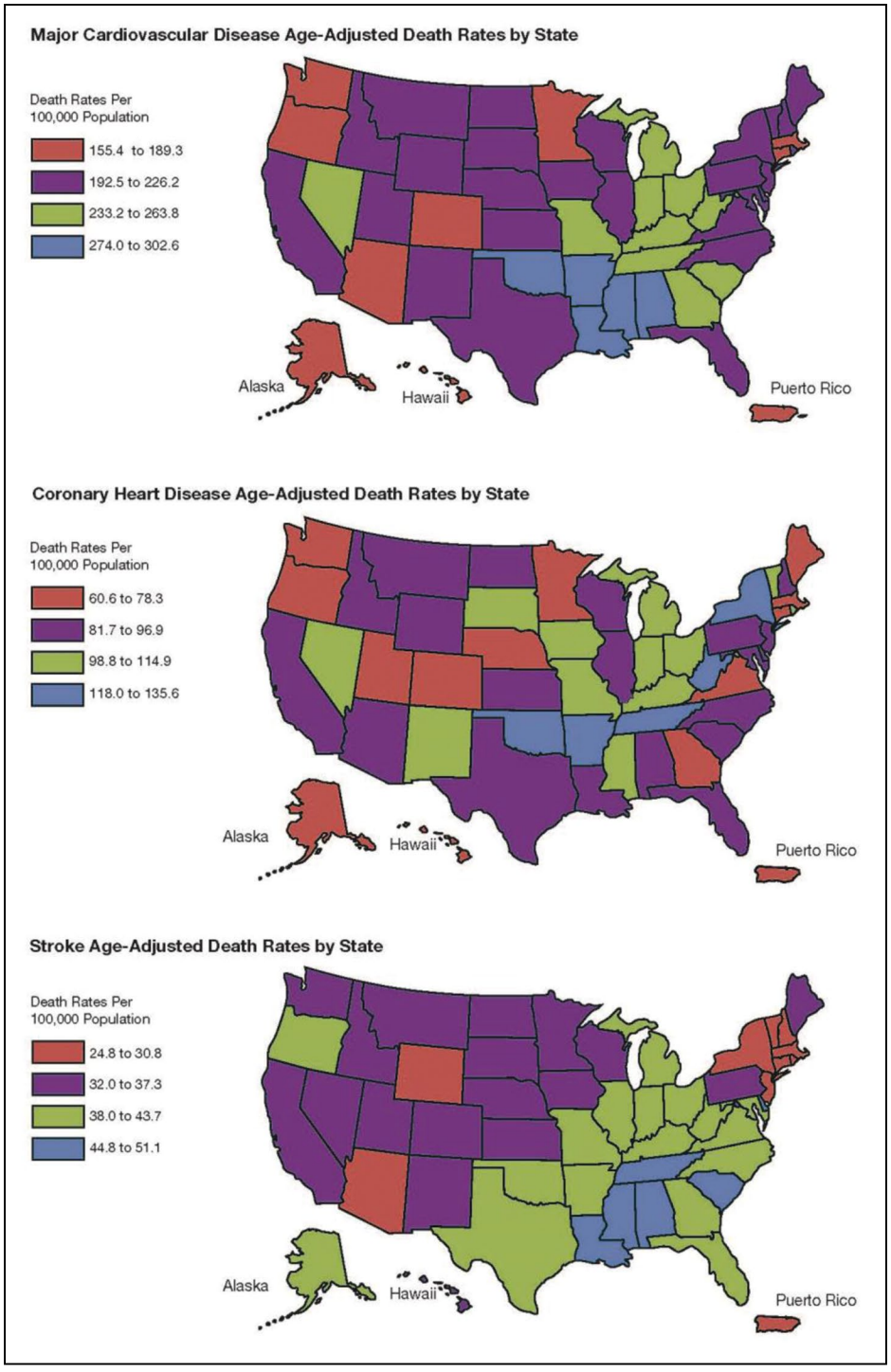

Chart 14-13. US maps corresponding to the state age-adjusted death rates per 100 000 population for cardiovascular disease, coronary heart disease, and stroke (including the District of Columbia), 2018.
Source: American Heart Association maps from unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System, 2018.[36]

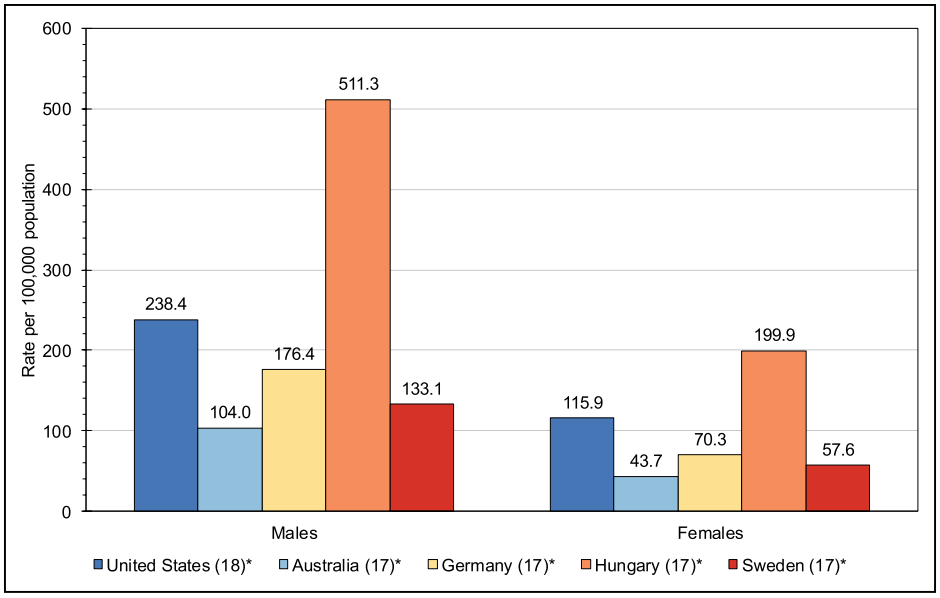

Chart 14-14. Death rates for cardiovascular disease (CVD) in selected countries for adults 35 to 74 years of age, 2017 to 2018.
Rates are adjusted to the European Standard Population. *International Classification of Diseases, 10th Revision* codes are I00 to I99 for CVD.
*Number in parentheses indicates year of most recent data available (17 is 2017 and 18 is 2018).
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.[47]

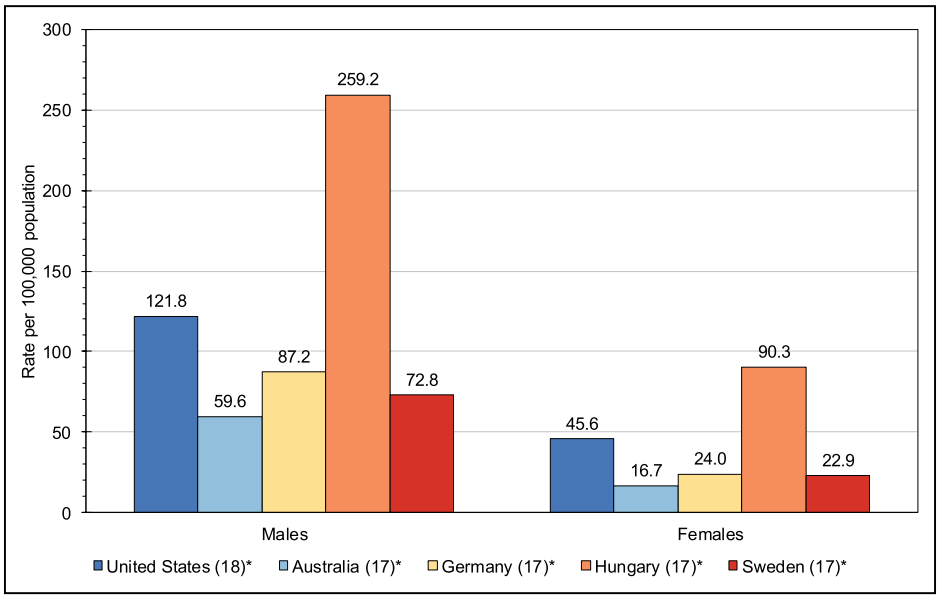

Chart 14-15. Death rates for coronary heart disease (CHD) in selected countries for adults 35 to 74 years of age, 2017 to 2018.
Rates are adjusted to the European Standard Population. *International Classification of Diseases, 10th Revision* codes are I20 to I25 for CHD.
*Number in parentheses indicates year of most recent data available (17 is 2017 and 18 is 2018).
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.[47]

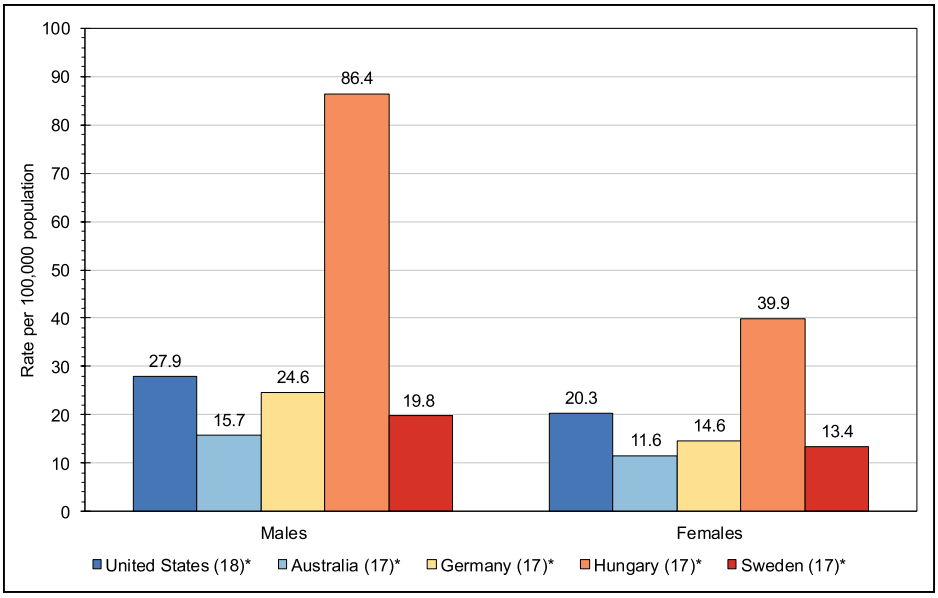

Chart 14-16. Death rates for stroke in selected countries for adults 35 to 74 years of age, 2017 to 2018.
Rates are adjusted to the European Standard Population. *International Classification of Diseases, 10th Revision* codes are I60 to I69 for stroke.
*Number in parentheses indicates year of most recent data available (17 is 2017 and 18 is 2018).
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.[47]

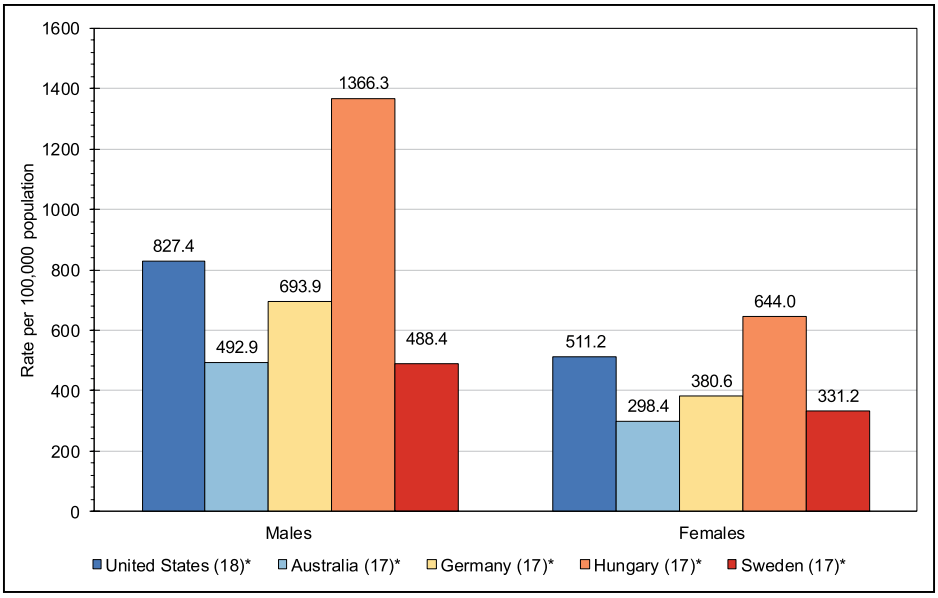

Chart 14-17. Death rates for all causes in selected countries for adults 35 to 74 years of age, 2017 to 2018.
Rates are adjusted to the European Standard Population. *International Classification of Diseases, 10th Revision* codes are A00 to Y89 for all causes.
*Number in parentheses indicates year of most recent data available (17 is 2017 and 18 is 2018).
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.[47]

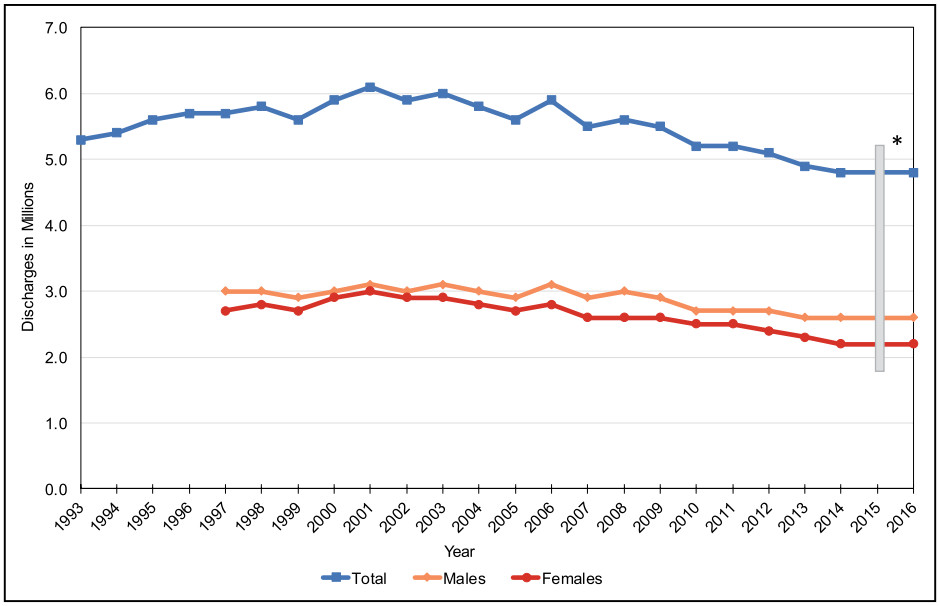

Chart 14-18. Hospital discharges for cardiovascular disease, United States, 1993 to 2016.
Hospital discharges include people discharged alive, dead, and status unknown.
*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from *International Classification of Diseases, 9th Revision* to *International Classification of Diseases, 10th Revision*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.[40]

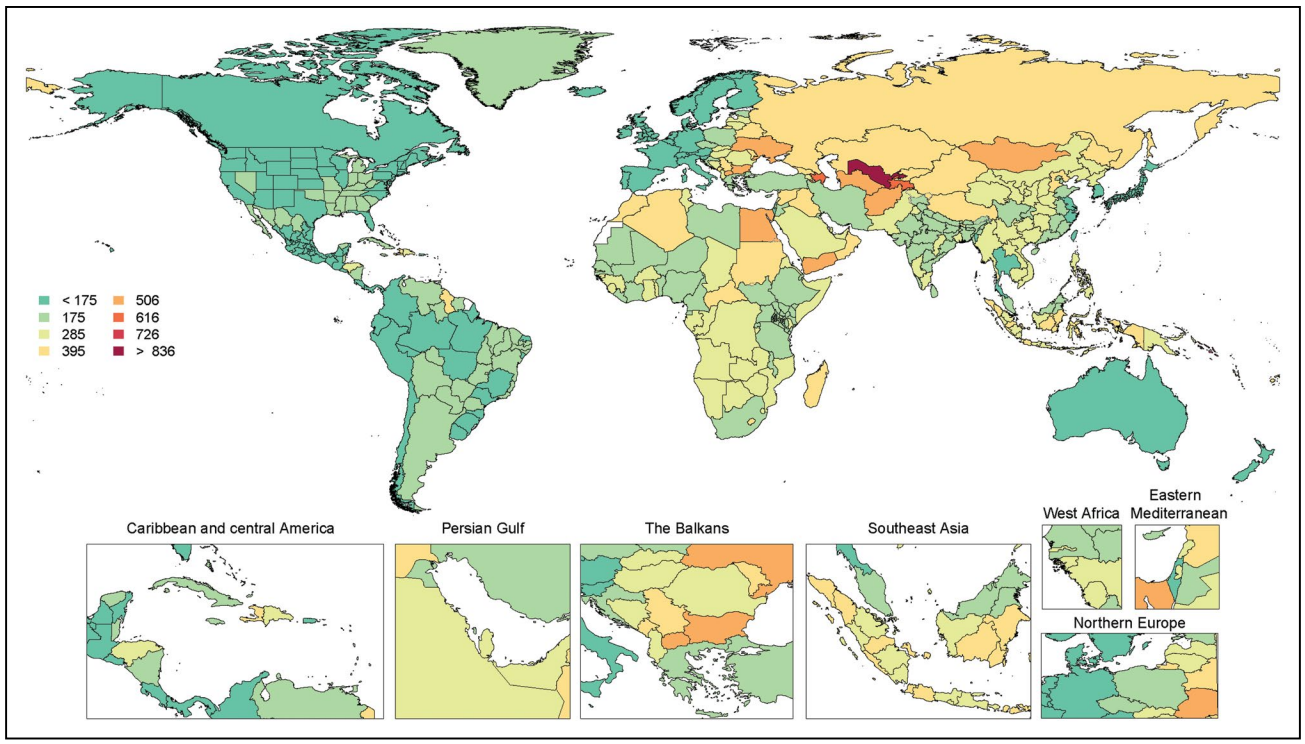

Chart 14-19. Age-standardized global mortality rates of cardiovascular disease per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[45] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[48]

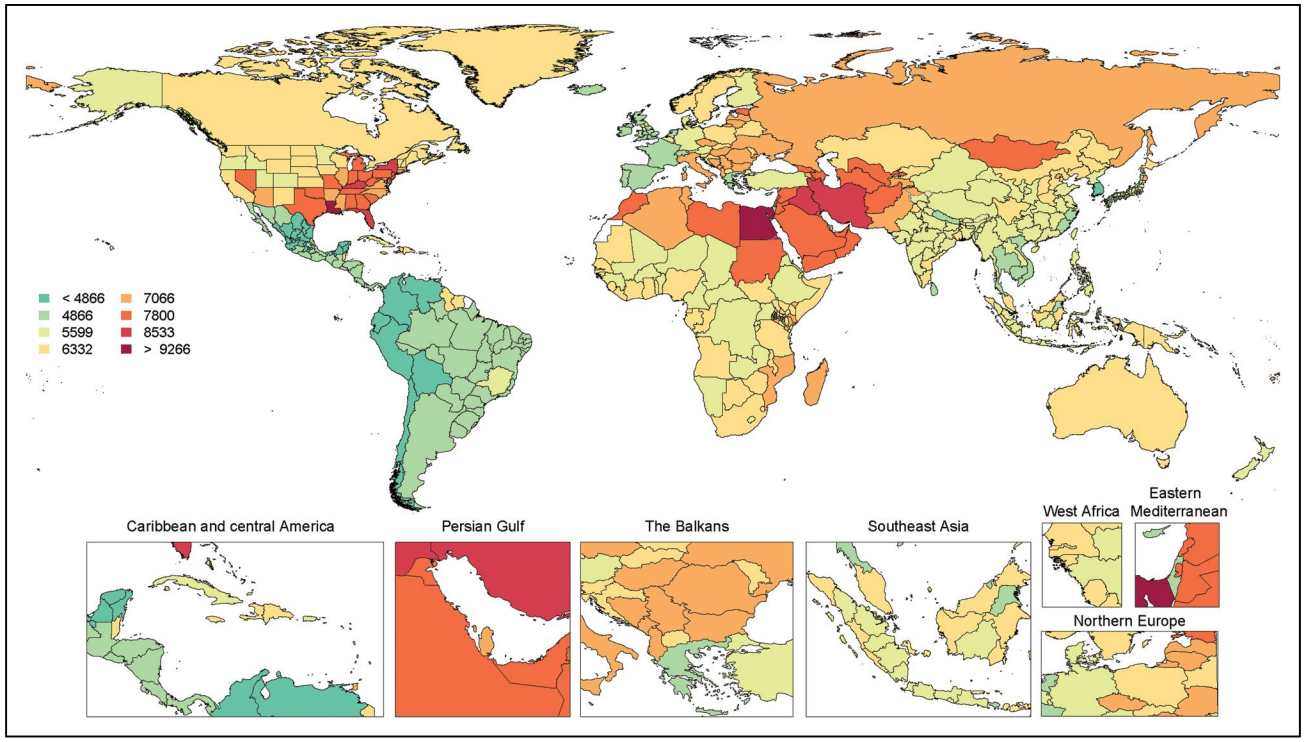

Chart 14-20. Age-standardized global prevalence rates of cardiovascular diseases per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[45] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[48]

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15. STROKE (CEREBROVASCULAR DISEASES AND VASCULAR CONTRIBUTIONS TO BRAIN HEALTH)

ICD-9 430 to 438; ICD-10 I60 to I69. See Table 15-1 and Charts 15-1 through 15-16

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Stroke Prevalence (See Table 15-1 and Chart 15-1)

- 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).

Abbreviations Used in Chapter 15

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACR	albumin-to-creatinine ratio
ACS	acute coronary syndrome
AF	atrial fibrillation
AHA	American Heart Association
AHI	apnea-hypopnea index
aHR	adjusted hazard ratio
AIS	acute ischemic stroke
aOR	adjusted odds ratio
ARIC	Atherosclerosis Risk in Communities study
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
CAS	carotid artery stenting
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research
CEA	carotid endarterectomy
CHD	coronary heart disease
CHS	Cardiovascular Health Study

(*Continued*)

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Abbreviations Used in Chapter 15 Continued

CI	confidence interval
CREST	Carotid Revascularization Endarterectomy Versus Stenting Trial
CRP	C-reactive protein
CSC	comprehensive stroke center
CVD	cardiovascular disease
CVH	cardiovascular health
DALY	disability-adjusted life-year
DBP	diastolic blood pressure
DHA	docosahexaenoic acid
DVT	deep vein thrombosis
EBP	elevated blood pressure
ED	emergency department
eGFR	estimated glomerular filtration rate
EPA	eicosapentaenoic acid
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 Study
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
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
ICH	intracerebral hemorrhage
IL	interleukin
IMT	intima-media thickness
IQR	interquartile range
IRR	incidence rate ratio
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
MCP-1/ CCL2	monocyte chemoattractant protein-1/chemokine (C-C motif) ligand 2
MEPS	Medical Expenditure Panel Survey
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction

(*Continued*)

Abbreviations Used in Chapter 15 Continued

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
NAMCS	National Ambulatory Medical Care Survey
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
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institutes of Neurological Disorders and Stroke
NIS	National (Nationwide) Inpatient Sample
NOMAS	Northern Manhattan Study
NVSS	National Vital Statistics System
OR	odds ratio
OSA	obstructive sleep apnea
PA	physical activity
PAR	population attributable risk
PE	pulmonary embolism
PHS	Physicians' Health Study
PREVEND	Prevention of Renal and Vascular End-Stage Disease
PROFESS	Prevention Regimen for Effectively Avoiding Second Stroke
PTB	preterm birth
QALY	quality-adjusted life-year
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
SBI	subclinical or silent brain infarcts
SBP	systolic blood pressure
SD	standard deviation
SDB	sleep-disordered breathing
SES	socioeconomic status
SHINE	Stroke Hyperglycemia Insulin Network Effort
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
UI	uncertainty interval
WHI	Women's Health Initiative
WHO	World Health Organization
WMH	white matter hyperintensity

- An estimated 7.6 million Americans ≥20 years of age self-report having had a stroke (extrapolated to 2018 [NHANES 2015–2018 data]). Overall stroke prevalence during this period was an estimated 2.7% (Table 15-1).
- Prevalence of stroke in the United States increases with advancing age in both males and females (Chart 15-1).
- According to data from the 2018 BRFSS[1] (unpublished NHLBI tabulation), stroke prevalence in adults is 3.4% (median) in the United States, with the lowest prevalence in Puerto Rico (1.3%) and Colorado (1.8%) and the highest prevalence in Louisiana and Tennessee (4.7%).
- 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, that other conditions mimic stroke, or both. On the basis of data from 18462 participants enrolled in a national cohort study, 17.8% of the population >45 years of age reported at least 1 symptom.[2] Stroke symptoms were more likely among Black than White individuals, 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).
- Projections show that by 2030 an additional 3.4 million US adults ≥18 years of age, representing 3.9% of the adult population, will have had a stroke, a 20.5% increase in prevalence from 2012.[3] The highest increase (29%) is projected to be in White Hispanic males.

Stroke Incidence (See Table 15-1)

- Each year, ≈795000 people experience a new or recurrent stroke (Table 15-1). Approximately 610000 of these are first attacks, and 185000 are recurrent attacks (GCNKSS, NINDS, and NHLBI; GCNKSS and NINDS data for 1999 provided July 9, 2008; unpublished estimates compiled by NHLBI).
- Of all strokes, 87% are ischemic, 10% are ICHs, and 3% are SAHs (GCNKSS, NINDS, 1999; unpublished NHLBI tabulation).

Temporal Trends

- In the multicenter ARIC study of Black and White adults, stroke incidence rates decreased by 32% (95% CI, 23%–40%) per 10 years during the 30-year period from 1987 to 2017 in adults ≥65 years of age. The decreases varied across age groups but were similar across sex and race.[4]

- In the FHS, a cohort with a large number of White individuals in the northeastern United States, age-adjusted incidence of first stroke per 1000 person-years in people ≥55 years of age declined from 7.6 in 1950 to 1977 to 6.2 in 1978 to 1989 to 5.3 in 1990 to 2004 in males and from 6.2 to 5.8 to 5.1 in females over the same periods. Lifetime risk for incident stroke for a person 65 years of age decreased significantly from 19.5% in 1950 to 1977 to 14.5% in 1990 to 2004 in males and from 18.0% to 16.1% in females.[5] Comparing data from 1962 to 1967 and 1998 to 2005 shows that the relative incidence in older adults ≥55 years of age declined by more than half (HR, 0.47 [95% CI, 0.36–0.60]).[6]
- Data from the Tromsø Study showed that changes in cardiovascular risk factors accounted for 57% (95% CI, 28%–100%) of the decrease in ischemic stroke incidence in people ≥30 years of age for the time period 1995 to 2012.[7]
- Per the GBD 2016 Lifetime Risk of Stroke Collaborators, the mean global lifetime risk of stroke increased from 22.8% in 1990 to 24.9% in 2016, a relative increase of 8.9% (95% UI, 6.2%–11.5%) after accounting for the competing risk of death attributable to any cause other than stroke.[8]
- In a systematic review/meta-analysis of trends in ischemic stroke subtypes between 1993 and 2015, an increasing temporal trend was noted for cardioembolism in White people (2.4% annually [95% CI, 0.6%–4.3%]) and for large-artery atherosclerosis in Asian people (5.7% annually [95% CI, 3.4%–8.2%]), with a corresponding decrease in small-artery occlusion in White people (–4.7% annually [95% CI, 1.9%–7.4%]).[9]

Race/Ethnicity

- In the national REGARDS cohort, in 27 744 participants followed up for 4.4 years (2003–2007), the overall age- and sex-adjusted Black participants/White participants IRR was 1.51 (95% CI, 1.26–1.81), but for those 45 to 54 years of age, it was 4.02 (95% CI, 1.23–13.11), whereas for those ≥85 years of age, it was 0.86 (95% CI, 0.33–2.20).[10]
- The BASIC Project demonstrated an increased incidence of ischemic stroke among Mexican American people compared with NH White people. According to population-based surveillance data from 2000 to 2010, the overall age- and sex-adjusted Mexican American individuals/White individuals IRR was 1.34 (95% CI, 1.23–1.46). For individuals 45 to 59 years of age, it was 1.94 (95% CI, 1.67–2.25); for those 60 to 74 years of age, it was 1.50 (95% CI, 1.35–1.67); and for those ≥75 years of age, it was 1.00 (95% CI, 0.90–1.11).[11] Mexican American people also had a higher incidence of ICH and SAH than NH White people.[12,13] The difference in risk for ICH decreased with older age (overall: RR, 1.75 [95% CI, 1.48–2.07]; 45–59 years of age: RR, 2.50 [95% CI, 1.82–3.42]; 60–74 years of age: RR, 1.88 [95% CI, 1.49–2.37]; and ≥75 years of age: RR, 1.37 [95% CI, 1.09–1.74]).
- In the ARIC study, stroke incidence rates per decade (from 1987–2017) showed similar declines over time in White and Black individuals (see the Temporal Trends section).[4]
- In NOMAS (NINDS) from 1993 to 1997, the age-adjusted incidence of first ischemic stroke per 1000 was 0.88 in White individuals, 1.91 in Black individuals, and 1.49 in Hispanic individuals. Among Black individuals, compared with White individuals, 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 Hispanic individuals, compared with White individuals, 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).[14]
- In an analysis of pooled SHS and ARIC data, there were 242 (7.6%) stroke events among 3182 American Indian participants without prior stroke followed up from 1988 to 2008; there were 613 (5.9%) stroke events among 10 413 White participants from 1987 to 2011. American Indian participants had higher stroke rates in unadjusted analyses. Results were attenuated after adjustment for vascular risk factors, which may be on the causal pathway for this association.[15]
- In REGARDS, the increased risk of ICH with age differed between Black and White individuals: There was a 2.25-fold (95% CI, 1.63–3.12) increase per decade older age in White individuals but no age association of ICH risk in Black individuals (HR, 1.09 [95% CI, 0.70–1.68] per decade older age).[16]

Sex

- Each year, ≈55 000 more females than males have a stroke (GCNKSS, NINDS).[17]
- 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%).[18]
- In the GCNKSS, sex-specific ischemic stroke incidence rates between 1993 to 1994 and 2015

declined significantly for both males and females. In males, there was a decline from 282 (95% CI, 263–301) to 211 (95% CI, 198–225) per 100 000. In females, the decline was from 229 (95% CI, 215–242) to 174 (95% CI, 163–185) per 100 000. This trend was not observed for ICH or SAH.[19]

- Age-specific incidence rates are substantially lower in females than males in younger and middle-aged groups, but these differences narrow so that in the oldest age groups, incidence rates in females are approximately equal to or even higher than those in males.[19,20]
- Racial and ethnic disparities in stroke risk may persist or even increase in elderly minority females.[20] In NOMAS, among 3298 stroke-free participants followed up through 2019, Black and Hispanic females ≥70 years of age had higher risk of stroke compared with White females after controlling for age, sex, education, and insurance status (Black females/White females: HR, 1.76 [95% CI, 1.10–2.80]; Hispanic females/White females: HR, 1.77 [95% CI, 1.04–3.00]).[21] This increased risk was not present among elderly Black or Hispanic males compared with White males.
- In a study of NH White and Black females from the WHI (N=126 018, 9% Black females) followed up through 2010, Black females had greater risk of total stroke than White females after adjustment for age (HR, 1.47 [95% CI, 1.33–1.63]).[22] Adjustment for socioeconomic factors and stroke risk factors attenuated this association, although the higher risk remained statistically significant in younger females <60 years of age (HR, 1.76 [95% CI, 1.09–2.83]).

TIA: Prevalence, Incidence, and Prognosis

- In a nationwide survey of US adults, the estimated prevalence of self-reported physician-diagnosed TIA increased with age and was 2.3% overall, which translates to 7.6 million individuals in the United States.[23] 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 health care provider.
- Incidence of TIA increases with age and varies by sex and race/ethnicity. Males, Black people, and Mexican American people have higher rates of TIA than their female and NH White counterparts.[12,24] Incidence was higher in males (1.17 per 1000 people) compared with females (1.02 per 1000) in the GCNKSS in 2010.[25]
- TIAs confer a substantial short-term risk of stroke, hospitalization for CVD events, and death. Of 1707 patients with TIA evaluated in the EDs of Kaiser Permanente Northern California from 1997 to 1998, 91 (5%) had a stroke within 2 days, and 180 (11%) experienced a stroke within 90 days. Predictors of stroke included age >60 years, diabetes, focal symptoms of weakness or speech impairment, and symptoms that lasted >10 minutes.[26,27]
- Prognosis after TIA may have improved over time. Contemporary studies report a 1.2% risk of stroke at 2 days and 7.4% risk of stroke at 90 days after TIA.[28]
- In a large multicenter TIA registry study, the 1-year stroke risk was 5.1% and 5-year stroke risk was 9.5%.[29] The combined risk of stroke, ACS, or death attributable to cardiovascular causes was 6.2% at 1 year and 12.9% at 5 years.[30]
- In the community-based Oxford Vascular Study, among patients with TIA, disability levels increased from 14% (modified Rankin Scale score >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%.[31]
- In a meta-analysis of 47 studies,[32] it was estimated that approximately one-third of patients with TIA 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.[33] In the Oxford Vascular Study, acute lesions on MRI were identified in 13% of participants with TIA.[34] In age- and sex-adjusted analyses, these participants had higher risk of recurrent ischemic stroke compared with individuals with TIA and negative MRI (HR, 2.54 [95% CI, 1.21–5.34]; *P=0*.014).

Recurrent Stroke: Incidence and Risk

- Among 128 789 Medicare beneficiaries from 1999 to 2013, the incidence of recurrent stroke per 1000 person-years was 108 (95% CI, 106–111) for White people and 154 (95% CI, 147–162) for Black people. Mortality after recurrence was 16% (95% CI, 15%–18%) for White people and 21% (95% CI, 21%–22%) for Black people. Compared with White people, Black people had higher risk of 1-year recurrent stroke (aHR, 1.36 [95% CI, 1.29–1.44]).[35]
- 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.[36] 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.

- From data for 12 392 patients 18 to 45 years of age who were hospitalized with ischemic or hemorrhagic stroke in the 2013 Nationwide Readmissions Database, the rate of recurrent stroke of either type per 100 000 index hospitalizations was 1814.0 at 30 days, 2611.1 at 60 days, and 2913.3 at 90 days.[37] Among patients without vascular risk factors at the index stroke (ie, hypertension, hypercholesterolemia, diabetes, 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. Diabetes 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 publications through September 2017, MRI findings of multiple lesions (pooled RR, 1.7 [95% CI, 1.5–2.0]), multiple-stage lesions (pooled RR, 4.1 [95% CI, 3.1–5.5]), multiple-territory lesions (pooled RR, 2.9 [95% CI, 2.0–4.2]), prior infarcts (pooled RR, 1.5 [95% CI, 1.2–1.9]), and isolated cortical lesions (pooled RR, 2.2 [95% CI, 1.5–3.2]) were associated with increased risk of ischemic stroke recurrence. A history of stroke or TIA was also associated with higher risk (pooled RR, 2.5 [95% CI, 2.1–3.1]). Risk of recurrence was lower for small- versus large-vessel stroke (pooled RR, 0.3 [95% CI, 0.1–0.7]) and for stroke resulting from an undetermined cause versus large-artery atherosclerosis (pooled RR, 0.5 [95% CI, 0.2–1.1]).[38]
- A meta-analysis of 104 studies with 71 298 patients with ischemic stroke found that moderate to severe WMH burden was associated with increased risk of any recurrent stroke (RR, 1.65 [95% CI, 1.36–2.01]) and recurrent ischemic stroke (RR, 1.90 [95% CI, 1.26–2.88]).[39]
- A study among 7101 patients with ischemic strokes followed up for 1 year found a significant association between WMH volume and recurrent strokes. This association by WMH quartile was stronger for recurrent hemorrhagic stroke (HR, 1, 7.32, 14.12, and 33.52, respectively) than for ischemic recurrence (HR, 1, 1.03, 1.37, and 1.61, respectively). However, the absolute incidence of ischemic stroke recurrence remained higher by WMH quartile (3.8%/y, 4.5%/y, 6.3%/y, and 8.2%/y) compared with hemorrhagic recurrence (0.1%/y, 0.4%/y, 0.6%/y, and 1.3%/y).[40]

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, 87% of the stroke risk could be attributed to modifiable risk factors such as HBP, obesity, hyperglycemia, hyperlipidemia, and renal dysfunction, and 47% could be attributed to behavioral risk factors such as smoking, sedentary lifestyle, and an unhealthy diet. Globally, 30% of the risk of stroke was attributable to air pollution.[41,42]

High BP
(See Chapter 8 for more information.)

- The evidence-based 2017 Hypertension Clinical Practice Guidelines recommend intensive BP control for primary and secondary stroke prevention. The guideline proposes a target BP of <130/80 mm Hg.[43] The recommendations are supported by an extensive evidence document accompanying the guidelines that shows consistent results from trials and meta-analyses for the lower BP target for lower stroke risks and prevention.[44]
- In a 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]).[45]
- A special report identified the highly significant global implications of the hypertension treatment and control strategies implementation on stroke risk reduction around the world.[46]
  - There was agreement across meta-analyses that intensive BP lowering appears to be most beneficial for reduction in risk of stroke.[47–49]
  - In a meta-analysis, there was 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.[50]
- Analyses determined that in both SPRINT and ACCORD participants, there was no increase in stroke risk with intensive lowering of SBP to achieve mean arterial pressure values <60 mm Hg, which suggests that stroke risks in hypertensive patients do not increase with extremely low mean arterial pressure or pulse pressure values.[51]
- The consistent results from 3 additional meta-analyses[52–54] indicated that SBP <130 mm Hg may be the most clinically advantageous BP target in the prevention of stroke.
- A scientific statement from the AHA identified resistant hypertension, defined as above-goal EBP of 130/80 mm Hg in a patient despite the concurrent use of 3 antihypertensive drug classes, as being significantly associated with greater risks of adverse cardiovascular events, including stroke.[55]
- In a meta-analysis (11 studies), hypertension was associated with risk of recurrent stroke (OR, 1.67 [95% CI, 1.45–1.92]).[56]

- In a secondary analysis of 17 916 patients in the PROFESS trial, BP variability, defined as the SD over repeated measurements, was associated with an increased risk of recurrent stroke.[57] For every 10-point increase in systolic variability, the HR for recurrent ischemic stroke was 1.15 (95% CI, 1.02–1.32).
- In analyses of the SPS3 trial participants, survivors of lacunar stroke with high (top tertile) WMH burden were most likely to benefit from intensive BP control in preventing recurrent stroke.[58]
- In a meta-analysis of 56 513 patients undergoing intravenous thrombolysis for AIS (26 studies), elevated pretreatment (aOR, 1.08 [95% CI, 1.01–1.16]) and posttreatment (aOR, 1.13[95% CI, 1.01–1.25]) SBP levels were associated with increased risk of symptomatic ICH.[59] Pretreatment (aOR, 0.91 [95% CI, 0.84–0.98]) and posttreatment (aOR, 0.70[95% CI, 0.57–0.87]) SBP values also were inversely related to lower likelihood of 3-month functional independence.

Diabetes
(See Chapter 9 for more information.)

- Diabetes increases ischemic stroke incidence at all ages, but this risk is most prominent (RR >5) before 65 years of age in both Black and White individuals. Overall, patients with ischemic stroke and diabetes are younger and more likely to have HBP, MI, and high cholesterol than nondiabetic patients.[60]
- The association between diabetes 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 diabetes was 2.28 (95% CI, 1.93–2.69) in females and 1.83 (95% CI, 1.60–2.08) in males.[61] Compared with males with diabetes, females with diabetes 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]).
- 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).[62]
- Diabetes 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 diabetes than in those without (HR, 1.45 [95% CI, 1.32–1.59]).[63]
- In the GWTG-Stroke registry, diabetes was associated with a higher risk of adverse outcomes over 3 years after stroke, including all-cause mortality (aHR, 1.24 [95% CI, 1.23–1.25]), all-cause hospital readmission (aHR, 1.22 [95% CI, 1.21–1.23]), a composite of mortality and cardiovascular readmission (aHR, 1.19 [95% CI, 1.18–1.20]), and ischemic stroke/TIA readmission (aHR, 1.18 [95% CI, 1.16–1.20]).[64]
- In a meta-analysis of 11 RCTs that included 56 161 patients with type 2 diabetes 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).[65]
- A meta-analysis of 28 RCTs involving 96 765 participants with diabetes 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 groups.[66]
- In NOMAS, duration of diabetes was associated with ischemic stroke risk (aHR per year with diabetes, 1.03 [95% CI, 1.02–1.04]).[67]
- In the SHINE trial, intensive treatment of hyperglycemia in patients with AIS was not associated with improved functional outcomes at 90 days (adjusted RR, 0.97 [95% CI, 0.87–1.08]; *P*=0.55).[68]

Disorders of Heart Rhythm
(See Chapter 17 for more information.)

- Because AF is often asymptomatic[69] and frequently undetected clinically,[70] the stroke risk attributed to AF could be substantially underestimated. In a meta-analysis of 50 studies, AF was detected in ≈24% (95% CI, 17%–31%) of patients with embolic stroke of undetermined source, depending on duration and type of monitoring used.[71]
- 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.[72]
- 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.[73]

- Important risk factors for stroke in the setting of AF include older age, hypertension, HF, diabetes, previous stroke or TIA, vascular disease, renal dysfunction, and female sex.[74–78] Biomarkers including high levels of troponin and BNP are associated with an increased risk of stroke in AF after adjustment for traditional vascular risk factors.[79]
- In patients with AF who are being treated with anticoagulation, presence of persistent AF versus paroxysmal AF is associated with higher risk of stroke.[80,81]
- Atrial flutter was associated with a lower risk of stroke than AF.[82]
- In a meta-analysis of 35 studies (N=2 458 010 patients), perioperative or postoperative AF was associated with an increased risk of early stroke (OR, 1.62 [95% CI, 1.47–1.80]) and later stroke (HR, 1.37 [95% CI, 1.07–1.77]). This risk was found in patients undergoing both noncardiac surgery (HR, 2.00 [95% CI, 1.70–2.35]) and cardiac surgery (HR, 1.20 [95% CI, 1.07–1.34]).[83]
- Other cardiac arrhythmias such as paroxysmal SVT[84] and excessive supraventricular ectopic activity[85] have been associated with a doubling of stroke risk in the absence of known AF. In the Copenhagen Holter Study (n=678 men and women 55–75 years of age with no history of AF, stroke, or CVD), excessive supraventricular ectopic activity was defined as the presence of either ≥30 premature atrial contractions per hour or any runs of ≥20 premature atrial contractions. Excessive supraventricular ectopic activity was associated with a doubling of the risk of stroke (HR, 1.96 [95% CI, 1.10–3.49]).

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.[86–89] For clarity, results for different types of cholesterol (TC, subfractions) are described in this section.
- In a nested case-control analysis using data from the Chinese Kadoorie Biobank prospective study of 489 762 Chinese individuals without prior stroke or HD who were not taking antithrombotic or lipid-modifying drugs (n=5475 with ischemic stroke, n=4776 with ICH, and n=6290 healthy controls), genetic markers predictive of LDL levels ("genetic instruments") were associated with ischemic stroke, and HDL level was inversely associated with ischemic stroke.[90] Each 1.0-mmol/L increase in LDL was associated with a 14% lower risk of ICH; this relationship held for the genetic instruments of LDL and was similar in those with and without hypertension at baseline. This analysis provides causal evidence that LDL levels are associated directly with ischemic stroke risk and inversely with hemorrhagic stroke risk.
- Another mendelian randomization study of lipid genetics also suggested an increased risk of large-artery ischemic stroke with increased LDL and a lower risk of small-vessel ischemic stroke with increased HDL.[91]
- An association between TC and ischemic stroke has otherwise been found in some prospective studies[92–94] but not others.[86,89,95] In the Women's Pooling Project, which included 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.[87] An association of elevated TC with risk of stroke was noted to be present in those 40 to 49 and 50 to 59 years of age but not in other age groups in the Prospective Studies Collaboration.[88] In a meta-analysis of data from 61 cohorts, TC was only weakly associated with risk of stroke, with no significant difference between males and females.[96]
- 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]).[97]
- A meta-analysis of 23 studies performed in the Asia-Pacific region showed no significant association between low HDL-C and stroke risk,[98] although another meta-analysis without geographic restriction demonstrated a protective association of HDL-C with stroke.[89]
- A Finnish study of >58 000 individuals followed up for >20 years found an inverse association of HDL-C with the risks of total and ischemic stroke in females.[86]
- In the SHS, a possible interaction was noted between diabetes status and HDL-C for risk of stroke such that higher HDL-C was protective against stroke risk in patients with diabetes but not in those without diabetes.[99] In a meta-analysis, no significant association was observed between HDL-C levels and risk of hemorrhagic stroke.[97]
- 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, the HR for ischemic stroke was 1.12 (95% CI, 1.04–1.20) for non–HDL-C[100] 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,[92] and LDL-C may have a stronger association for large-artery atherosclerotic subtype.[101]

- Among 13 951 patients in the Copenhagen Heart Study followed up for 33 years, increasing levels of nonfasting triglycerides were associated with increased risk of ischemic stroke in both males and females,[102] although in ARIC, PHS, and SHS, there was no association.[99,103,104]
- In a prospective cohort study of 27 397 women enrolled in the Women's Health Study, LDL-C levels <70 mg/dL and low triglyceride levels were associated with increased risk of hemorrhagic stroke. Compared with those with LDL-C levels of 100 to 129.9 mg/dL, women with LDL-C levels <70 mg/dL had a greater risk of hemorrhagic stroke (RR, 2.17 [95% CI, 1.05–4.48]); compared with women in the highest quartile of triglyceride levels, those in the lowest quartile had increased risk of hemorrhagic stroke (RR, 2.00 [95% CI, 1.18–3.39].[105]

Smoking/Tobacco Use (See Chapter 3 for more information.)

- Current smoking is associated with an increased prevalence of MRI-defined SBI.[106]
- A 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 cigarettes per day).[107] This is much higher than what would be predicted from a linear or log-linear dose-response relationship between smoking and risk of stroke.[107]
- 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.[108]
- Discontinuation of smoking reduces stroke risk similarly for males and females.[108]
- Exposure to secondhand smoke, also called 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.[109,110]
  - 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%).[111]
  - 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 ≥80 years of age (HR, 1.24 [95% CI, 1.05–1.46]).[112] Overall, the increased risk was most evident for SAH (HR, 1.66 [95% CI, 1.02–2.70]) in all age groups.
  - A study using NHANES data found that individuals with a prior stroke have 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).[113]
- Use of smokeless tobacco is associated with an increased risk of fatal stroke.
  - In 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]).[114]
  - US smokeless tobacco users had a higher risk of stroke than nonusers, but this association was not observed in Swedish smokeless tobacco users. This difference may be attributable to differences in product type and use patterns between the 2 countries.[115]
- Microvascular damage, more specifically, widening of the venules as a result of smoking, may mediate the effect of smoking on the risk of ischemic stroke.[116]
- Smoking is perhaps the most important modifiable risk factor in preventing SAH, with the highest PAR (38%–43%) of any SAH risk factor.[117]
- The FINRISK study found a strong association between current smoking and SAH compared with nonsmoking (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.[118]

Physical Inactivity (See Chapter 4 for more information.)

- A systematic review in the GBD 2019 study demonstrated that the burden of stroke attributable to physical inactivity was ≈1.68% globally and 2.75% in high-income countries.[41,42]
- Physical inactivity is a significant risk factor for stroke in middle-aged and elderly populations.[119,120]
- The NOMAS cohort study (3298 males and females with an average of 14 years of follow-up) showed that inactive elderly participants (≥80 years of age) had 1.6 times greater risk of incident stroke (95% CI, 1.05–2.42) compared with active elderly participants. This association was nonsignificant in participants with <80 years of age.[121]

- In the UK Biobank cohort study (N=66 438, 40–69 years of age), cardiorespiratory fitness was inversely associated with ischemic stroke (HR,0.71 [95% CI, 0.57–0.89]) but not with hemorrhagic stroke (HR,0.96 [95% CI, 0.68-0.1.53]).[122]
- The REGARDS study (≥45 years of age) reported a race-specific association between cardiorespiratory fitness and incident stroke. The White participants in the highest tertile of cardiorespiratory fitness had a 46% lower risk of ischemic stroke (95% CI, 31%–57%) compared with their counterparts in the lowest tertile of cardiorespiratory fitness but not hemorrhagic stroke (HR, 0.67 [95% CI, 0.33–1.36]). These associations were not present in Black participants (ischemic stroke: HR, 1.00 [95% CI, 0.74–1.37]; hemorrhagic strokes: HR, 1.98 [95% CI, 0.87–4.52]).[123]
- The Oslo Ischemia Cohort Study assessed change in cardiorespiratory fitness levels between baseline and after 7 years from the baseline examination with follow-up over 23.6 years (N=1403). Middle-aged Norwegian males (40–59 years of age) who became fit from unfit between the 2 examinations had 66% lower risk (95% CI, 33%–83%) of incident stroke compared with those who became unfit from fit. Those males who became unfit from fit had 2.35 times (95% CI, 1.49–3.63) greater risk of incident stroke compared with those who were continuously fit.[124]
- Studies have also demonstrated a significant association between sedentary time and risk of CVD, including stroke, that was independent of PA levels.[125,126] In the REGARDS study, screen time >4 h/d was associated with 37% higher (HR, 1.37 [95% CI, 1.10–1.71]) risk of stroke over a 7-year follow-up.[127]
- A case-control study (mean, 67.2 years of age) showed that patients with stroke (n=40) had greater sitting time (10.9 h/d versus 8.2 h/d) with lower moderate and vigorous PA (4.9 m/d versus 38 m/d) than did controls (n=23).[128]
- 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]).[129]
- In the CHS, both a greater amount of leisure-time PA (across quintiles, P_{trend}=0.001) and exercise intensity (categories: high, moderate, and low versus none, P_{trend}<0.001) were 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.[130] In the Cooper Center Longitudinal Study of participants who underwent evaluation at the Cooper Clinic in Dallas, TX, investigators found that cardiorespiratory fitness in midlife 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 diabetes, hypertension, and AF.[131]
- Similarly, a prospective study of young Swedish males demonstrated that the lowest compared with the highest tertiles of fitness (HR, 1.70 [95% CI, 1.50–1.93]) and muscle strength (HR, 1.39 [95% CI, 1.27–1.53]) were associated with higher risk of stroke over 42 years of follow-up.[132]
- Several 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; however, more frequent or strenuous activity was not associated with increased protection against stroke.[133]
  - In the California Teachers Study of 61 256 females with PA data, meeting AHA guidelines of moderate PA was associated with a lower risk of ischemic stroke. No association was observed between meeting AHA guidelines for strenuous activity and risk of total stroke.[134]
  - 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.[135]

Nutrition

(See Chapter 5 for more information.)

- In a study based on the NHANES 1999 to 2002 and 2009 to 2012 data sets (≥25 years of age), the most significant number of diet-related stroke deaths were related to low vegetable intake (<300 g/d), low fruit intake (<400 g/d), and high sodium intake (>2 g/d).[136]
- A case-control international study (INTERSTROKE) involving 32 countries (stroke cases, 13 447; controls, 13 472; mean, 62.2 years of age) reported that people who adopted a healthy diet (highest tertile) had a 40% lower odds of having a stroke (95% CI, 33%–47%) compared with people with poor diets (lowest tertile).[137]
- Dietary patterns (eg, Mediterranean or Nordic diet) are associated with stroke risk.[138]
- A meta-analysis of 6 RCTs including 10 950 participants (41–67 years of age) showed that those who adopted a Mediterranean diet had a 35%

lower risk of fatal and nonfatal strokes (95% CI, 15%–50%) compared with controls.[138]

- In the Danish cohort study including 55 338 males and females (50–64 years of age) with follow-up over 13.5 years, those who had the highest healthy Nordic diet scores (including fish, apples, pears, cabbages, root vegetables, rye bread, and oatmeal) had a 14% lower risk of total stroke (95% CI, 2%–24%) than those who had the lowest Nordic diet scores.[139]
- A meta-analysis comprising 185 cohort studies with 58 clinical trials revealed that high fiber intake (highest quantile) is associated with 22% (95% CI, 12%–31%) lower risk of incident stroke compared with the lowest quantile of fiber intake. Those people who consumed 25 to 29 g of fiber intake per day had the greatest health benefits.[140]
- The FHS (N=2888, >45 years of age) showed that those who consumed ≥1 artificially sweetened soft drinks per day (eg, diet cola) had 1.97 times (95% CI, 1.1–3.55) and 2.34 times (95% CI, 1.24–4.45) the risk of total and ischemic stroke, respectively, compared with those who consumed 0 artificially sweetened soft drinks per week.[141]
- In the Danish Diet, Cancer and Health cohort study (N=57 053), there was no association between omega-3 fatty acids intake (highest versus lowest quantile) and ischemic stroke (HR, 1.06 [95% CI, 0.93–1.21]) during an average of 13.5 years of follow-up.[142]
- In an RCT (N=25 871), those participants (males ≥50 years of age; females ≥55 years of age) who consumed omega-3 fatty acids 1 g/d (EPA 460 mg plus DHA 380 mg) for an average of 5.3 years had a stroke risk similar to that of controls (RR, 1.04 [95% CI, 0.83–1.31]).[143]

Kidney Disease (See Chapter 12 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}.[144]
- A meta-analysis showed that macroalbuminuria increased incident stroke risk (RR, 2.65 [95% CI, 2.25–3.14]) more than microalbuminuria (RR, 1.58 [95% CI, 1.39–1.80]; *P* for heterogeneity <0.001, I^2=96%).[145]
- A meta-analysis showed that 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]).[146]
- A meta-analysis of 12 studies found that a urine ACR of >30 mg/mmol was associated with an increased risk of stroke (RR, 1.67 [95% CI, 1.49–1.86]; *P*<0.001).[147]
- 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.[148]
- Among 232 236 patients in the GWTG-Stroke registry, admission eGFR 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 mL·min^{-1}·1.73 m^{-2} without dialysis (OR, 2.52 [95% CI, 2.07–3.07]) compared with eGFR ≥60 mL·min^{-1}·1.73 m^{-2}. Lower eGFR was also associated with decreased likelihood of being discharged home.[149]
- 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 (aOR, 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 (aOR, 1.30 [95% CI, 1.11–1.52]; *P* for interaction=0.046).[150]

Risk Factor Issues Specific to Females

- In a meta-analysis of 11 studies of stroke incidence published between 1990 and January 2017, the pooled crude rate of pregnancy-related stroke was 30.0 per 100 000 pregnancies (95% CI, 18.8–47.9). The crude rates per 100 000 pregnancies were 18.3 (95% CI, 11.9–28.2) for antenatal/perinatal stroke and 14.7 (95% CI, 8.3–26.1) for postpartum stroke.[151]
- Among 80 191 parous females in the WHI Observational Study, those who reported breastfeeding for at least 1 month had a 23% lower risk of stroke than those who never breastfed (HR, 0.77 [95% CI, 0.70–0.83]). The strength of the association increased with increasing breastfeeding

duration (1–6 months: HR, 0.81 [95% CI, 0.74–0.90]; 7–12 months: HR, 0.75 [95% CI, 0.66–0.85]; ≥13 months: HR, 0.74 [95% CI, 0.65–0.83]; *P* for trend<0.01). The strongest association was observed among NH Black females (HR, 0.54 [95% CI, 0.37–0.71]).[152]

- In a systematic review and meta-analysis of 78 studies including >10 million participants, any hypertensive disorder during pregnancy, including gestational hypertension, preeclampsia, or eclampsia, was associated with a greater risk of ischemic stroke; late menopause (after 55 years of age) and gestational hypertension were associated with a greater risk of hemorrhagic stroke; and oophorectomy, hypertensive disorder during pregnancy, PTB, and stillbirth were associated with a greater risk of any stroke.[153]
- In the setting of AF, females have a significantly higher risk of stroke than males.[154–158]
- In the UK Million Women Study, there was a U-shaped relationship between age at menarche and risk of incident stroke.[159] Compared with females experiencing menarche at 13 years of age, both those experiencing menarche at ≤10 years of age and those experiencing menarche at ≥17 years of age 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 meta-analysis of 32 studies, females who experienced menopause before 45 years of age had an increased risk of stroke compared with females ≥45 years of age 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]).[160]
- 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[161–164] and recent stroke or TIA.[165]
- In a nested case-control study of the UK'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.[166]
- 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.[167,168]
- Among people living with HIV, females had a higher incidence of stroke or TIA than males, especially at younger ages.[169] Compared with HIV-uninfected females, females living with HIV had a 2-fold higher incidence of ischemic stroke.[170]

SDB and Sleep Duration (See Chapter 13 for more information.)

- SDB 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.[171]
- OSA may be particularly associated with stroke occurring at the time of waking up ("wake-up stroke"). In a meta-analysis of 5 studies (N=591 patients), patients with wake-up stroke had a higher AHI than those with non–wake-up stroke, and there was an increased incidence of severe OSA in those with wake-up stroke (OR, 3.18 [95% CI, 1.27–7.93]).[172]
- OSA is also common after stroke.[173,174] 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%.[175] The proportion of patients with cerebrovascular disease with severe OSA (AHI >30) ranged from 8% to 64%.
- In a 2019 meta-analysis of 89 studies (N=7096 patients; 54 studies performed within 1 month of stroke, 23 at 1–3 months, and 12 after 3 months), the prevalence of SDB with AHI >5 episodes per hour was 71% (95% CI, 66.6%–74.8%) and >30 episodes per hour was 30% (95% CI, 24.4%–35.5%).[176] Severity and prevalence of SDB were similar at all time periods after stroke. In the BASIC Project, Mexican American people had a higher prevalence of poststroke SDB, defined as an AHI ≥10, than NH White people after adjustment for confounders (prevalence ratio, 1.21 [95% CI, 1.01–1.46]).[173]
- Also in the BASIC Project, infarction involving the brainstem (versus no brainstem involvement) was associated with increased odds of SDB, defined as an AHI ≥10, with an OR of 3.76 (95% CI, 1.44–9.81) after adjustment for demographics, risk factors, and stroke severity. In this same study, ischemic stroke subtype was not found to be associated with the presence or severity of SDB.[177]
- OSA is associated with higher poststroke mortality.[178–180]
- Sleep duration is also associated with stroke risk. In a meta-analysis of 14 prospective cohort studies, long sleep, defined mostly as self-reported sleep ≥8 to 9 hours per night, was associated with incident stroke, with an HR of 1.46 (95% CI, 1.26–1.69)

after adjustment for demographics, vascular risk factors, and comorbidities.[181] In another meta-analysis, short sleep, defined as sleep ≤5 to 6 hours per night, was also associated, although to a lesser magnitude, with incident stroke (HR, 1.15 [95% CI, 1.07–1.24]) after adjustment for similar factors.[182]

- 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 h/d. Both short and long sleep durations were associated with increased stroke risk. 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).[183]
- 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.[184]

Psychosocial Factors

- 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]).[185]
- In a case-control study (INTERSTROKE) of 26 919 participants (mean age, 62.2 years) from 32 countries, participants with psychological distress had 2.8 times (95% CI, 1.78–2.72) greater odds of having a stroke than did control participants.[137]
- In a prospective cohort study in New South Wales of 221 677 participants (45–79 years of age) with an average of 4.7 years of follow-up, high psychological distress was associated with increased risk of fatal and nonfatal strokes in females (HR 1.44 [95% CI, 1.09–1.92]) and males (HR, 1.24 [95% CI, 0.97–1.59]) compared with those with a low level of psychological distress.[186]
- The relationship between changes in depressive symptoms and risk of first stroke was examined among 4319 participants in the CHS. Compared with participants who had persistently low depressive symptoms, those who had persistently high depressive symptoms for 2 consecutive annual assessments had an increased risk of stroke (aHR, 1.65 [95% CI, 1.06–2.56]). New onset of symptoms was not significantly associated with stroke risk (aHR, 1.44 [95% CI, 0.97–2.14]). There was no increased stroke risk for participants whose depressive symptoms improved (HR, 1.02 [95% CI, 0.66–1.58]).[187]
- 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 behavioral factors (HR, 0.94 [95% CI, 0.20–4.31]).[188]
- Among 13 930 patients with ischemic stroke and 28 026 control subjects 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.[189] 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]).
- Among 479 054 participants in the UK Biobank study who were followed up for a mean of 7.1 years, social isolation (HR, 1.39 [95% CI, 1.25–1.54]) and loneliness (HR, 1.36 [95% CI, 1.20–1.55]) were associated with higher risk of incident stroke in analyses adjusted for demographic characteristics. However, after adjustment for biological factors, health behaviors, depressive symptoms, socioeconomic factors, and chronic diseases, these relationships were no longer statistically significant. In fully adjusted analyses, social isolation, but not loneliness, was associated with increased risk of mortality after stroke (HR, 1.32 [95% CI, 1.08–1.61]).[190]

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.[191] Long work hours have also been linked to stroke. Meta-analytical findings from 24 cohort studies from the United States, Europe, and Australia revealed a dose-response

relationship between working >40 h/wk and incident stroke.[192]
- 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.[193]
- In a nationwide Danish registry study of data from 2003 to 2012 (n=60 503 strokes), long-term, but not short-term, mortality after stroke was inversely related to income for all causes of death.[194] There was a 5.7% absolute difference in mortality between the lowest and highest income groups at 5 years after stroke.
- In the WHO MONICA-psychological program, among a random sample from a Russian/Siberian population 25 to 64 years of age, a social network index was associated with stroke risk. During 16 years of follow-up, the risk of stroke in the people with a low level of social network was 3.4 times higher for males (95% CI, 1.28–5.46) and 2.3 times higher for females (95% CI, 1.18–4.49).[195]

Family History and Genetics

- Genetic studies have identified genetic variants associated with risk of ischemic stroke, with distinct genetic associations[196] for different stroke subtypes.
  - 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.[197,198]
- The largest multiethnic GWAS of stroke conducted to date reports 32 genetic loci, including 22 not previously reported.[199] 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 associated exclusively with large-artery stroke. However, 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 GWAS focused on small-vessel stroke from the International Stroke Consortium identified a novel association with a region on chromosome 16q24.2.[200]
- Studies have also identified genetic loci unique to non-European ethnicity populations. For example, 1 study of Black individuals from MESA found that variants within the *SERGEF* gene were associated with carotid artery IMT, as well as with stroke.[201]
- Low-frequency genetic variants (ie, allele frequency <5%) may also contribute to risk of large- and small-vessel stroke. *GUCY1A3*, for example, with a minor allele frequency in the lead SNP of 1.5%, was associated with large-vessel stroke.[202] The gene encodes the α1-subunit of soluble guanylyl cyclase, which plays a role in both nitric oxide–induced vasodilation and platelet inhibition and has been associated with early MI.
- Monogenic forms of ischemic stroke have much higher risk associated with the underlying genetic variant but are rare.[203,204]
  - 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.[196]
- ICH also appears to have a genetic component, with heritability estimates of 34% to 74%, depending on the subtype.[205] A GWAS of ICH suggests that 15% of this heritability is attributable to genetic variants in the *APOE* gene and 29% is attributable to non-*APOE* genetic variants.[205]
- Other genes strongly associated with ICH are *PMF1* and *SLC25A44*, which have been linked to ICH with small-vessel disease.[206,207]
- Genetic predisposition to higher MCP-1/CCL2 concentrations was associated with high risk of any stroke, including associations with large-artery stroke, ischemic stroke, and cardioembolic stroke, but not small-vessel stroke or ICH, implicating inflammation in stroke pathogenesis.[208]
- Genetic determinants of coagulation factors, including factor XI and factor VII, have been implicated in the pathogenesis of ischemic stroke.[209,210]

Awareness of Stroke Warning Signs and Risk Factors

- An analysis of the NHIS demonstrated that awareness of stroke symptoms and signs among US adults remains suboptimal but improved from 2009 to 2014. In 2014, 68.3% of the survey respondents were able to recognize 5 common stroke symptoms,

and 66.2% demonstrated knowledge of all 5 stroke symptoms and the importance of calling 9-1-1.[211]

- Knowledge of 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.[212]
- 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).[213] Sudden confusion or difficulty speaking and sudden numbness or weakness of the face, arm, or leg were the stroke symptoms most commonly identified correctly, whereas sudden headache was the least; 60% of females and 58% of males incorrectly identified sudden chest pain as a stroke symptom.
- In a single-center study of 144 stroke survivors, Hispanic people scored lower on a test of stroke symptoms and the appropriate response to those symptoms than NH White people (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%).[214] 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.[215] Only 68% of patients without a history of stroke were able to identify the most common symptoms of stroke.
- A study of a community-partnered intervention among minority seniors found that participants would respond to only half of presented stroke symptoms by immediately calling 9-1-1 (49% intervention, 54% control at baseline). This rate increased to 68% among intervention participants with no change for controls.[216]

Stroke Mortality

(See Table 15-1 and Charts 15-2 through 15-7)

- In 2018 (unpublished NHLBI tabulations using CDC WONDER[217] and the NVSS[218]):
  - On average, every 3 minutes 33 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, chronic lower respiratory disease, and unintentional injuries/accidents.
  - The number of deaths with stroke as an underlying cause was 147 810 (Table 15-1); the age-adjusted death rate for stroke as an underlying cause of death was 37.1 per 100 000, whereas the age-adjusted rate for any mention of stroke as a cause of death was 62.8 per 100 000.
  - Approximately 64% of stroke deaths occurred outside of an acute care hospital.
  - In 2018, NH Black males and females had higher age-adjusted death rates for stroke than NH White, NH Asian, NH American Indian or Alaska Native, and Hispanic males and females in the United States (Chart 15-2).
  - More females than males die of stroke each year because of a larger number of elderly females than males. Females accounted for 57.5% of US stroke deaths in 2018.
- Conclusions about changes in stroke death rates from 2008 to 2018 are as follows[217]:
  - The age-adjusted stroke death rate decreased 11.9% (from 42.1 per 100 000 to 37.1 per 100 000), whereas the actual number of stroke deaths increased 10.2% (from 134 148 to 147 810 deaths).
  - The decline in age-adjusted stroke death rates for males and females was similar (–10.9% and –12.8%, respectively).
  - Crude stroke death rates declined most among people 35 to 44 years of age (–14.6%; from 4.8 to 4.1 per 100 000), 65 to 74 years of age (–12.0%; from 87.3 to 76.8 per 100 000), and 75 to 84 years of age (–18.3%; from 313.3 to 256.0 per 100 000). In comparison, crude stroke death rates declined more modestly among those 25 to 34 years of age (–7.7%; 1.3 and 1.2 per 100 000), 45 to 54 years of age (–10.2%; 13.7 to 12.3 per 100 000), 55 to 64 years of age (–1.0%; 30.6 to 30.3 per 100 000), and >85 years of age (–8.1%; 1071.0 to 984.3 per 100 000). Despite the improvements noted since 2008, there has been a recent flattening or increase in death rates among all age groups (Charts 15-3 and 15-4).
  - Age-adjusted stroke death rates declined by ≈7% or more among all racial/ethnic groups; however, in 2018, rates remained higher among NH Black people (52.3 per 100 000; change since 2008, –12.7%) than among NH White people (35.9 per 100 000; –11.4%), NH Asian/Pacific Islander people (29.6 per 100 000; –16.1%), NH American Indian/Alaska Native people (30.4 per 100 000; –9.8%), and Hispanic people (32.0 per 100 000; –7.0%).
- There are substantial geographic disparities in stroke mortality, with higher rates in the southeastern United States, known as the "stroke belt" (Chart 15-5). This area is usually defined to

include the 8 southern states of North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. 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).[219]

- 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 15-6 and 15-7). The probability of death within 1 year of a stroke was lowest in Black males 45 to 64 years of age (Chart 15-6). The probability of death within 5 years of a stroke was lowest for White males 45 to 64 years of age (Chart 15-7).
- 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 White people for both males and females in contract health services delivery area counties in the United States and were highest in younger age groups (35–44 years of age). Stroke mortality rates and the rate ratios for American Indian/Alaska Native people to White people 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.[220]
- 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 attributed mainly to the decrease in mortality among those ≤65 years of age (absolute decrease of 14.2 deaths per 100 strokes after 10 years).[221]
- 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.[13]
- Projections of stroke mortality from 2012 to 2030 differ on the basis of what factors are included in the forecasting.[222] Conventional projections that incorporate only 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 ≥65 years of age. Moreover, the trend-based projection method reveals that the disparity in stroke deaths among NH Black people compared with NH White people 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.[222]

Complications and Recovery (See Chart 15-8)

- Recurrent stroke is common (Chart 15-8).
- 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).[223] Approximately 3% of males and 2% of females reported that they were disabled because of stroke.
- In data from the NIS (2010–2012), among 395 411 patients with stroke, 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.[224]
- Common complications after stroke include both short-term complications such as seizures, DVT, PE, urinary infection, aspiration pneumonia, decubitus ulcers, and constipation and long-term 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.[225] 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.
- In a systematic review of 47 studies (N=139 432 patients, mean age, 68.3 years, mean NIHSS score 8.2), the pooled frequency of poststroke pneumonia was 12.3% (95% CI, 11%–13.6%). The frequency was lower in stroke units (8% [95% CI, 7.1%–9%]) than other locations (*P* interaction=0.001). The frequency of poststroke urinary tract infection was 7.9% (95% CI, 6.7%–9.3%) and of any poststroke infection was 21% (95% CI, 13%–29.3%).[226]

- 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.[227]
- In the PROFESS trial, among 15754 participants with ischemic stroke, 1665 patients (10.6%) reported new 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.[228] Long-standing 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 23751 patients with stroke and 11240 patients with TIA, 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.[229] The risk among stroke survivors compared with healthy control subjects was ≈50% higher (aHR for those with stroke versus control subjects, 1.47 [95% CI, 1.35–1.60]).
- Long-term insomnia occurred in 16% of stroke survivors in an Australian cohort. Insomnia was associated with depression, anxiety, disability, and failure to return to work.[230]
- Among 190 mild to moderately disabled survivors >6 months after stroke who were 40 to 84 years of age, 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.[231]
- 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.[232] Inflammatory biomarkers (CRP, IL-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.[233]
- The 30-day hospital readmission rate after discharge from rehabilitation for stroke was 12.7% among fee-for-service Medicare patients. The mean rehabilitation length of stay for stroke was 14.6 days.[234]
- 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.[235]
- A national study of inpatient rehabilitation after first stroke found that Black patients were younger, had a higher proportion of hemorrhagic stroke, and were more disabled on admission than NH White patients. Compared with NH White patients, Black and Hispanic patients 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 White patients, Black patients also had less improvement in functional status per inpatient day.[236]
- Black people were less likely to report independence in activities of daily living and instrumental activities of daily living than White people 1 year after stroke after controlling for stroke severity and comparable rehabilitation use.[237]
- Hospital characteristics also predict functional outcomes after stroke. In an analysis of the AVAIL study, which included 2083 patients with ischemic stroke 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.[238]
- 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, postacute care, and secondary prevention).[239] 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.
- In a meta-analysis of 55 studies, return to work after stroke occurred in 56.7% at 1 year (95% CI, 48.3%–65.1%) and 66.7% at 2 years (95% CI, 60.2%–73.2%) in population-based studies.[240] 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%).[241]

Depression

- 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.[242] Suicidality is also increased after stroke.[243]

- 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 to 25% (95% CI, 16%–33%) at 1 to 5 years and to 23% (95% CI, 14%–31%) at 5 years.[244]
- Poststroke depression is associated with higher mortality. Among 15 prospective cohort studies (N=250 294 participants), poststroke depression was associated with an increased all-cause mortality (HR, 1.59 [95% CI, 1.30–1.96]).[245]
- A meta-analysis of 8 RCTs assessing the efficacy of preventive pharmacological interventions among 776 initially nondepressed patients with stroke 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.[246]
- 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.[247]

Functional and Cognitive Impairment and Dementia

Functional and cognitive impairment and dementia are common after stroke, with the incidence increasing with duration of follow-up.

- 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.[248–251] In NOMAS, 210 of 3298 participants had an ischemic stroke during follow-up and had functional assessments with the Barthel index before and after stroke.[250] 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.[251] 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]).
- 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 assessment afterward. 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]).[252]
- 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.[253] Follow-up time tended to be shorter in studies without evidence of decline.
- Of 127 Swedish survivors assessed for cognition at 10 years after stroke, poststroke cognitive impairment was found in 46% with a Mini-Mental State Examination threshold of <27 and in 61% with a Montreal Cognitive Assessment threshold of <25.[254]
- In 2 prospective studies, 11% to 23% of patients with incident lacunar stroke developed vascular dementia during a 3-year follow-up.[255] Vascular dementia may develop annually in 3% to 5% of patients with lacunar stroke.[256]
- Among 109 patients with ischemic stroke, NIHSS score (β=−0.54 [95% CI, −0.99 to −0.89]) and preexisting leukoaraiosis severity (β=−1.45 [95% CI, −2.86 to −0.03]) independently predicted functional independence, primarily through an effect on cognitive rather than motor scores.[257]
- Black people are at higher risk for dementia than White people within 5 years of ischemic stroke. In an analysis of South Carolina data from 2000 to 2012 (n=68 758 individuals with a diagnosis of ischemic stroke), Black race increased risk for 5 categories of dementia after incident stroke (HR,

1.37 for Alzheimer disease to HR, 1.95 for vascular dementia).[258]

- In a study of 90-day poststroke outcomes among patients with ischemic stroke in the BASIC Project, Mexican American people scored worse on neurological, functional, and cognitive outcomes than NH White people after multivariable adjustment.[259]
- In a retrospective analysis of the 2016 BRFSS, Black (OR, 1.58 [95% CI,1.54–1.63]) and Hispanic (OR, 2.302 [95% CI, 2.19–2.42]) individuals more frequently reported worsening confusion or memory loss that interfered with day-to-day activities than did White individuals.[260]

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 who present 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.[261]
- A history of infertility, preeclampsia, prolonged rupture of membranes, and chorioamnionitis are independent maternal risk factors for perinatal arterial ischemic stroke. However, maternal health and pregnancies are normal in most cases.[262]
- The most common cause of arterial ischemic stroke in children is a cerebral arteriopathy, found in more than half of all cases.[263,264] 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.[265]
- 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.[266] 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%).[267]
- 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.[268]
- In a post hoc analysis, head or neck trauma in the prior week was a strong risk factor for childhood arterial ischemic stroke (aOR, 36 [95% CI, 5–281]), present in 10% of cases.[269]
- Exposure to minor infection in the prior month was also associated with stroke and was present in one-third of cases (aOR, 3.9 [95% CI, 2.0–7.4]).[269] The effect of infection on pediatric stroke risk is short-lived, lasting for days; 80% of infections preceding childhood stroke are respiratory.[270] A prospective study of 326 children with arterial stroke revealed that serological 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).[271] 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.[272] In contrast, a population-based controlled study suggested a minimal association between perinatal stroke and thrombophilia,[273] and therefore, routine testing is not recommended in very young children.
- In a prospective Swiss registry,[274] 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).[275]
- 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.[276]
- Compared with referent children with asthma, childhood stroke survivors have greater impairments in adaptive behaviors, social adjustment, and social participation, even if their intelligence quotient is normal.[277] Severity of disability after perinatal stroke correlates with maternal psychosocial outcomes such as depression and quality of life.[278]

- Despite current treatment, at least 1 of 10 children with ischemic or hemorrhagic stroke will have a recurrence within 5 years.[279,280] Among 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.[36] The sole predictor of recurrence was the presence of an arteriopathy, which increased the risk of recurrence 5-fold compared with an idiopathic AIS (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.[281] The recurrence risk after perinatal stroke, however, was negligible.
- More than 25% of survivors of perinatal ischemic strokes develop delayed seizures within 3 years; those with larger strokes are at higher risk.[282] The cumulative risk of delayed seizures after later childhood stroke is 13% at 5 years and 30% at 10 years.[283] Children with seizures within 7 days of their stroke have the highest risk for delayed seizures, >70% by 5 years after the stroke.[284] Among survivors of ICH in childhood, 13% developed delayed seizures and epilepsy within 2 years.[285]
- Pediatric stroke teams and stroke centers[286] 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% had TIAs, and 14% had other neurological emergencies, which underscores the need for prompt evaluation of children with "brain attacks."[287]
- 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.[288]
- 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.[289]

Stroke in Young Adults and in Midlife

- Approximately 10% of all strokes occur in individuals 18 to 50 years of age.[290]
- In the NIS, hospitalizations for AIS increased significantly for both males and females and for certain racial/ethnic groups among younger adults 18 to 54 years of age.[291] From 1995 to 2011 through 2012, hospitalization rates almost doubled for males 18 to 34 and 35 to 44 years of age. Hospitalization rates for ICH and SAH remained stable, however, with the exception of declines among males and NH Black patients 45 to 54 years of age with SAH.
- 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 White individuals 20 to 54 years of age compared with 128 per 100 000 (95% CI, 106–149) among Black individuals of the same age. Both races had a significant increase in the incidence rate from 1993 to 1994.[292] 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 35 to 39 years of age, 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]; $P<0.0001$).[293] Rates of stroke in those 40 to 44, 45 to 49, and 50 to 54 years of age also increased significantly. Stroke rates in those >55 years of age decreased during these time periods.
- Stroke incidence may differ by sex among younger adults. In the GCNKSS, incidence in males 20 to 44 years of age increased from 15 to 31 per 100 000 ($P<0.05$) in the interval from 1993 and 1994 to 2015; the incidence in females remained stable, from 20 to 26 per 100 000 ($P>0.05$).[19] In the REGARDS cohort, middle-aged females 45 to 64 years of age had lower risk of stroke than males (White females/males IRR, 0.68 [95% CI, 0.49–0.94]; Black females/males IRR, 0.72 [95% CI, 0.52–0.99]).[20]
- Vascular risk factors are common among patients with stroke 20 to 54 years of age. During 2005, in the biracial GCNKSS, hypertension prevalence was estimated at 52%, hyperlipidemia at 18%, diabetes at 20%, CHD at 12%, and current smoking at 46%.[292]
- In the NIS, the prevalence of stroke risk factors also increased from 2003 to 2004 through 2011 to 2012 among those hospitalized for stroke.[291] These increases in prevalence were seen among both males and females 18 to 64 years of age. Absolute increases in prevalence were seen for hypertension (range of absolute increase, 4%–11%), lipid disorders (12%–21%), diabetes (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.[291] Among males, the prevalence of ≥3 risk factors among patients with stroke increased from 9% to 16% at 18 to 34 years of age, 19% to 35% at 35 to 44 years of age, 24% to 44% at 45 to 54 years of age, and 26% to 46% at 55 to 64 years of age. Among females, the prevalence of ≥3 risk factors among patients with stroke increased from 6% to 13% at 18 to 34 years of age, 15% to 32% at 35 to 44 years of age, 25% to 44% at 45 to 54 years of age, and 27% to 48% at 55 to 65 years of age (*P* for trend <0.001).
- In the FUTURE study, the 30-day case fatality rate among patients with stroke 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.[294]
- In the FUTURE study, after a mean follow-up of 13.9 years, 44.7% of young patients with stroke had poor functional outcome, defined as a modified Rankin Scale 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 1-point increase).[295]
- In a county-level study, stroke mortality rates among middle-aged US adults 35 to 64 years of age increased from 14.7 per 100 000 in 2010 to 15.4 per 100 000 in 2016.[296] Rates decreased among older adults ≥65 years of age from 299.3 per 100 000 in 2010 to 271.4 per 100 000 in 2016.

Stroke in Older Adults

- Patients with stroke >85 years of age make up 17% of all patients with stroke, and in this age group, stroke is more prevalent in females than in males.[297]
- 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 patients with stroke who were >80 years of age.[129] In addition, the proportion of ischemic strokes attributable to AF increases with age and may reach 40% or higher in very elderly patients with stroke.[298]
- Very elderly patients have a higher risk-adjusted mortality,[299] have greater disability,[299] have longer hospitalizations,[300] receive less evidence-based care,[213,215] and are less likely to be discharged to their original place of residence.[300]
- Over the period 2010 to 2050, the number of incident strokes is expected to more than double, with the majority of the increase among the elderly (≥75 years of age) and minority groups.[301]
- A study of 1346 patients treated with endovascular therapy for AIS with large-vessel occlusion found that being ≥80 years of age was an independent predictor of poor outcomes (modified Rankin Scale score 2–6) and mortality after thrombectomy. This negative effect persisted when accounting for technique, location of stroke, or success of recanalization. Furthermore, being ≥80 years of age was an independent predictor of higher rates of postprocedural hemorrhage.[302]
- Based on large-scale cohort studies and meta-analyses, a Markov model suggested that for individuals ≥80 years of age who are functionally independent at baseline, intravenous thrombolysis with tPA improved QALYs only by 0.83 QALY; for patients with baseline disability, intravenous thrombolysis yielded only an additional 0.27 QALY over endovascular thrombectomy.[303]

Organization of Stroke Care

- Among hospitals participating in GWTG-Stroke from 2013 to 2015, rates of defect-free care were high for both CSCs (94.6%) and primary stroke centers (94.0%). For ED admissions, CSCs had higher rates of intravenous tPA (14.3% versus 10.3%) and endovascular thrombectomy (4.1% versus 1.0%). Door-to-tPA time was shorter for CSCs (median, 52 versus 61 minutes; adjusted risk ratio, 0.92 [95% CI, 0.89–0.95]), and a greater proportion of patients at CSCs had times to tPA that were ≤60 minutes (79.7% versus 65.1%; aOR, 1.48 [95% CI, 1.25–1.75]). CSCs had in-hospital mortality rates that were higher for both ED admissions (4.6% versus 3.8%; aOR, 1.14 [95% CI, 1.01–1.29]) and transfers (7.7% versus 6.8%; aOR, 1.17 [95% CI, 1.05–1.32]).[304]
- 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 CSC 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.[305]
- 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.[306] Hospitals certified between 2009 and 2013 also had lower in-hospital and 30-day mortality than centers certified before 2009.

Hospital Discharges and Ambulatory Care Visits (See Table 15-1)

- From 2006 to 2016, the number of inpatient discharges from short-stay hospitals with stroke as the principal diagnosis declined slightly, from 897 000 in 2006 to 874 000 in 2016 (Table 15-1).
- In 2016, the average length of stay for discharges with stroke as the principal diagnosis was 6.2 days (HCUP,[307] unpublished NHLBI tabulation).
- In 2016, there were 590 000 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,[308] unpublished NHLBI tabulation). In 2016, physician office visits for a first-listed diagnosis of stroke totaled 2 155 000 (NAMCS,[309] unpublished NHLBI tabulation).
- Age-specific AIS hospitalization rates from 2000 to 2010 decreased for individuals 65 to 84 years of age (–28.5%) and ≥85 years of age (–22.1%) but increased for individuals 25 to 44 years of age (43.8%) and 45 to 64 years of age (4.7%). Age-adjusted AIS hospitalization rates were lower in females, and females had a greater rate of decrease from 2000 to 2010 than males (–22.1% versus –17.8%, respectively).[310]
- An analysis of the 2011 to 2012 NIS for AIS found that after risk adjustment, all racial/ethnic minorities except Native American people had a significantly higher likelihood of length of stay ≥4 days than White people.[311]

Operations and Procedures

- In 2014, an estimated 86 000 inpatient CEA procedures were performed in the United States. CEA is the most frequently performed surgical procedure to prevent stroke (HCUP,[307] unpublished NHLBI tabulation).
- Although rates of CEA decreased between 1997 and 2014, the use of CAS increased dramatically from 2004 to 2014 (HCUP,[307] unpublished NHLBI tabulation).
- In-hospital mortality for CEA decreased steadily from 1993 to 2014 (HCUP,[307] unpublished NHLBI tabulation).
- In a meta-analysis of cohort studies published by May 2016, the risk of procedural stroke or death after CEA was 3.44% (95% CI, 2.70%–4.23%) in symptomatic patients and 1.28% (95% CI, 0.91%–1.71%) in asymptomatic patients. After CAS, the risk of stroke or death was 4.77% (95% CI, 3.67%–5.99%) for symptomatic patients and 2.59% (95% CI, 1.77%–3.56%) for asymptomatic patients. Procedural stroke/death rates were lower in studies of CEA that completed recruitment after 2005 for both symptomatic (5.11% versus 2.68%) and asymptomatic (3.17% versus 1.50%) patients; rates for CAS did not change over time.[312]
- In a meta-analysis of 5 RCTs comparing CEA and CAS in asymptomatic patients, there was a trend toward increased incidence of stroke or death for patients who underwent CAS versus CEA (any periprocedural stroke: RR, 1.84 [95% CI, 0.99–3.40]; periprocedural nondisabling stroke: RR, 1.95 [95% CI, 0.98–3.89]; any periprocedural stroke or death: RR, 1.72 [95% CI, 0.95–3.11]). The risk ratios were 1.24 (95% CI, 0.76–2.03) for long-term stroke and 0.92 (95% CI, 0.70–1.21) for the composite of periprocedural stroke, death, MI, or long-term ipsilateral stroke.[313]
- In a Cochrane review that analyzed data from 6092 patients in 3 trials of CEA, surgery was associated with an increased risk of ipsilateral ischemic stroke within 5 years for patients with <30% stenosis (RR, 1.27 [95% CI, 0.80–2.01]), had no benefit for those with 30% to 49% stenosis (RR, 0.93 [95% CI, 0.62–1.38]), and reduced the risk of stroke for those with 50% to 69% stenosis (RR, 0.84 [95% CI, 0.60–1.18]) and 70% to 99% stenosis without near-occlusion (RR, 0.47 [95% CI, 0.25–0.88]); there was no benefit for patients with near-occlusions (RR, 1.03 [95% CI, 0.57–1.84]).[314]
- A meta-analysis of 6526 patients from 5 trials with a mean follow-up of 5.3 years indicated no significant difference in the composite outcome of periprocedural death, stroke, MI, or nonperiprocedural ipsilateral stroke for patients who underwent CAS versus CEA. CAS was associated with increased odds of any periprocedural or nonperiprocedural ipsilateral stroke (OR, 1.50 [95% CI, 1.22–1.84]) and periprocedural minor stroke (OR, 2.43 [95% CI, 1.71–3.46]). CAS was associated with reduced odds of periprocedural MI (OR, 0.45 [95% CI, 0.27–0.75]), cranial nerve palsy (OR, 0.07 [95% CI, 0.04–0.14]), and the composite of death, stroke, MI, or cranial nerve palsy (OR, 0.75 [95% CI, 0.63–0.93]).[315]
- In the Medicare population, the in-hospital stroke rate and mortality were similar for CEA and CAS.[316]
- In the Medicare population, 30-day readmission rates and long-term risk of adverse clinical outcomes associated with CAS were similar to those for CEA after adjustment for patient- and provider-level factors.[316,317]
- Evidence on comparative costs of CEA and CAS is mixed; whereas some studies found CAS to be associated with significantly higher costs than CEA,[318] particularly among asymptomatic patients,[319] and that they might be less cost-effective in general,[320] CREST found that the overall cost of CAS was not different from that of CEA (US $15 055 versus US $14 816).[321]

- 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 among patients with large-vessel occlusion, regardless of patient age, NIHSS score above the thresholds for inclusion, or receipt of intravenous thrombolysis.[322] Retrospective analyses of patient databases have found similar results.[323]
- 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.[324]

Cost
(See Table 15-1)

- In 2016 to 2017 (average annual; MEPS,[325] unpublished NHLBI tabulation):
  - The direct and indirect cost of stroke in the United States was $49.8 billion (Table 15-1).
  - The estimated direct medical cost of stroke was $30.8 billion. This includes hospital outpatient or office-based provider visits, hospital inpatient stays, ED visits, prescribed medicines, and home health care.
  - 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 $7866.
- 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.[326]
- The total cost of stroke in 2035 (in 2015 dollars) is projected to be $81.1 billion for NH White people, $32.2 billion for NH Black people, and $16.0 billion for Hispanic people.[326]

Global Burden of Stroke

Prevalence
(See Charts 15-9 through 15-12)

- The GBD 2019 Study used statistical models and data on prevalence, incidence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 369 diseases and injuries in 204 countries and territories. In 2019[42]:
  - Global prevalence of stroke was 101.5 million people (95% UI, 93.2–110.5 million), whereas that of ischemic stroke was 77.2 million (95% UI, 68.9–86.5 million), that of ICH was 20.7 million (95% UI, 18.0–23.4 million), and that of SAH was 8.4 million (95% UI, 7.2–9.8 million).
  - Globally, there was a 3.6% increase (95% UI, 2.0%–5.4%) in the ischemic stroke age-standardized prevalence rate from 2010 to 2019 and a 1.9% decrease (95% UI, −3.4% to −0.4%) from 1990 to 2019.
  - Globally, there was an 2.9% decrease (95% UI, −3.8% to −2.1%) in the ICH age-standardized prevalence rate from 2010 to 2019 and a 16.8% decrease (95% UI, −18.2% to −15.4%) from 1990 to 2019.
  - Globally, there was a 1.6% decrease (95% UI, −2.3% to −0.8%) in the SAH age-standardized prevalence rate from 2010 to 2019 and a 12.9% decrease (95% UI, −15.0% to −11.5%) from 1990 to 2019.
  - Overall, age-standardized stroke prevalence rates are highest in Oceania, Southeast Asia, North Africa and the Middle East, and East Asia (Chart 15-9).
  - Countries in parts of North Africa and the Middle East, East Asia, southern sub-Saharan Africa, high-income North America, and Southeast Asia have the highest prevalence rates of ischemic stroke (Chart 15-10).
  - The prevalence of ICH is high in Oceania and Southeast Asia (Chart 15-11).
  - Age-standardized prevalence of SAH is high in high-income Asia Pacific, high-income North America, Oceania, and Eastern Europe (Chart 15-12).

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.[327]

Mortality
(See Charts 15-13 through 15-16)

- In 2019[42]:
  - There were 6.6 million deaths (95% UI, 6.0–7.0 million) attributable to stroke worldwide.
  - The absolute number of stroke deaths worldwide increased 43.3% (95% UI, 31.0%–55.4%) between 1990 and 2019; however,

the age-standardized death rate decreased 36.4% (95% UI, –41.6% to –31.2%).
  - The absolute number of stroke deaths worldwide increased 12.2% (95% UI, 5.2%–19.2%) between 2010 and 2019; however, the age-standardized death rate for the 9-year period decreased 14.7% (95% UI, –19.8% to –9.6%).
  - Globally, a total of 3.3 million individuals (95% UI, 3.0–3.5 million) died of ischemic stroke, 2.9 million (95% UI, 2.6–3.1 million) died of ICH, and 0.4 million (95% UI, 0.3–0.4 million) died of SAH.
  - Several countries in Eastern Europe, Central and Southeast Asia, and Oceania have the highest rates of stroke mortality (Chart 15-13).
  - Countries in Eastern Europe and Central Asia have the highest mortality rates attributable to ischemic stroke (Chart 15-14).
  - ICH mortality is highest in Oceania, Central Asia, Southeast Asia, and parts of sub-Saharan Africa (Chart 15-15).
  - Mortality attributable to SAH is highest in parts of Asia (Chart 15-16).
- 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).[327]

Brain Health

Like CVH, brain health can be defined in terms of the absence of disease or the presence of a healthy state. Optimal brain health has been defined as "an optimal capacity to function adaptively in the environment."[328] This definition includes the capacity to perform all the diverse tasks for which the brain is responsible, including movement, perception, learning and memory, communication, problem solving, judgment, decision making, and emotion. Stroke and cerebrovascular disease more broadly are increasingly recognized to be important precursors to cognitive decline and dementia, indicating an absence of brain health. Conversely, measures of systemic and cerebral vascular health have been associated with healthy aging and retained cognitive function.

- In a 2010 survey of 1007 Americans, 31% of respondents reported being most afraid of developing Alzheimer disease. Alzheimer disease ranked second in feared diseases, after cancer but ahead of HD, stroke, and diabetes.[329]
- In the Framingham study, the overall lifetime risk of stroke or dementia was >1 in 3,[330] depending on age cohort and sex. The lifetime risk of any type of dementia for a 65-year-old woman was 21.7%; the lifetime risk of any type of dementia for a 65-year-old man was 14.3%. The lifetime risk of Alzheimer disease was 17.2% for a 65-year-old woman and 9.1% for a 65-year-old man.
- In an analysis of administrative claims data of Medicare fee-for-service beneficiaries enrolled during 2011 to 2013 (and >68 years of age; n=21.6 million), the overall prevalence of a claim for a service or treatment for any dementia subtype was 14.4%.[331] The most common subtype was Alzheimer disease (43.5%), followed by vascular dementia (14.5%), Lewy body dementia (5.4%), frontotemporal dementia (1.0%), and alcohol-induced dementia (0.7%). The prevalence of other types of diagnosed dementia was 0.2%.
- In an analysis of the first 141 autopsies from the Rush Memory and Aging Project longitudinal cohort,[332] a mixture of brain pathologies in patients with dementia was common. Among 50 individuals with dementia, 19 (38.0%) had Alzheimer disease and infarcts, 15 (30.0%) had pure Alzheimer disease, 6 (12%) had vascular dementia, and 6 (12%) had Alzheimer disease with Lewy body disease. More than 50% had multiple diagnoses. Even among those without diagnosed dementia (n=91), pathological abnormalities were common: 22 (22.4%) had pure Alzheimer disease, and 16 (17.6%) had infarcts. Only 20 individuals (14.2%) had no acute or chronic brain abnormalities. After accounting for age, those with multiple diagnoses were almost 3 times (OR, 2.8 [95% CI, 1.2–6.7]) more likely to exhibit dementia as those with 1 pathological diagnosis.
- As the US population ages, the number of individuals with Alzheimer disease will increase dramatically from 2010 to 2050.[333] According to a modeling study, according to estimates in a population of 10 800 participants from the Chicago Health and Aging Project in the United States, in 2010, there were 4.7 million individuals ≥65 years of age with Alzheimer disease (95% CI, 4.0–5.5 million): 0.7 million 65 to 74 years of age, 2.3 million 75 to 84 years of age, and 1.8 million ≥85 years of age. By 2050, the number of people with Alzheimer disease is projected to be 13.8 million, with 7.0 million ≥85 years of age.
- Vascular disease risk factors, and particularly risk factors present in midlife, are associated with cognitive impairment, with risk of dementia overall, and with risk of Alzheimer disease.
- The AHA's ideal CVH metrics are associated with reduced cognitive decline. Among 1033 participants in NOMAS (mean age at initial cognitive assessment, 72±8 years; 39% male; 65% Hispanic, 19% Black, and 16% White), 3% had 0 ideal factors, 15% had 1 factor, 33% had 2 factors, 30% had 3 factors, 14% had 4 factors, 4% had 5 factors, 1% had 6 factors, and 0% had

7 factors.[334] Having more ideal CVH factors was associated with less decline in neuropsychological tests of processing speed. The association was driven by nonsmoking and better glucose levels. Among those with better cognitive performance at initial assessment, ideal CVH was also associated with less decline in executive function and episodic memory testing.

- Among 15 744 participants 44 to 66 years of age at baseline enrolled in the ARIC study, modifiable risk factors present at midlife for late-life dementia included smoking (HR, 1.41 [95% CI, 1.23–1.61]), diabetes (HR, 1.77 [95% CI, 1.53–2.04]), prehypertension (HR, 1.31 [95% CI, 1.14–1.51]), and hypertension (HR, 1.39 [95% CI, 1.22–1.59]).[335] Nonmodifiable and sociodemographic risk factors for dementia included older age (HR, 8.06 [95% CI, 6.69–9.72] for participants 60–66 years of age), Black race (HR, 1.36 [95% CI, 1.21–1.54]), *APOE* ε4 genotype (HR, 1.98 [95% CI, 1.78–2.21]), and lower educational attainment (HR, 1.61 [95% CI, 1.28–2.03] for less than a high school education).
- Hypertension in midlife, but not early adulthood, is associated with late-life dementia risk among females. In an analysis of 5646 long-term members of the Kaiser Permanente Northern California integrated health care delivery system, among whom 532 individuals (9.4%) were diagnosed with dementia, midadulthood hypertension was associated with an increased risk of dementia among females (HR, 1.65 [95% CI, 1.25–2.18]) but not males.[336] Hypertension in early adulthood was not associated with dementia.
- In another analysis among members of the Kaiser Permanente Northern California health care delivery system who had lived in California for at least 23 years (n=7423), those who were born in a "high stroke mortality state," defined as a state in the top quintile of stroke mortality rates (ie, Alabama, Alaska, Arkansas, Louisiana, Mississippi, Oklahoma, Tennessee, South Carolina, and West Virginia), were at increased risk of dementia in late life after adjustment for age, sex, and race (HR, 1.28 [95% CI, 1.13–1.46]).[337] These results suggest that early-life behavioral and other patterning may influence late-life development of dementia.
- Imaging markers and other biomarkers of Alzheimer disease are present in individuals destined to develop dementia ≥20 years before the onset of clinical symptoms.[338] Evidence of β-amyloid precedes development of τ-related neurodegeneration and hippocampal volume loss.[339]
- Midlife vascular risk factors are associated with amyloid deposition in the brain,[340] indicating Alzheimer pathology, as well as undifferentiated or vascular dementia. Among 322 participants without dementia in an ARIC positron emission tomography–amyloid imaging substudy (mean age, 52 years; 58% female; 43% Black), elevated midlife BMI was associated with a 2-fold increase in amyloid deposition (OR, 2.06 [95% CI, 1.16–3.65]). After adjustment for potential confounders, compared with no midlife vascular risk factors, those with 1 (OR 1.88 [95% CI, 0.95–3.72]) and 2 (OR 2.88 [95% CI, 1.46–5.69]) vascular risk factors had increased amyloid deposition. Late-life vascular risk factors were not significantly associated with late-life brain amyloid deposition.
- Brain infarcts without overt clinical manifestations (SBIs) are present in a high proportion of unselected generally healthy individuals in population-based studies using MRI, ranging from 8% of those at a mean of 64 years of age in an Austrian population[341] to 28% of those at a mean age of 75 years in the CHS study.[342,343]
- SBIs are associated with progression to dementia and cognitive decline.[342] Among 1015 participants 60 to 90 years of age in the Rotterdam Scan Study,[344] the presence of SBIs on baseline brain MRI doubled the risk of dementia (HR, 2.26 [95% CI, 1.09–4.70]). SBIs on the baseline MRI were also associated with worse performance on neuropsychological tests and a steeper decline in global cognitive function.
- In CHS, 1919 participants had 2 MRI scans separated by 5 years, and worsening of white matter disease on a semiquantitative scale was evident in 538 participants (28%).[345] Those with increased interval development of WMH burden had greater decline on the modified Mini-Mental State Examination and the Digit Symbol Substitution Test after controlling for potential confounding factors, including occurrence of interval TIA or stroke.
- In a meta-analysis of 9 studies, SBIs were associated with decline in cognitive function on the Mini-Mental State Examination score (standardized mean difference, –0.47 [95% CI, –0.72 to –0.22]).[346] In the same meta-analysis, among 4 studies, SBIs were associated with cognitive dysfunction on the Montreal Cognitive Assessment Scale (standardized mean difference, –3.36 [95% CI, –5.90 to –0.82]).
- A diagnosis of HF is associated with cognitive decline. Among 4864 males and females in CHS initially free of HF and stroke, 496 participants who developed incident HF had greater adjusted declines over 5 years on the modified Mini-Mental State Examination than those without HF (10.2 points [95% CI, 8.6–11.8] versus 5.8 points [95% CI, 5.3–6.2]).[347] The effect did not vary significantly by HFrEF versus HFpEF.

- Diabetes is associated with risk of both vascular dementia and Alzheimer disease. In a meta-analysis of 14 studies (N=2 310 330, with 102 174 patients with dementia), diabetes was associated with an independent increased risk of any dementia in both females (pooled RR, 1.62 [95% CI, 1.45–1.80]) and males (pooled RR, 1.58 [95% CI, 1.38–1.81]).[348] The risk for vascular dementia was 2.34 (95% CI, 1.86–2.94) in females and 1.73 (95% CI, 1.61–1.85) in males; the risk for nonvascular dementia was 1.53 (95% CI, 1.35–1.73) in females and 1.49 (95% CI, 1.31–1.69) in males.
- In a meta-analysis of 18 longitudinal studies (N=246 786 participants), SDB was associated with all-cause dementia (pooled RR, 1.18 [95% CI, 1.02–1.36]), Alzheimer disease (pooled RR, 1.20 [95% CI, 1.03–1.41]), and vascular dementia (pooled RR, 1.23 [95% CI, 1.04–1.46]).[349]
- In a systematic review of racial disparities in dementia prevalence and incidence in the United States that included 114 studies, the prevalence of dementia for those ≥65 years of age ranged from 7.2% to 20.9% in cohorts of Black individuals. Dementia prevalence was 6.3% in Japanese American people, 12.9% in Caribbean Hispanic American people, and 12.2% in Guamanian Chamorro people. The annual incidence of dementia for Black people ≥65 years of age (mean, 2.6%) and Caribbean Hispanic people (mean, 3.6%) was significantly higher than for Mexican American, Japanese American, and non-Latino White people (0.8%–2.7%; $P<0.001$).[350]
- Data from a nationally representative population-based longitudinal survey of US adults, the Health and Retirement Study, provide evidence that the prevalence of dementia among those ≥65 years of age declined significantly in the United States from 11.6% in 2000 to 8.8% in 2012 ($P<0.001$).[351]
- Estimated US spending on dementias more than doubled from $38.6 billion (95% CI, $34.1–42.8 billion) in 1996 to $79.2 billion (95% CI, $67.6–$90.8 billion) in 2016. Spending on dementias was among the top 10 health care costs in the United States in 2016.[352]

Table 15-1. Stroke in the United States

Population group	Prevalence, 2015–2018: age ≥20 y	New and recurrent attacks, 1999, all ages	Mortality, 2018: all ages*	Hospital discharges, 2016: all ages	Cost, 2016–2017
Both sexes	7 600 000 (2.7% [95% CI, 2.4%–3.1%])	795 000	147 810	874 000	$49.8 Billion
Males	3 500 000 (2.6%)	370 000 (46.5%)†	62 844 (42.5%)†	438 000	…
Females	4 100 000 (2.8%)	425 000 (53.5%)†	84 966 (57.5%)†	436 000	…
NH White males	2.3%	325 000‡	45 741	…	…
NH White females	2.5%	365 000‡	64 789	…	…
NH Black males	4.1%	45 000‡	8851	…	…
NH Black females	4.9%	60 000‡	10 622	…	…
Hispanic males	2.4%	…	5260	…	…
Hispanic females	1.7%	…	5986	…	…
NH Asian males	1.4%	…	2524§	…	…
NH Asian females	1.0%	…	3043§	…	…
NH American Indian or Alaska Native	…	…	703	…	…

CIs have been added for overall prevalence estimates in key chapters. CIs have not been included in this table for all subcategories of prevalence for ease of reading.

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 Hispanic and non-Hispanic people. Estimates for White people include other non-Black races.

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

Sources: Prevalence: Unpublished National Heart Lung and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey, 2015 to 2018.[353] Percentages for racial/ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2018 US population. Incidence: Greater Cincinnati/Northern Kentucky Stroke Study and National Institutes of Neurological Disorders and Stroke data for 1999 provided on July 9, 2008. US estimates compiled by NHLBI. See also Kissela et al.[354] Data include children. Mortality: Unpublished NHLBI tabulation using National Vital Statistics System.[218] These data represent underlying cause of death only. Mortality for NH Asian people includes Pacific Islander people. Hospital discharges: Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2017.[307] Data include those inpatients discharged alive, dead, or status unknown. Cost: Unpublished NHLBI tabulation using Medical Expenditure Panel Survey.[325] Data include estimated direct and indirect costs for 2016 to 2017 (average annual).

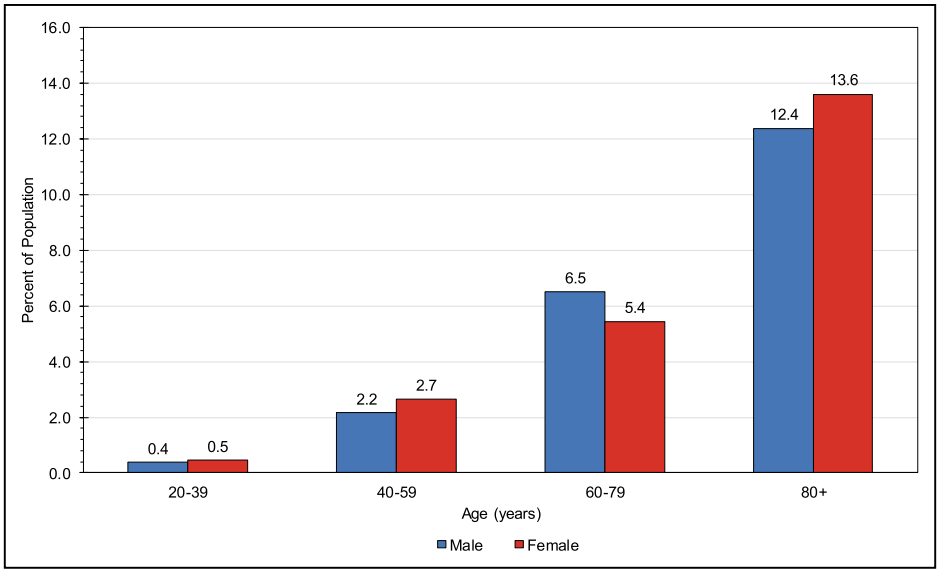

Chart 15-1. Prevalence of stroke by age and sex, United States (NHANES, 2015–2018).
NHANES indicates National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2015 to 2018.[353]

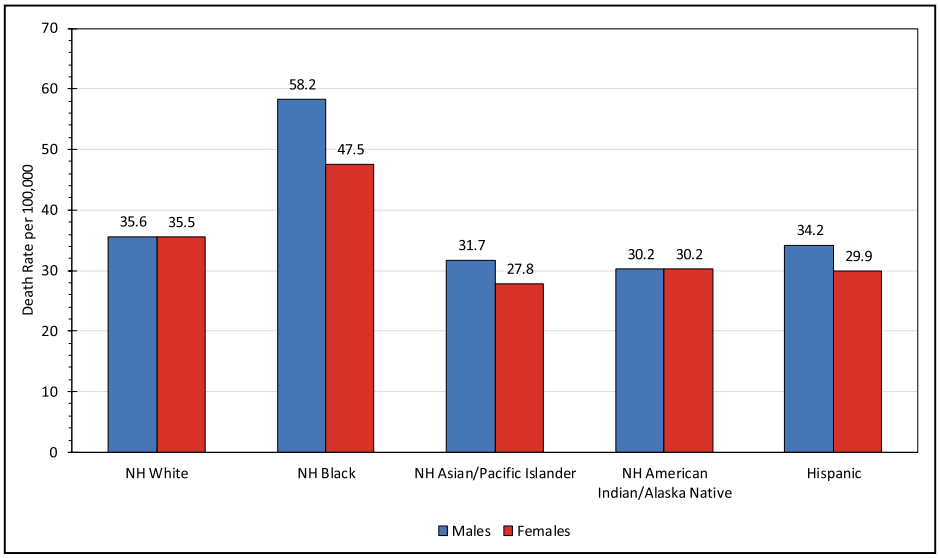

Chart 15-2. Age-adjusted death rates for stroke by sex and race/ethnicity, United States, 2018.
Death rates for the American Indian or Alaska Native and Asian or Pacific Islander populations are known to be underestimated. Stroke includes *International Classification of Diseases, 10th Revision* codes I60 through I69 (cerebrovascular disease). Mortality for NH Asian people includes Pacific Islander people.
NH indicates non-Hispanic.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[217]

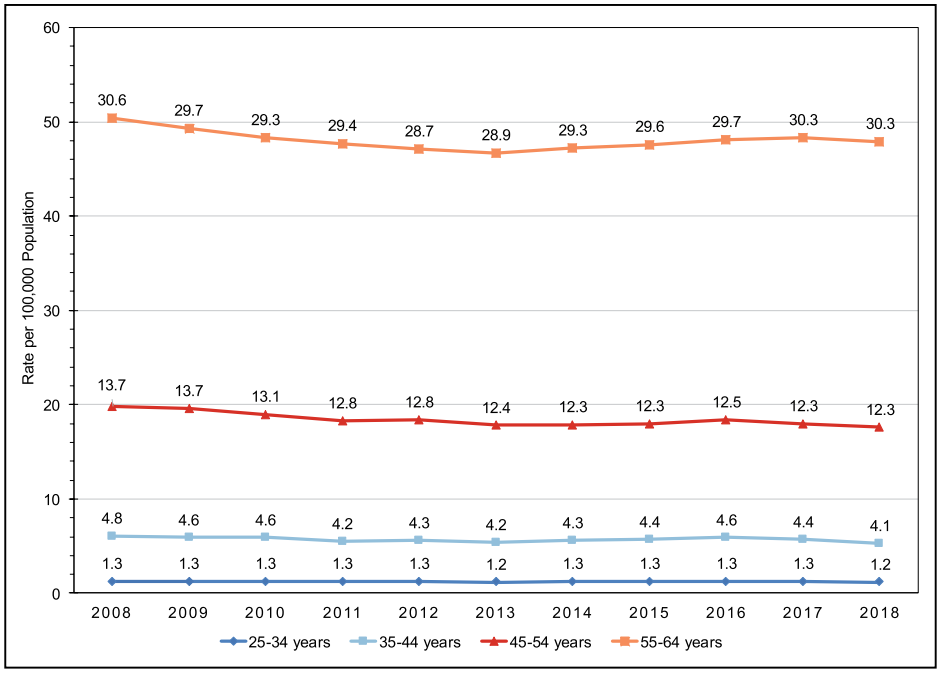

Chart 15-3. Crude stroke mortality rates among young US adults (25–64 years of age), 2008 to 2018.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[217]

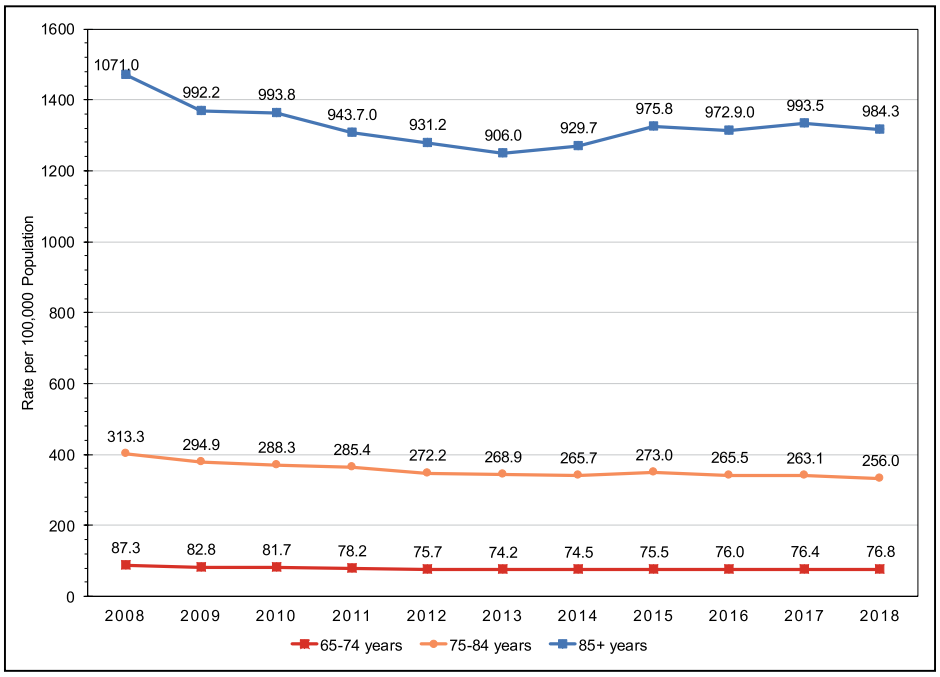

Chart 15-4. Crude stroke mortality rates among older US adults (≥65 years of age), 2008 to 2018.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[217]

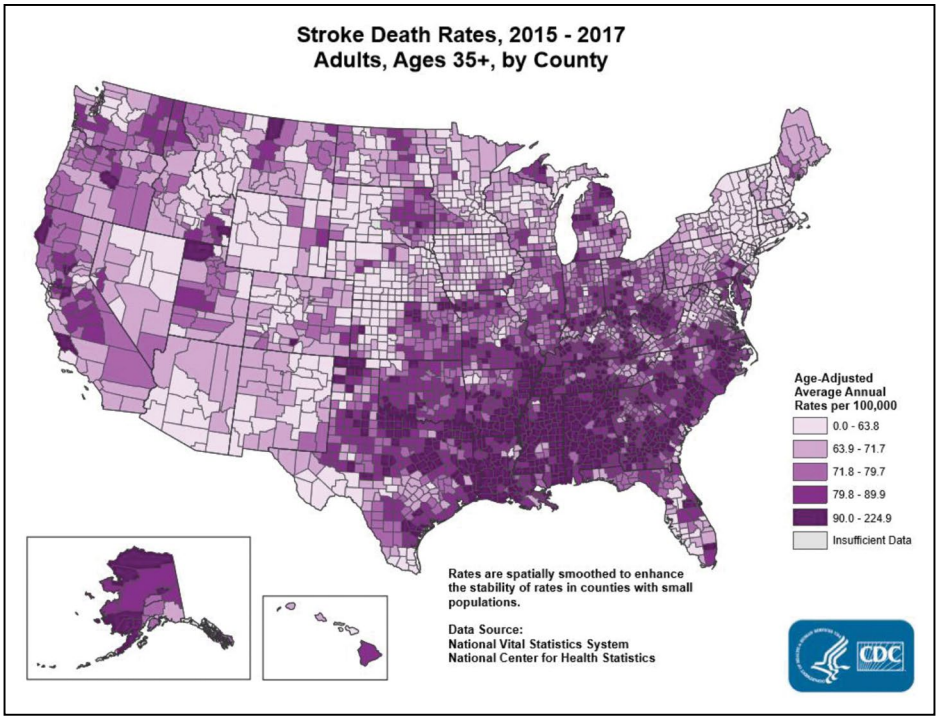

Chart 15-5. Stroke death rates, 2015 through 2017, among adults ≥35 years of age, by US county.
Rates are spatially smoothed to enhance the stability of rates in counties with small populations. *International Classification of Diseases, 10th Revision* codes for stroke: I60 through I69.
Source: Reprinted from National Vital Statistics System.[355]

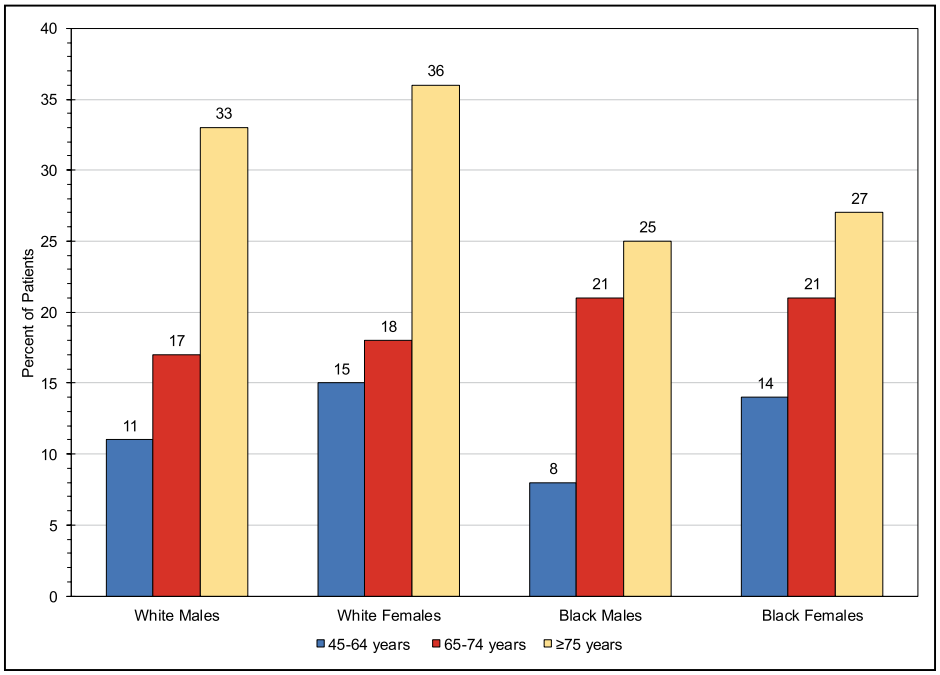

Chart 15-6. Probability of death within 1 year after first stroke, United States, 1995 to 2011.*
*Data years 1986 to 2011 for those who were 45 to 64 years of age because of the small number of events.
Source: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using pooled data 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 NHLBI.

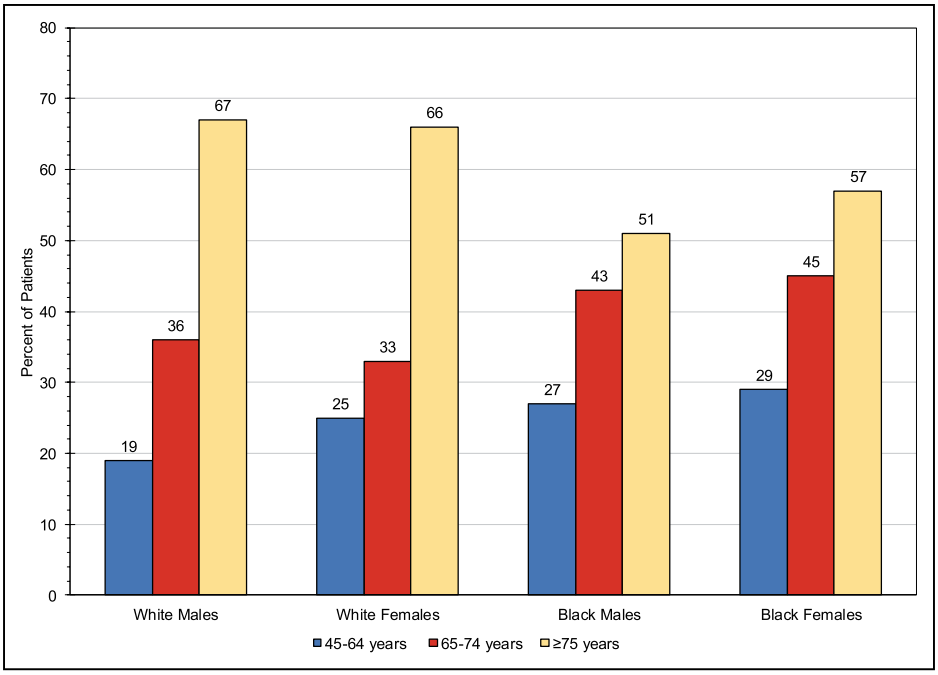

Chart 15-7. Probability of death within 5 years after first stroke, United States, 1995 to 2011.*
*Data years 1986 to 2011 for those who were 45 to 64 years of age because of the small number of events.
Source: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using pooled data 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 NHLBI.

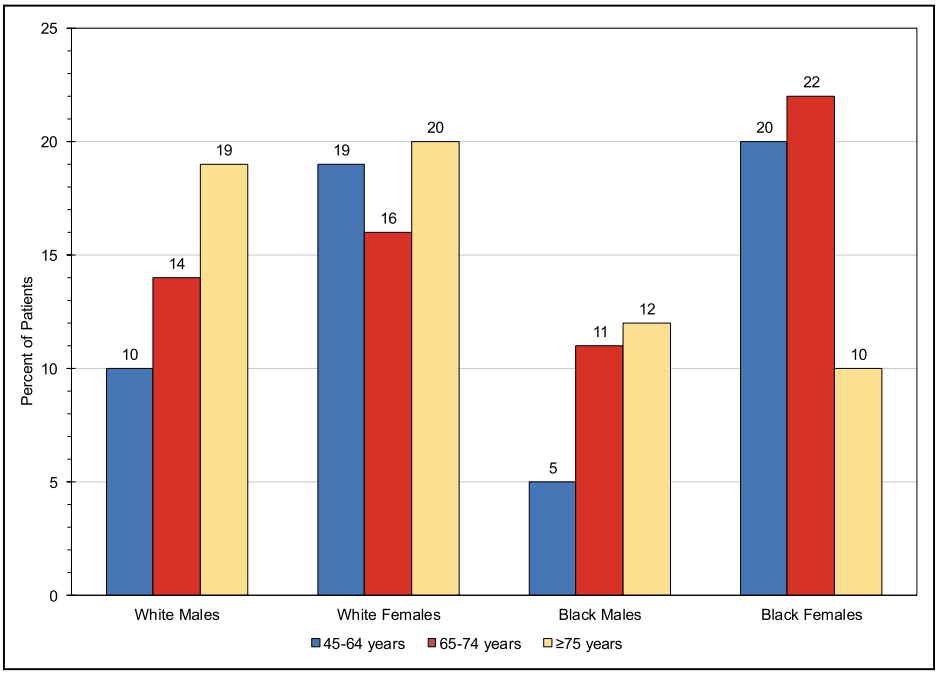

Chart 15-8. Probability of recurrent stroke in 5 years after first stroke, United States, 1995 to 2011.*
*Data years 1986 to 2011 for those who were 45 to 64 years of age because of the small number of events.
Source: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using pooled 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 NHLBI.

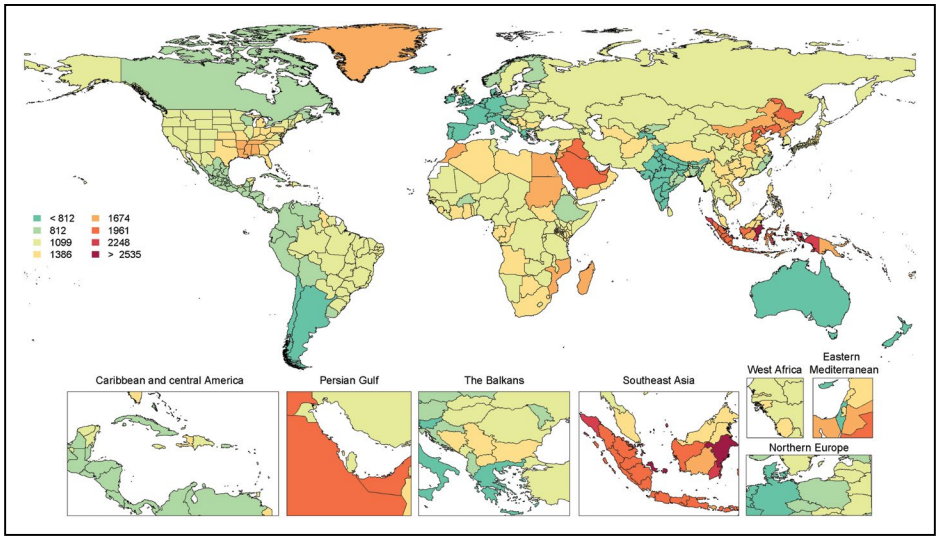

Chart 15-9. Age-standardized global prevalence rates of total stroke (all subtypes) per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[42] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[356]

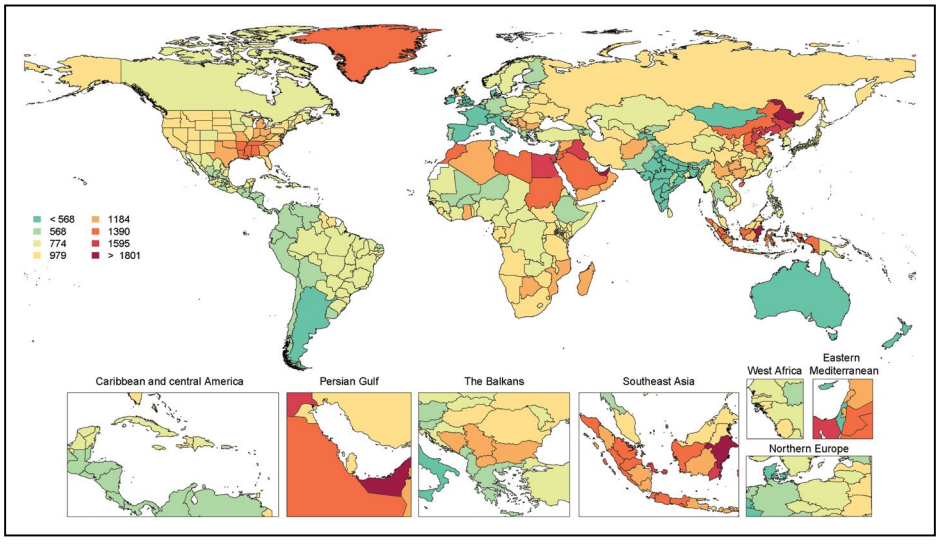

Chart 15-10. Age-standardized global prevalence rates of ischemic stroke per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[42] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[356]

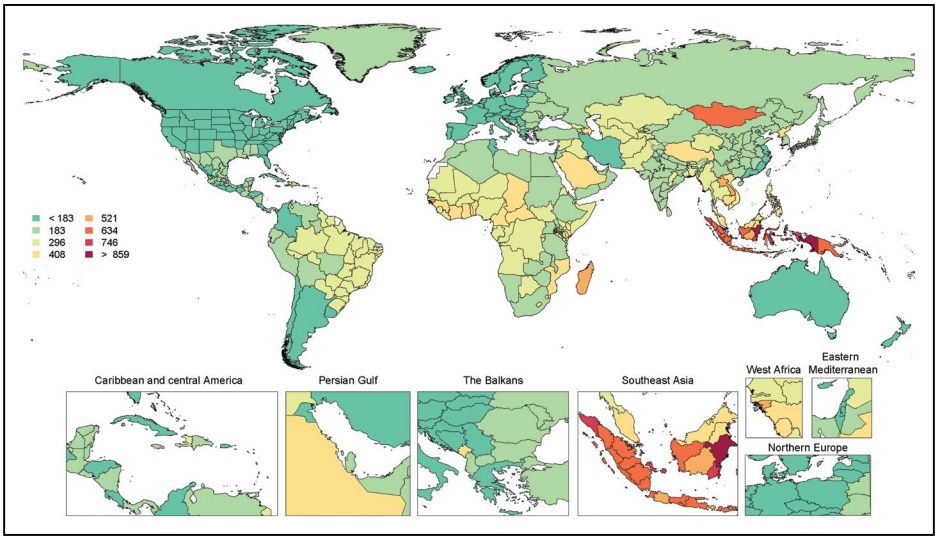

Chart 15-11. Age-standardized global prevalence rates of intracerebral hemorrhage per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[42] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[356]

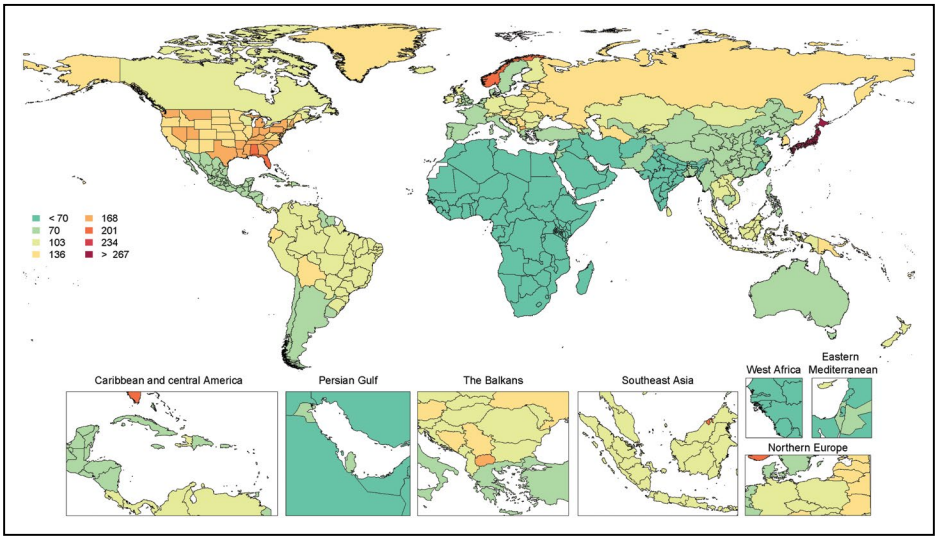

Chart 15-12. Age-standardized global prevalence rates of subarachnoid hemorrhage per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[42] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[356]

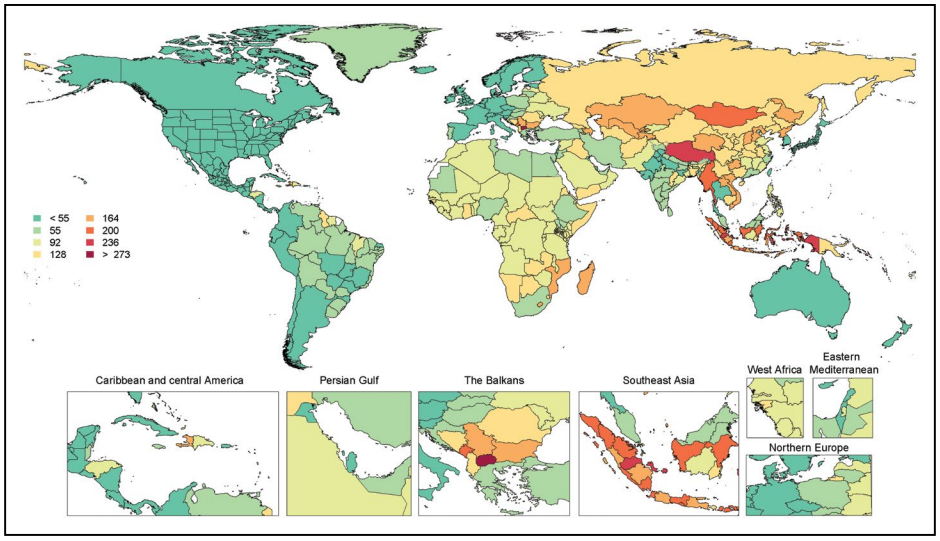

Chart 15-13. Age-standardized global mortality rates of total stroke (all subtypes) per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[42] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[356]

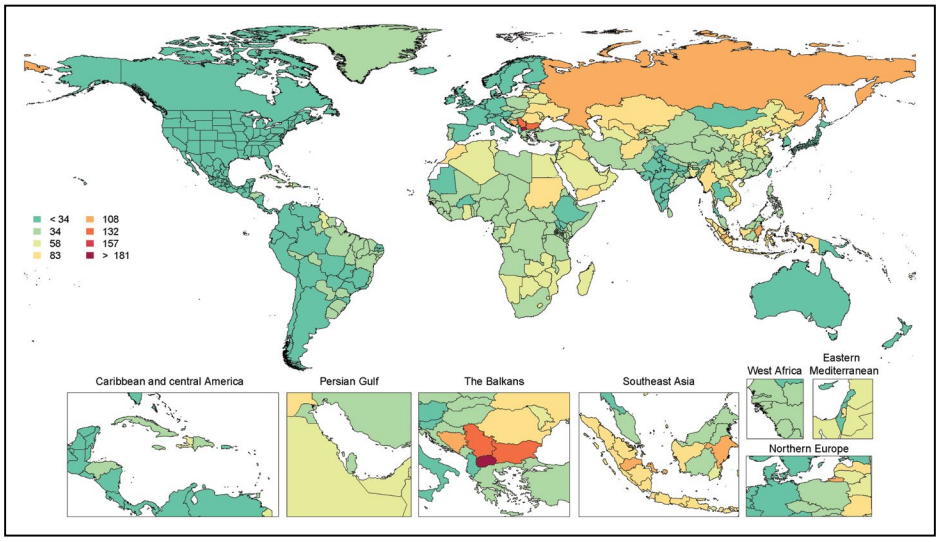

Chart 15-14. Age-standardized global mortality rates of ischemic stroke per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[42] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website. [356]

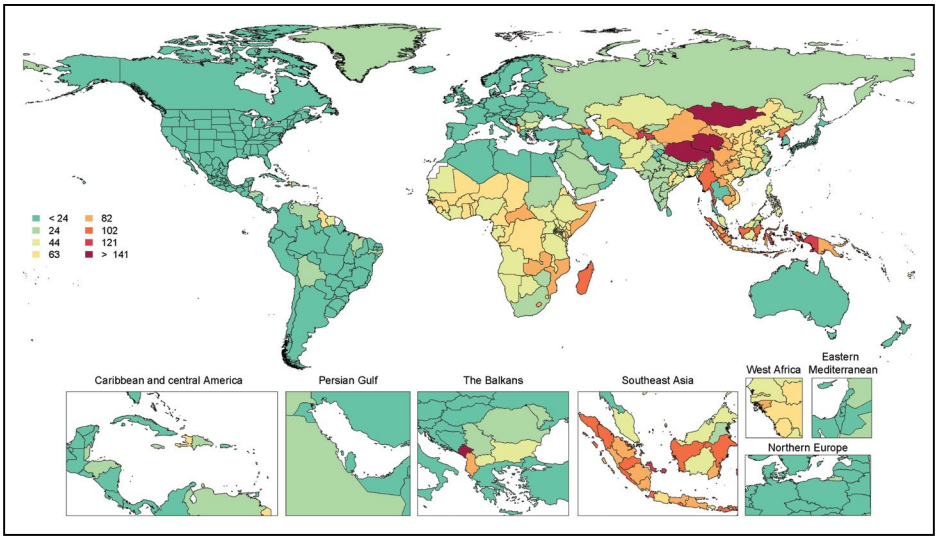

Chart 15-15. Age-standardized global mortality rates of intracerebral hemorrhage per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[42] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[356]

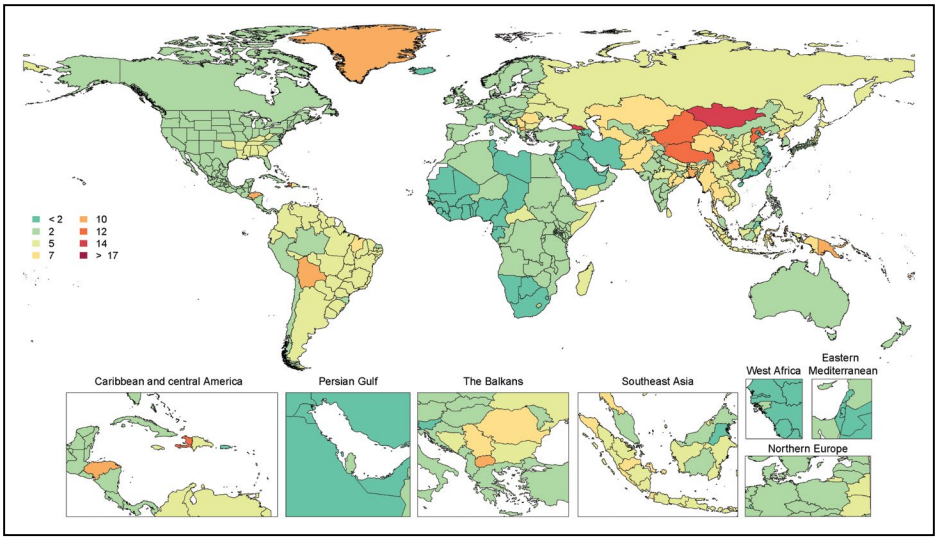

Chart 15-16. Age-standardized global mortality rates of subarachnoid hemorrhage per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[42] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[356]

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16. CONGENITAL CARDIOVASCULAR DEFECTS AND KAWASAKI DISEASE

See Tables 16-1 through 16-3 and Charts 16-1 through 16-7

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Congenital Cardiovascular Defects *ICD-9* 745 to 747; *ICD-10* Q20 to Q28.

CCDs arise from abnormal or incomplete formation of the heart, valves, and blood vessels. CCDs range in severity from minor abnormalities not requiring treatment to complex malformations, including absent, hypoplastic, or atretic portions of the heart. Thus, there is significant variability in their presentation and requirements for care affecting morbidity, mortality, and health care costs in both 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] However, health outcomes generally continue to improve for CCDs, including survival, which has led to a population shift into adulthood for these patients.

Abbreviations Used in Chapter 16

ACS	acute coronary syndrome
AF	atrial fibrillation
AHA	American Heart Association
AMI	acute myocardial infarction
aOR	adjusted odds ratio
ASD	atrial septal defect
CABG	coronary artery bypass graft
CCD	congenital cardiovascular defect
CDC	Centers for Disease Control and Prevention
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research
CI	confidence interval
GBD	Global Burden of Disease Study
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HF	heart failure
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
IE	infective endocarditis
IHD	ischemic heart disease
IQR	interquartile range
IRR	incidence rate ratio

(*Continued*)

Abbreviations Used in Chapter 16 Continued

IVIG	intravenous immunoglobulin
KD	Kawasaki disease
NH	non-Hispanic
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NVSS	National Vital Statistics System
OR	odds ratio
PAH	pulmonary arterial hypertension
PTB	preterm birth
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 16-1 through 16-3)

The 32nd Bethesda Conference estimated that the total number of adults living with CCDs in the United States in 2000 was 800 000.[1] In 2010, the estimated prevalence of CCDs in all age groups was 2.4 million (Table 16-1). The annual birth prevalence of CCDs ranged from 2.4 to 13.7 per 1000 live births (Table 16-2). In the United States, 1 in 150 adults is expected to have some form of congenital heart defect, including a range from minor lesions such as bicuspid aortic valve to severe CCDs such as HLHS.[6] 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 16-3). 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.[7] The expected growth rates of the congenital heart defects population vary from 1%/y to 5%/y, depending on age and the distribution of lesions.[8]

Estimates of the distribution of lesions in the CCD population using available data vary on the basis of 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

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

addition, there would be 3.0 million people alive with bicuspid aortic valves.[8] 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.[8] 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.[8]

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.[9] The overall birth prevalence of CCDs at the Bhabha Atomic Research Center Hospital in Mumbai, India, from 2006 through 2011 was 13.28 per 1000 live births.[10]

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 estimating birth prevalence and population prevalence challenging. 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,[11] pulse oximetry,[12] and echocardiography during infancy.

Overall Birth Prevalence (See Table 16-2)

- According to population-based data from the Metropolitan Atlanta Congenital Defects Program (Atlanta, GA), a CCD occurred in 1 of every 111 births (1995–1997) to 125 births (1998–2005) (live, still, or >20 weeks' gestation). Some defects showed variations by sex and racial distribution.[13]
- According to population-based data from Alberta, Canada, CCDs had a total birth prevalence of 12.42 per 1000 total births (live, still, or >20 weeks' gestation).[14]
- 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 16-2).
- In Europe, all infants undergoing cardiac intervention in England and Wales from 2005 to 2010 were identified through a national registry, and CCD incidence was shown to be higher in Asian and Black individuals than in the reference population of White individuals (IRR, 1.5 for Asian individuals [95% CI, 1.4–1.7] and 1.4 for Black individuals [95% CI, 1.3–1.6]).[15]

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), atrioventricular septal defect (0.47 per 1000 births), and HLHS (0.23 per 1000 births).[16,17]
- 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; atrioventricular septal defect, 0.4 per 1000 births; and TGA (0.2 per 1000 births).[13]
- Bicuspid aortic valve occurs in 13.7 of every 1000 people; these defects vary in severity, but aortic stenosis and regurgitation can progress throughout life.[18]

Risk Factors

- Numerous genetic and nongenetic exposure risk factors are thought to contribute to CCDs.[19,20]
- 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.[21]
- 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%).[22]
- Known maternal risks include smoking[23,24] 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,[25] and septal defects (particularly for heavy smokers [≥25 cigarettes daily]).[26] Maternal smoking might account for 1.4% of all congenital heart defects.
- Exposure to secondhand smoke has also been implicated as a risk factor.[27]
- 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]).[28]
- Maternal binge drinking[29] 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 (aOR, 12.65).[29]

- Maternal obesity is associated with CCDs. A meta-analysis of 14 studies of females without gestational diabetes showed that infants born to mothers who were moderately and severely obese had 1.1 and 1.4 times greater risk of CCDs, respectively, than infants born to normal-weight mothers.[30–32] 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.[31]
- Maternal diabetes, including gestational diabetes, 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).[33,34] Pregestational diabetes has been associated with CCDs, specifically TOF.[35]
- Preeclampsia is considered a risk factor for CCDs, although not critical defects.[36]
- Folate deficiency is a well-documented risk for congenital malformations, including CCDs, and folic acid supplementation is routinely recommended during pregnancy.[19] 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 secundum ASD (OR, 0.63 [95% CI, 0.40–0.98]).[36] 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).[37]
- An observational study from Quebec, Canada, of 1.3 million births from 1990 to 2005 found a 6%/y 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.[38]
- Maternal infections, including rubella and chlamydia, have been associated with congenital heart defects.[39,40]

Screening

It has been almost a decade since pulse oximetry screening for CCDs was instituted as part of the US uniform screening panel for newborns and endorsed by the AHA and the American Academy of Pediatrics.[41,42] At present, all 50 states and the District of Columbia have laws or regulations mandating newborn screening for identification of previously unidentified CCDs,[43] and several studies have demonstrated the benefit of such screening.[44–46]

- 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).[47]
- A meta-analysis of 13 studies that included 229 421 newborns found that 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%).[48]
- An 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.[49]
- Reports outside of the United States have shown similar performance of pulse oximetry screening in identifying critical CCDs,[50] with a sensitivity and specificity of pulse oximetry screening for critical congenital heart defects of 100% and 99.7%, respectively.

Social Determinants

Several studies have demonstrated variations in CCD outcomes based on factors such as ethnicity, race, and socioeconomics.[15,51–54]

- In a review of 15 533 infants with CCD born between 2004 and 2013, survival among infants with univentricular CCDs was improved for those whose fathers were >35 years of age (71.6% [95% CI, 63.8%–80.3%]) compared with those who were younger (59.7% [95% CI, 54.6%–65.2%]), and factors associated with survival in biventricular CCDs included maternal education, race or ethnicity, and marital status.[51]
- A single-center cross-sectional study in China reviewed 2037 survivors of critical congenital HD 2 to 12 years of age between 2012 and 2015. Health-related quality of life mean scores were significantly lower in the low socioeconomic group than in the medium and high socioeconomic groups: total generic scores, 71.2±7.9 versus 75.0±8.0 and 76.0±7.9, respectively (P<0.001); psychosocial functioning, 70.8±9.0 versus 74.4±8.4 and 75.3±8.4 (P<0.001); physical functioning, 71.6±0.4 versus 76.0±9.7 and 77.1±9.4 (P<0.001); heart symptoms, 71.9±11.6 versus 75.7±11.0 and 76.8±10.3 (P<0.001); and cognitive problems, 65.4±11.1 versus 69.4±12.1 and 74.6±13.6 (P<0.001).[55]
- 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 (4.32 per 1000); patent ductus arteriosus and ASD contributed to the increased prevalence.[56]

Genetics and Family History

- CCDs can have a heritable component. There is a greater concordance of CCDs in monozygotic than dizygotic twins.[57] Among parents with ASD or VSD, 2.6% and 3.7%, respectively, have children who are similarly affected, 21 times the estimated population frequency.[58] However, the majority of CCDs occur in families with no other history of CCDs, which supports the possibility of de novo genetic events; in fact, a large study of next-generation sequencing in CCDs suggests that 8% of cases are attributable to de novo variation.[59] The genetic basis of CCDs has been reviewed.[60]
- A report from Kaiser Permanente data showed that monochorionic twins were at particular increased risk for CCDs (RR, 11.6 [95% CI, 9.2–14.5]).[61]
- Large chromosomal abnormalities are found in 8% to 10% of individuals with CCDs.[59] For example, aneuploidies such as trisomy 13, 18, and 21 account for 9% to 18% of CCDs.[62] The specific genes responsible for CCDs that are disrupted by these abnormalities are difficult to identify. Studies suggest that *DSCAM* and *COL6A* contribute to Down syndrome–associated CCDs.[63]
- Copy number variants contribute to 3% to 25% of CCDs that occur as part of a syndrome and to 3% to 10% of isolated CCDs and have been shown to be overrepresented in larger cohorts of patients with specific forms of CCDs.[64] The most common copy number variant is del22q11, which encompasses the *TBX1* (T-box transcription factor) gene and presents as DiGeorge syndrome and velocardiofacial syndrome. Others include del17q11, which causes William syndrome.[65]
- Point mutations in single genes are found in 3% to 5% of CCDs[59] and include mutations in a core group of cardiac transcription factors (*NKX2.5*, *TBX1*, *TBX2*, *TBX3*, *TBX5*, *GATA4* and *MEF2*),[65–67] *ZIC3*, and the *NOTCH1* gene (dominantly inherited and found in ≈5% of cases of bicuspid aortic valve) and related NOTCH signaling genes.[68]
- Consortia studies have allowed analysis of specific subtypes of CCD through aggregation across centers. For example, a genome-wide study of conotruncal heart defects identified 8 candidate genes (*ARF5*, *EIF4E*, *KPNA1*, *MAP4K3*, *MBNL1*, *NCAPG*, *NDFUS1*, and *PSMG3*), 4 of which had not been previously associated with heart development. [69] Another study of nonsyndromic TOF in 829 patients with TOF found rare variants in *NOTCH1* and *FLT4* in almost 7% of patients with TOF.[70]
- Rare monogenic CCDs also exist, including monogenic forms of ASD, heterotaxy, severe mitral valve prolapse, and bicuspid aortic valve.[65]
- Complications related to CCD also may have a genetic component; whole-exome sequence study identified *SOX17* as a novel candidate gene for PAH in patients with CCD patients.[71]
- There is no exact consensus currently on the role, type, and utility of clinical genetic testing in people with CCDs,[65] 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]
- The diagnostic yield for CCD genetic panels in familial, nonsyndromic cases is 31% to 46% and is even lower in nonfamilial disease.[72,73] Use of whole-exome genetic testing has been shown to improve rates of detection.[74]
- A Pediatric Cardiac Genomics Consortium has been developed to provide and better understand phenotype and genotype data from large cohorts of patients with CCDs.[75]

Mortality
(See Table 16-1 and Charts 16-1 through 16-5)

In 2018:

- Mortality related to CCDs was 2903 deaths (Table 16-1), a 15.0% decrease from 2008 (unpublished NHLBI tabulation using NVSS[76]).
- CCDs (*ICD-10* Q20–Q28) were the most common cause of infant deaths resulting from birth defects (*ICD-10* Q00–Q99); 21.8% of infants who died of a birth defect had a heart defect (*ICD-10* Q20–Q24; unpublished NHLBI tabulation using NVSS[76]).
- The age-adjusted death rate (deaths per 100 000 people) attributable to CCDs was 0.9, a 18.2% decrease from 2008 (unpublished NHLBI tabulation using CDC WONDER[77]).
- 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.[78]
- Death rates attributed to CCDs decrease as gestational age advances toward 40 weeks.[79] In-hospital mortality of infants with major CCDs is independently associated with late-PTB (OR, 2.70 [95% CI, 1.69–4.33]) compared with delivery at later gestational ages.[80,81]

- 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, with higher complication rates and longer lengths of stay.[82] 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.[83]
- 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),[84] 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%).[85] The mortality rate was 8.6% (95% CI, 8.2%–9.1%) for neonates, 2.8% (95% CI, 2.6%–3.0%) for infants, 1.0% (95% CI, 0.9%–1.1%) for children (>1–18 years of age), and 1.5% (95% CI, 1.3%–1.8%) for adults (>18 years of age).[85]
- Another 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, increased mortality in CCD patients remains 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%).[86]
- 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.[87]
- In Mexico, 70 741 deaths were attributed to CCD during the years 2000 to 2015, with the standardized mortality rates increased from 3.3 to 4 per 100 000 individuals and mortality rates increased in the age group <1 year of age from 114.4 to 146.4 per 100 000 live births.[88]
- 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.[89]
- Trends in overall age-adjusted death rates attributable to CCDs showed a decline from 1999 to 2018 (Chart 16-1); this varied by race/ethnicity and sex (Charts 16-2 and 16-3). During this time, there was an overall decline in the age-adjusted death rates attributable to CCDs in NH Black, NH White, and Hispanic people (Chart 16-2), although death rates increased between 2017 and 2018 for NH White and NH Black people. From 1999 to 2018, death rates declined in both males and females (Chart 16-3) and in age groups 1 to 4, 5 to 14, 15 to 24, and ≥25 years of age (Chart 16-4) in the United States.
- CCD-related mortality varies substantially by age, with children 1 to 4 years of age demonstrating higher mortality rates than any age group other than infants from 1999 to 2018 (Chart 16-4).
- The US 2018 age-adjusted death rate (deaths per 100 000 people) attributable to CCDs was 1.01 for NH White males, 1.39 for NH Black males, 0.80 for Hispanic males, 0.83 for NH White females, 1.06 for NH Black females, and 0.68 for Hispanic females (Chart 16-5). Infant (<1 year of age) mortality rates were 27.8 for NH White infants, 42.8 for NH Black infants, and 25.6 for Hispanic infants (unpublished NHLBI tabulation using CDC WONDER[77]).
- Mortality after congenital heart surgery also differs between races/ethnicities, even after adjustment for access to care. One study found that a higher risk of in-hospital mortality was associated with non-White race (OR, 1.36 [95% CI, 1.19–1.54]) and Medicaid insurance (OR, 1.26 [95% CI, 1.09–1.46]).[90] One center's experience suggested that race was independently associated with neonatal surgical outcomes only in patients with less complex CCDs.[91] Another center found that a home monitoring program can reduce mortality even in this vulnerable population.[92]
- Female infants with high-risk CCDs had a 39% higher adjusted mortality compared with males.[92,93] According to CDC multiple-cause death data from 1999 to 2006, sex differences in mortality over time varied with age. Between 18 and 34 years of age, mortality over time decreased significantly in females but not in males.[94]
- 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%.[95] 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%.[96]
- 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%; $P<0.0001$).[97] 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 48828 patient-years of follow-up, missed appointments and delay in care were predictors of mortality.[98]

Complications

- Data from the HCUP's Kids' Inpatient Database from 2000, 2003, and 2006 show that male children had more CCD surgeries in infancy, more high-risk surgeries, and more procedures to correct multiple cardiac defects.[92,93]
- Long-term effects of CCDs include arrhythmias, IE, and HF.[99–101]
- Individuals with congenital HD are at increased risk of AF. In an analysis in Sweden including 21982 patients with congenital HD and 219816 control subjects, risk of developing AF was 22 times higher (HR, 22.0 [95% CI, 19.3–25.1]) in those with congenital HD compared with referents without congenital HD.[102] By age 42, ≈8% of patients with congenital HD had been diagnosed with AF.

Health Care Use: Hospitalizations (See Table 16-1)

- In 2016, the total number of hospital discharges for CCDs for all ages was 45000 (Table 16-1).
- Hospitalization of infants with CCDs is common; one-third of patients with congenital heart defects require hospitalization during infancy,[103,104] often in an ICU.
- Adults with CCD and HF-related admissions increased according to data from the Pediatric Health Information Systems database 2005 to 2015. A total of 562 admissions occurred at 39 pediatric hospitals, increasing from 4.1% to 6.3% ($P=0.015$) during the study period.[105] Compared with adults with non-CCD HF-related admissions, they also demonstrated increased length of stay ≥7 days (aOR, 2.5 [95% CI, 2–3.1]), incident arrhythmias (aOR, 2.8 [95% CI, 1.7–4.5]), and in-hospital mortality (aOR, 1.9 [95% CI, 1.1–3.1]).[106]

Cost

- Using HCUP 2013 NIS data, 1 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.[107]
- Among pediatric hospitalizations (0–20 years of age) in the HCUP 2012 Kids' Inpatient Database[108]:
  - 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 $51302 ($32088–$100058) in children who underwent cardiac surgery, $21920 ($13068–$51609) in children who underwent cardiac catheterization, $4134 ($1771–$10253) in children who underwent noncardiac surgery, and $23062 ($5529–$71887) in children admitted for medical treatments.
  - The mean cost of CCDs was higher in infancy ($36601) than in older ages and in those with critical congenital heart defects ($52899).
- A Canadian study published in 2017 demonstrated increasing hospitalization costs for children and adults with CCDs, particularly those with complex lesions, which appeared to be independent of inflation or length of stay.[109]
- A US study evaluating cost and length of stay in neonates with HLHS revealed significant regional differences in cost, length of stay, and mortality.[110]

Global Burden of CCDs

(See Charts 16-6 and 16-7)

- The GBD 2019 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 369 diseases and injuries in 204 countries and territories.[111] In 2019:
  - Prevalence of congenital heart anomalies was an estimated 13.3 million people.
  - There were 200000 deaths attributed to congenital heart anomalies worldwide.
  - Age-standardized mortality rates of congenital heart anomalies are lowest in high-income countries (Chart 16-6).
  - The age-standardized prevalence of congenital heart anomalies is highest in Asia (Chart 16-7).

Kawasaki Disease

ICD-9 446.1; *ICD-10* M30.3.

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. The most significant 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.[112] The cause of KD is unknown but may be an immune response to an acute infectious illness based in part on genetic susceptibilities.[113,114]

Prevalence

- KD is the most common cause of acquired HD in children in the United States and other developed countries.[115]

Incidence

- A review of HCUP/Kids' Inpatient Database for KD hospitalizations in children <18 years of age in the United States during 2009 to 2012 revealed 10 486 hospitalizations for KD of 12 678 005 total hospitalizations. The incidence of KD was estimated at 6.35 per 100 000.[116]
- The incidence was estimated 20.8 per 100 000 US children <5 years of age in 2006.[117] This was calculated from 2 databases and limited by reliance on weighted hospitalization data from 38 states.
- Boys have a 1.5-fold higher incidence of KD than girls.[117]
- Although KD can occur into adolescence (and rarely adulthood), 76.8% of US children with KD are <5 years of age.[117]
- Race-specific incidence rates indicate that KD is most common among Americans of Asian and Pacific Islander descent (30.3 per 100 000 children <5 years of age), occurs with intermediate frequency in NH Black (17.5 per 100 000 children <5 years of age) and Hispanic (15.7 per 100 000 children <5 years of age) children, and is least common in White children (12.0 per 100 000 children <5 years of age).[117]
- Geographic variation in KD incidence exists 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 of age) than in the continental United States.[118] Within Hawaii, the race-specific rates of KD per 100 000 children <5 years of age 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.[118]
- 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.[117,118]
- KD rarely recurs. Recurrences constitute 2% to 4% of total KD cases in both the United States and Japan,[119] and the 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).[120,121]
- A nationwide retrospective cohort study in Taiwan including 13 260 patients diagnosed with KD from 1997 to 2011 demonstrated a >2-fold incidence increase during the study period (28.58–60.08 per 100 000).[122]

Secular Trends

- Although the incidence of KD is rising worldwide, there has been no clear secular trend in the United States, but recent data are lacking. US hospitalizations for KD were 17.5 and 20.8 per 100 000 children <5 years of age in 1997 and 2006, respectively, but the test for linear trend was not significant.[117]

Genetics/Family History

- Approximately 1% of KD cases have a positive family history of KD. Among siblings of patients with KD, the RR of KD is ≈10-fold compared with the general population (2.1% rate within 1 year of index case onset). Among identical twins, concordance is ≈13%.[115]
- A variety of genetic variants have been associated with KD susceptibility or development of coronary artery lesions in KD; however, thus far, these variants have not explained differences in incidence between ancestry groups (eg, Japanese versus European).[113,123]

Treatment and Control

- Treatment of acute KD rests on diminishing the inflammatory response with IVIG, which reduces the incidence of coronary artery aneurysms (from 25% to ≈4% for aneurysms defined by absolute dimensions).[115] Aspirin is routinely used for its anti-inflammatory and antiplatelet effects, but it does not reduce the incidence of coronary artery aneurysms.
- 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 patients and less severe KD cases is not certain.[124]
- Resistance to IVIG, defined as recurrent or persistent fever ≥36 hours after completion of IVIG infusion, occurs in 10% to 20% of patients with KD. Predictive models for IVIG resistance have been developed in Asian populations but have not been useful in North American patients. Treatment of IVIG resistance is currently not standardized.[115]
- 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).[125,126]

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.[115,127]

- 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).[115] Estimates are complicated by variability in ascertainment methods (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 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.[128] Risk factors for coronary artery abnormalities include younger age, male sex, late treatment, and failure to respond to initial IVIG with defervescence.[128–131]
- 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 data from Japan.[132–134] Mortality is related to thrombosis or rupture of rapidly expanding aneurysms or, less commonly, shock or macrophage activation syndrome with multiorgan failure.[115,134,135]
- 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.[136] Findings were similar in a Japanese study of 76 patients with giant aneurysms diagnosed since 1972 and followed up through 2011 and in a Canadian study of 1356 patients with KD diagnosed in 1990 to 2007 and followed up for up to 15 years.[125,137]
- A 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).[138] 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 of age with ACS who underwent coronary angiography for suspected myocardial ischemia in San Diego, CA, from 2005 to 2009, 5% had aneurysms consistent with late sequelae of KD.[139]
- In 2018, US mortality attributable to KD was 2 patients for underlying mortality and 8 patients for all-cause mortality (unpublished NHLBI tabulation using CDC WONDER[77]).

Health Care Use

- In 2016, there were 6000 all-listed diagnoses hospital discharges for KD, with 4000 males and 2000 females (HCUP,[140] unpublished NHLBI tabulation).

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.[134,141,142]
- In Japan, the cumulative incidence of KD at 10 years of age 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.[143] With different methodology with complete capture of cases through the national health insurance program, Taiwan recorded a cumulative incidence of 2.8% by 5 years of age in 2014.[142]
- 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, Germany with 7.2 per 100 000 children <5 years of age in 2011 to 2012, and the United Kingdom and Ireland with 4.6 per 100 000 children <5 years of age in 2014 to 2015.[121,144–148]
- However, the incidence of KD is rising worldwide, with potential contributions from improved recognition, diagnosis of incomplete KD more often, and true increasing incidence.[134,142,145,148]

Table 16-1. CCDs in the United States

Population group	Estimated prevalence, 2010, all ages	Mortality, 2018, all ages*	Hospital discharges, 2016, all ages
Both sexes	2.4 million	2903	45 000
Males	…	1574 (54.2%)†	25 000
Females	…	1329 (45.8%)†	20 000
NH White males	…	937	…
NH White females	…	809	…
NH Black males	…	292	…
NH Black females	…	231	…
Hispanic males	…	254	…
Hispanic females	…	213	…
NH Asian or Pacific Islander males	…	57	…
NH Asian or Pacific Islander females	…	53	…
NH American Indian or Alaska Native	…	42	…

CCD indicates congenital cardiovascular defect; ellipses (…), 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: Prevalence: Gilboa et al.[149] Mortality: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics System.[76] These data represent underlying cause of death only. Hospital discharges: unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2016.[140] Data include those inpatients discharged alive, dead, or status unknown.

Table 16-2. Annual Birth Prevalence of CCDs in the United States, 1930 to 2010

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.

Source: Data derived from van der Linde et al[9] and Parker et al.[16]

Table 16-3. Estimated US Prevalence of CCDs and Percent Distribution by Type, 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
Atrioventricular 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; 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.[8]

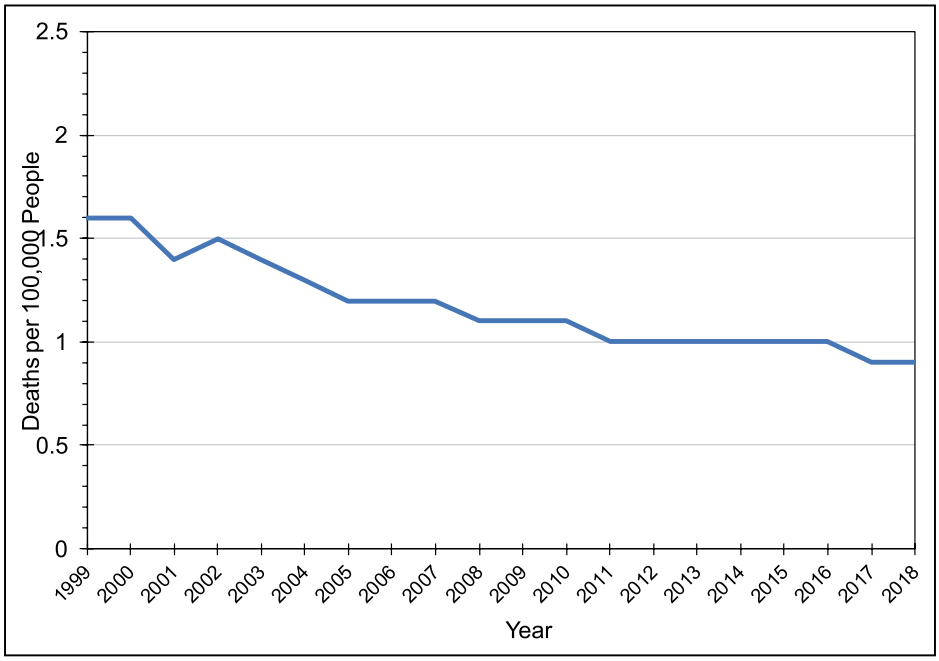

Chart 16-1. Trends in age-adjusted death rates attributable to congenital cardiovascular defects, United States, 1999 to 2018.
Source: Unpublished National Heart Lung and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[77]

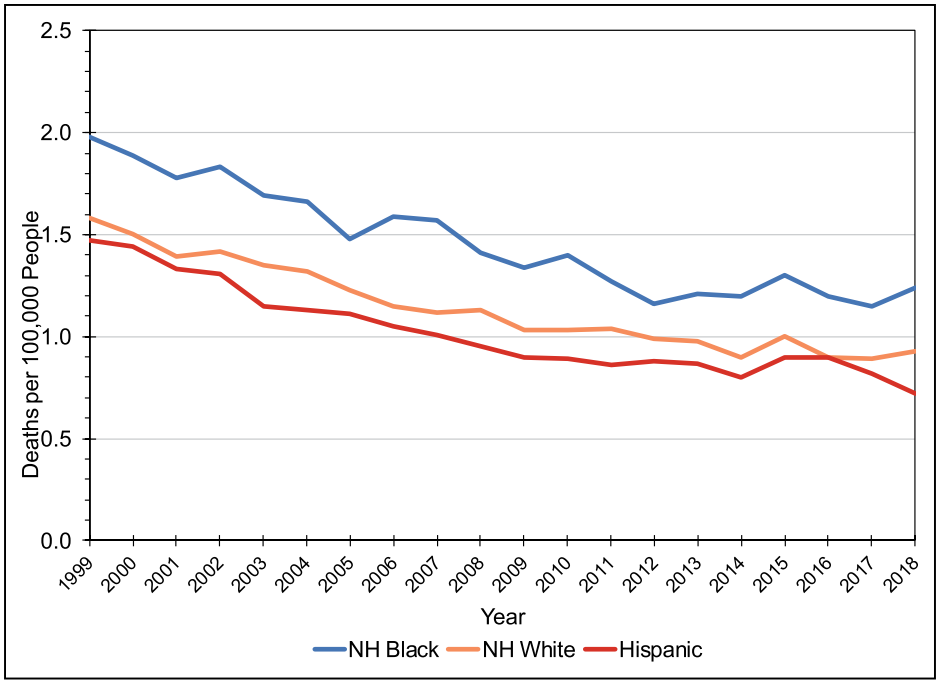

Chart 16-2. Trends in age-adjusted death rates attributable to congenital cardiovascular defects by race/ethnicity, United States, 1999 to 2018.
NH indicates non-Hispanic.
Source: Unpublished National Heart Lung and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[77]

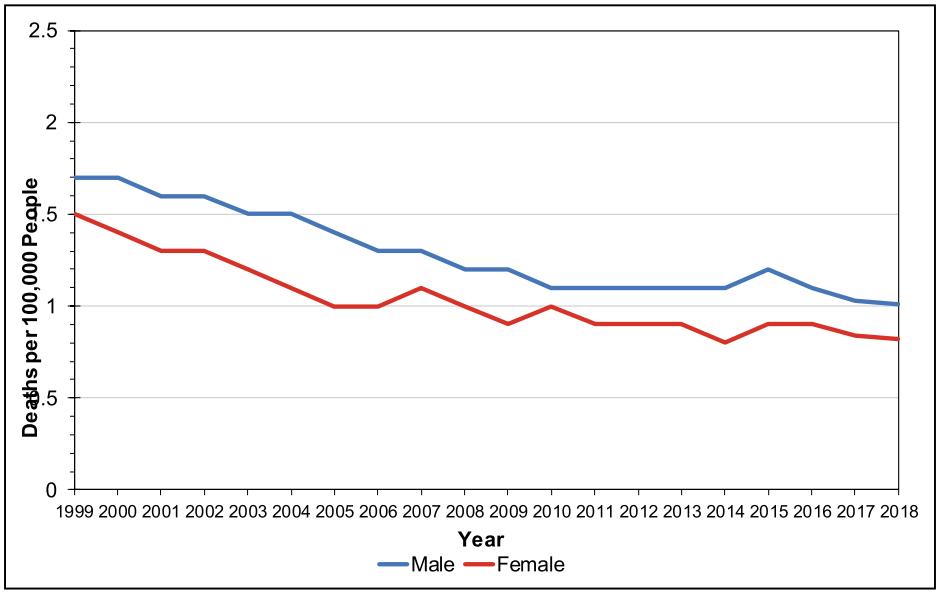

Chart 16-3. Trends in age-adjusted death rates attributable to congenital cardiovascular defects by sex, United States, 1999 to 2018.
Source: Unpublished National Heart Lung and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[77]

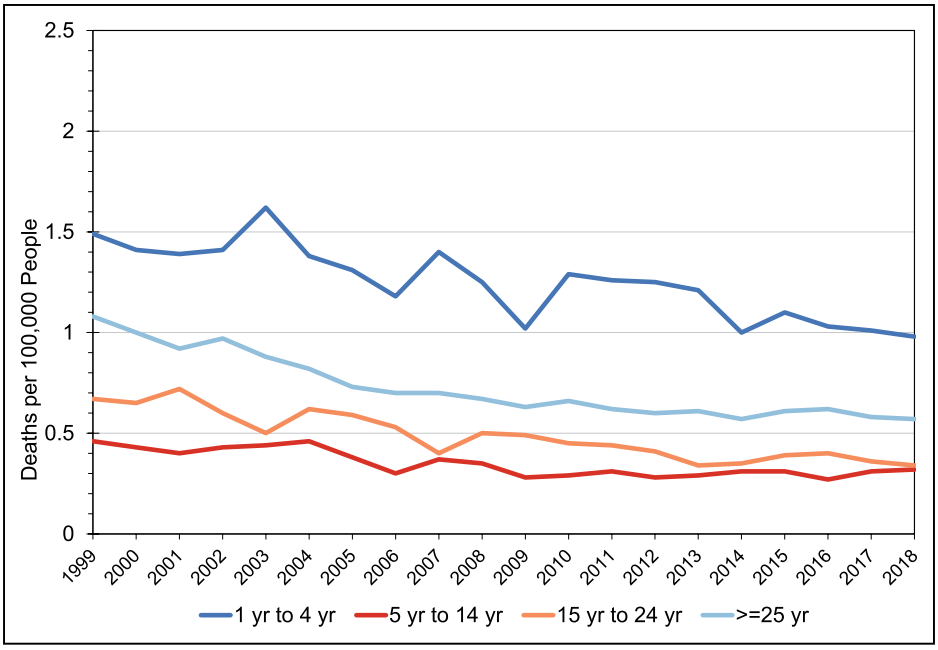

Chart 16-4. Trends in age-specific death rates attributable to congenital cardiovascular defects by age at death, United States, 1999 to 2018.
Source: Unpublished National Heart Lung and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[77]

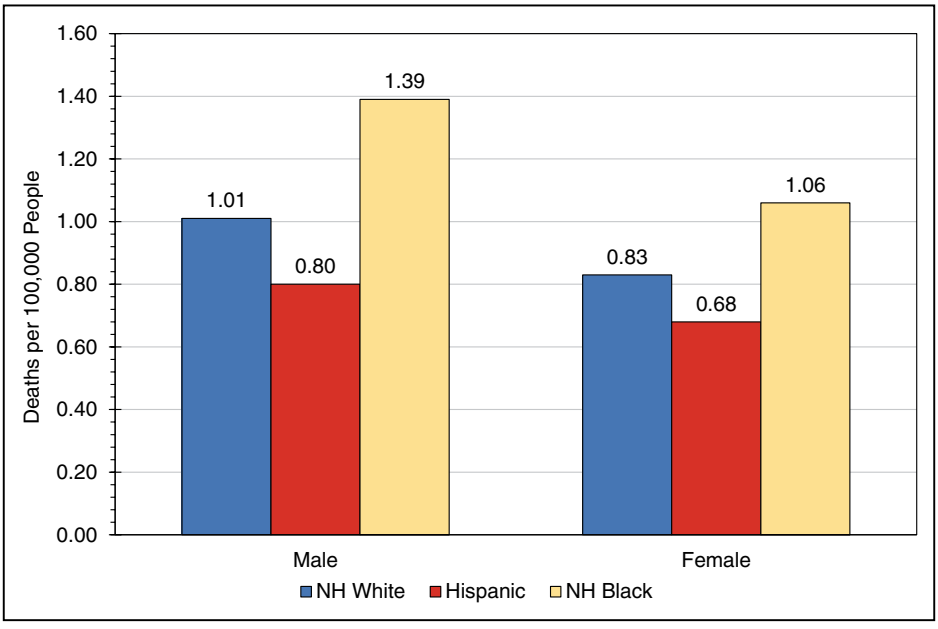

Chart 16-5. Age-adjusted death rates attributable to congenital cardiovascular defects by sex and race/ethnicity, United States, 2018.
NH indicates non-Hispanic.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[77]

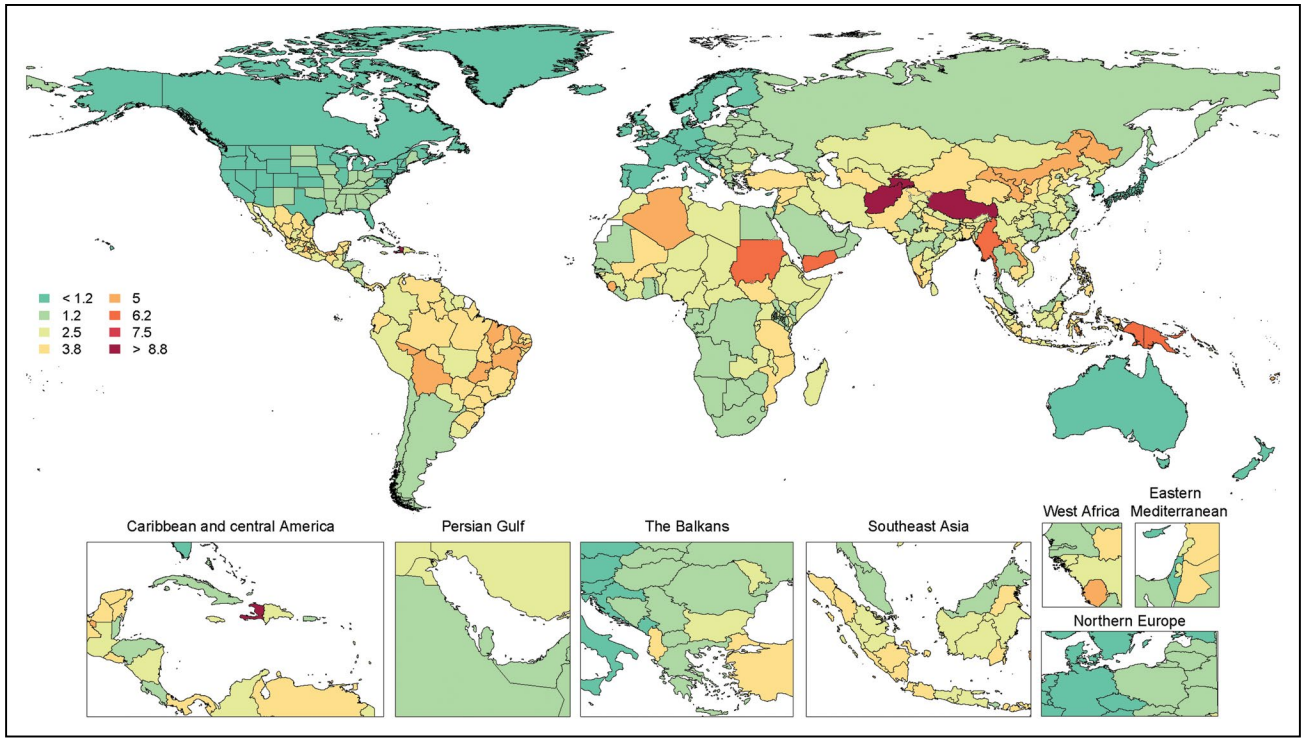

Chart 16-6. Age-standardized global mortality rates of congenital heart anomalies per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[111] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[150]

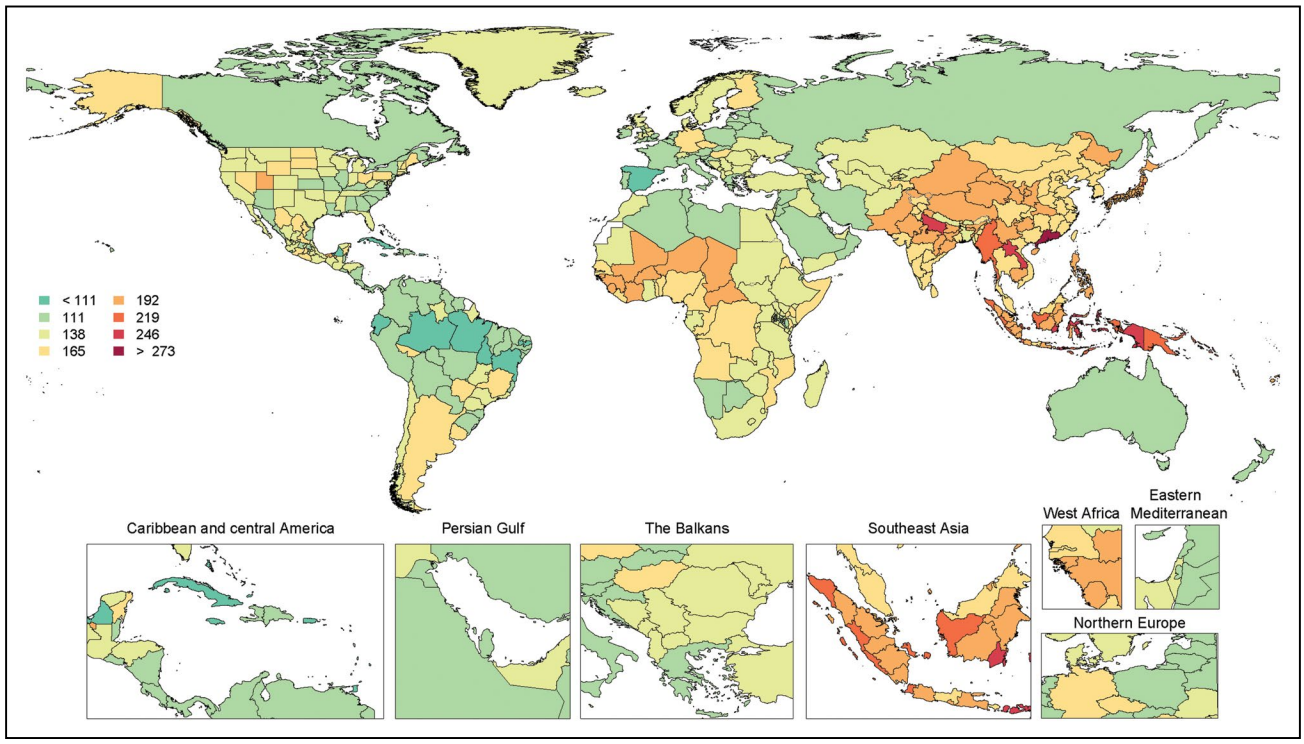

Chart 16-7. Age-standardized global prevalence rates of congenital heart anomalies per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[111] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[150]

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17. DISORDERS OF HEART RHYTHM

See Table 17-1 and Charts 17-1 through 17-9

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Arrhythmias (Disorders of Heart Rhythm)

2018: Mortality—53 895. Any-mention mortality—564 182.

Bradyarrhythmias

ICD-9 426.0, 426.1, 427.81; *ICD-10* I44.0 to I44.3, I49.5.

2018: Mortality—1345. Any-mention mortality—7409.

2016: Hospital discharges—97 000.

2016: Mean hospital charges—$74 846; in-hospital death rate—1.15%; mean length of stay—3.9 days.

Abbreviations Used in Chapter 17

ACCORD	Action to Control Cardiovascular Risk in Diabetes
AF	atrial fibrillation
aHR	adjusted hazard ratio
AIS	acute ischemic stroke
AMI	acute myocardial infarction
aOR	adjusted odds ratio
ARIC	Atherosclerosis Risk in Communities study
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
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CHADS2	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)

(*Continued*)

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Abbreviations Used in Chapter 17 Continued

CHA2DS2-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
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
CVH	cardiovascular health
DALY	disability-adjusted life-year
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
DOAC	direct oral anticoagulant
ECG	electrocardiogram
ED	emergency department
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 Study
GLORIA-AF	Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation
GRS	genetic risk score
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
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
ICU	intensive care unit
IQR	interquartile range
IRR	incidence rate ratio
Look AHEAD	Look: Action for Health in Diabetes
LVH	left ventricular hypertrophy
MESA	Multi-Ethnic Study of Atherosclerosis
MET	metabolic equivalent
MI	myocardial infarction
MRI	magnetic resonance imaging
NAMCS	National Ambulatory Medical Care Survey
NCDR	National Cardiovascular Data Registry

(*Continued*)

Abbreviations Used in Chapter 17 Continued

NCHS	National Center for Health Statistics
NEDS	Nationwide Emergency Department Sample
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
NVSS	National Vital Statistics System
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
PAF	population attributable fraction
PAR	population attributable risk
PCI	percutaneous coronary intervention
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
SDB	sleep disordered breathing
SES	socioeconomic status
SNP	single-nucleotide polymorphism
SSS	sick sinus syndrome
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
TIA	transient ischemic attack
UI	uncertainty interval
USD	US dollars
VF	ventricular fibrillation
WC	waist circumference
WHS	Women's Health Study
WPW	Wolff-Parkinson-White
YLL	years of life lost

Atrioventricular Block

Prevalence and Incidence

- In a healthy sample of participants from the ARIC study (mean, 53 years of age), the prevalence of first-degree atrioventricular block (PR-interval prolongation) 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, 45 years of age) 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 ranged between 1.9% (sex-pooled 95% CI, 1.3%–3.0%) and 3.7% (95% CI, 3.1%–4.3%) in population-based studies conducted in different European countries.[3–5]
- No population-based studies have reported the prevalence of second-degree atrioventricular block. On the basis of results from clinical series, Mobitz II second-degree atrioventricular block is rare in healthy individuals (≈0.003%), whereas Mobitz I (Wenckebach) is observed in 1% to 2% of healthy individuals <20 years of age, especially during sleep.[6]
- The prevalence of third-degree atrioventricular block in the general adult population is very low. The prevalence was 0.04% in the Icelandic Reykjavik Study[7] and 0.6% in a large sample of people with hypertension and without diabetes enrolled with Veterans Health Administration hospitals.[8]
- In an analysis of standard 12-lead ECGs from 264 324 Brazilian primary care patients, prevalence of complete atrioventricular block was 0.05%, ranging from 0.02% in individuals 20 to <40 years of age to 0.3% in people ≥80 years of age.[9]
- In 122 815 recordings from 122 454 unique patients prescribed 14-day continuous single-lead electrocardiographic monitoring with the Zio patch device between 2011 and 2013, prevalence of high-grade atrioventricular block (defined as either Mobitz II or complete heart block) was 1.2% (1486 of all tracings).[10]
- An English registry study estimated the incidence of infant complete atrioventricular block as 2.1 per 100 000 live births.[11]

Risk Factors

- In healthy individuals from MESA without CVD or its risk factors, PR interval was longer with advancing age, in males compared with females, and in Black compared with White individuals.[12]
- Although first-degree atrioventricular block and Mobitz type I second-degree atrioventricular block can occur in apparently healthy people, presence of Mobitz II second- or third-degree atrioventricular block usually indicates underlying HD, including CHD, and HF.[6]
- Reversible causes of atrioventricular block include electrolyte abnormalities, drug-induced atrioventricular block, perioperative atrioventricular block attributable to hypothermia, or inflammation near

the atrioventricular conduction system after surgery in this region.[13]
- Long sinus pauses and atrioventricular block can occur during sleep apnea. In the absence of symptoms, these abnormalities are reversible.[13,14]

Prevention

- Detection and correction of reversible causes of acquired atrioventricular block could be of potential importance in preventing symptomatic bradycardia and other complications of atrioventricular block.[13]

Complications (See Chart 17-1)

- In the FHS, PR-interval prolongation (>200 milliseconds) 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]).[15] Compared with people with a PR interval ≤200 milliseconds, those with a PR interval >200 milliseconds had an absolute increased risk per year of 1.0% for AF, 0.5% for pacemaker implantation, and 2.1% for death (Chart 17-1).
- In a large, prospective, regional French registry of 6662 patients with STEMI (2006–2013), high-degree atrioventricular block was noted in 3.5% of individuals. In 64% of cases, high-degree atrioventricular block was present on admission. Although patients with high-degree atrioventricular 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 (OR, 0.99 [95% CI, 0.60–1.66]).[16]

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, SSS accounted for 48% of implantations of first permanent pacemakers in the United States in 1997.[17,18]
- Sinus node dysfunction is commonly present with other causes of bradyarrhythmias (carotid sinus hypersensitivity in 42% of patients and advanced atrioventricular conduction abnormalities in 17%).[19,20]
- The incidence rate of SSS was 0.8 per 1000 person-years of follow-up in 2 US cohorts that included White and Black participants, ARIC and CHS.[21] The incidence increased with advancing age (HR, 1.73 [95% CI, 1.47–2.05] per 5-year increment). Investigators projected that in the United States, the number of new cases of SSS per year would rise from 78 000 in 2012 to 172 000 in 2060.[21]

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).[22]
- Idiopathic degenerative disease is probably the most common cause of sinus node dysfunction.[23]
- In 28 different studies on atrial pacing for sinus node dysfunction, median annual incidence of second- and third-degree atrioventricular block was 0.6% (range, 0%–4.5%) and overall prevalence was 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.[24]
- In the CHS and ARIC studies, factors associated with incident SSS included White (versus Black) race (Black participants: HR, 0.59 [95% CI, 0.37–0.98]), 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.[21]

Complications (See Chart 17-2)

- 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 of patients with sinus node dysfunction who had pacemaker therapy,[28] mortality among those with ventricular pacing only was 63% compared with 40% among those with DDD pacing at the 7-year follow-up.
- In 19 893 males and females >45 years of age from the ARIC and CHS cohorts, incidence of SSS 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.[13,31] 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 467 in 1993 to 616 in 2009, although overall use plateaued in 2001. 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, which increased by 102%, whereas implantation for all other indications did not increase (Chart 17-2).[33]
- In 5831 participants of the MESA cohort, a heart rate <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.[34]

SVT (Excluding AF and Atrial Flutter)

ICD-9 427.0; *ICD-10* I47.1.

2018: Mortality—178. Any-mention mortality—1646.

2016: Hospital discharges—40 000 (18 000 male; 22 000 female).

Prevalence, Incidence, and Risk Factors (See Chart 17-3)

- Data from the Marshfield Epidemiologic Study Area in Wisconsin suggested that 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 of age: RR, 5.3) were significant risk factors (Chart 17-3).[35]
- 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, 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.[36] 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 for clinical indications, prevalence of SVT (defined as at least a single run of ≥8 beats) was 31%.[37]
- 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.[38]
- In a study of 3554 consecutive males 17 to 21 years of age applying for a pilot's license and 3700 symptomatic patients with arrhythmia, 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.[39]

Complications

- Rare cases of incessant SVT can lead to a tachycardia-induced cardiomyopathy,[40] and rare cases of sudden death attributed to SVT as a trigger have been described.[41]
- 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 no 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).[42]
- 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.[43]
- 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 years 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.[44]

Types of SVT

- Among those presenting for invasive electrophysiological study and ablation, atrioventricular nodal reentrant tachycardia (a circuit that requires 2 atrioventricular nodal pathways) is the most common mechanism of SVT[45,46] and usually represents the majority of cases (56% in 1 series of 1754 cases).[46]
- Atrioventricular 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 a study by Porter et al[46]), and atrial tachycardia is the third most common (17% in a series of 1754 SVT cases from Porter et al[46]).
- According to a US-based national pediatric electrophysiology registry study, in children, atrioventricular reentrant tachycardia was the most common SVT mechanism (68%), whereas the remainder of the patients had atrioventricular nodal reentrant tachycardia (32%).[47]
- Atrioventricular reentrant tachycardia prevalence decreases with age, whereas atrioventricular nodal reentrant tachycardia and atrial tachycardia prevalences increase with advancing age.[46]
- The majority of patients with atrioventricular reentrant tachycardia were males (55%), whereas females constituted the majority with atrioventricular nodal reentrant tachycardia (70%) or atrial tachycardia (62%) in the study by Porter et al.[46]
- 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[48] and adults,[49] with a prevalence in hospitalized adults estimated at 0.05% to 0.32%.[49] The average age at onset in adults is 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).[49] In a study of older ambulatory adults in Greece, the mortality in follow-up did not differ by whether multifocal atrial rhythms were detected on baseline ECG.[50]

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.[51] In an ECG study of 32 837 Japanese students, a WPW electrocardiographic pattern was reported in 0.07%, 0.07%, and 0.17% of elementary, junior high, and high school students, respectively.[52]

Complications

- WPW syndrome, a diagnosis reserved for those with both ventricular preexcitation (evidence of an anterograde conducting atrioventricular 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.[53]
- A cohort study from Intermountain Healthcare with ≈8 years of follow-up reported that rates of cardiac arrest were low and similar between patients with WPW and control subjects 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 patients with WPW developed AF compared with 3.8% of those without WPW.[54]
- Asymptomatic adults with ventricular preexcitation appear to be at no increased risk of sudden death compared with the general population.[55,56]
- 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.[57]
- In a meta-analysis of 20 studies involving 1869 asymptomatic patients with a WPW electrocardiographic pattern followed up for 11 722 person-years, the rate of sudden death was estimated to be 1.25 (95% CI, 0.57–2.19) per 1000 person-years in a random-effects model used because of heterogeneity across studies. Risk factors for sudden death included male sex, inclusion in a study of children (<18 years of age), and inclusion in an Italian study.[58]
- Several studies in asymptomatic children with ventricular preexcitation detected by screening suggest a benign prognosis.[56,59] 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.[60] 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 of follow-up. The incidence of sudden death was 1.1 per 1000 person-years in patients without structural HD.[61]

AF and Atrial Flutter

ICD-9 427.3; *ICD-10* I48.

2018: Mortality—25 845. Any-mention mortality—175 326.

2016: Hospital discharges—465 010 (234 370 male; 230 370 female).

Prevalence

- The prevalence of AF in the United States was estimated to rise from ≈5.2 million in 2010 to 12.1 million in 2030.[62]
- 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).[63]
- Among Medicare patients ≥65 years of age who were diagnosed from 1993 to 2007, the prevalence of AF increased ≈5%/y, from 41.1 per 1000 beneficiaries to 85.5 per 1000 beneficiaries.[64]
  - In 2007, in the 5% Medicare sample, there were 105 701 older adults with AF: 93.8% were White, 3.7% were Black, and 2.6% were other/unknown race.[64]
  - The prevalence rate per 1000 beneficiaries was 90.8 in older adults of White race, 46.3 in older adults of Black race, and 47.5 in older adults of other/unknown race.[64]
- Data from a California health plan suggested that compared with White people, Black people (OR, 0.49 [95% CI, 0.47–0.52]), Asian people (OR, 0.68 [95% CI, 0.64–0.72]), and Hispanic people (OR, 0.58 [95% CI, 0.55–0.61]) have a significantly lower adjusted prevalence of AF.[65]
- In an analysis involving the entire South Korean population, prevalence of AF more than doubled, from 0.73% in 2006 to 1.53% in 2015, and was estimated to reach 5.81% in 2060.[66]

Incidence (See Chart 17-4)

- 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 increase (P=0.02).[64]
- Investigators from MESA estimated the age- and sex-adjusted incidence rate of hospitalized AF per 1000 person-years as 11.2 (95% CI, 9.8–12.8) in NH White people, 6.1 (95% CI, 4.7–7.8) in Hispanic people, 5.8 (95% CI, 4.8–7.0) in NH Black people, and 3.9 (95% CI, 2.5–6.1) in Chinese people.[67]
- 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 Black people (HR, 0.84 [95% CI, 0.82–0.85]; P<0.001), Hispanic people (HR, 0.78 [95% CI, 0.77–0.79]; P<0.001), and Asian people (HR, 0.78 [95% CI, 0.77–0.79]; P<0.001; Chart 17-4).[68] Incidence of AF in American Indian people in the same California database was similar to that in White people and higher than in Black, Asian, and Hispanic people.[69]
- 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 White people versus 5.4 (95% CI, 4.6–6.3) in Asian people and 4.6 (95% CI, 4.0–5.3) in Black people.[70]
- From data from a health insurance claims database covering 5% of the United States, the incidence of AF was estimated at 1.2 million new cases in 2010 and was projected to increase to 2.6 million new cases in 2030.[62]
- In an analysis involving the entire South Korean population, incidence of AF between 2006 and 2015 has remained flat, with an overall incidence during this period of 1.77 new cases per 1000 person-years.[66]

Lifetime Risk and Cumulative Risk (See Chart 17-5)

- In studies from FHS and the BiomarCaRE Consortium, the lifetime risk for AF in individuals of European ancestry was estimated to be ≈1 in 3.
  - In the BiomarCaRE study based on 4 European community-based studies, the incidence increased after 50 years of age in males and 60 years of age in females, but the cumulative incidence of AF was similar, at >30%, by 90 years of age.[71]
  - In an FHS report based on participants with DNA collected after 1980, the lifetime risk of AF after 55 years of age was 37.1%, which was influenced by both clinical and genetic risk.[72] In a subsequent study from FHS, the lifetime risk of AF varied by risk factor burden. In individuals with optimal risk profile, the lifetime risk was 23.4% (95% CI, 12.8%–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 (Chart 17-5).[73]
- 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 Black males (95% CI, 13%–24%), and 22% in Black females (95% CI, 16%–25%).[74]
- In a medical insurance database study from the Yunnan Province in China, the estimated lifetime risk of AF at 55 years of age was 21.1% (95% CI,

19.3%–23.0%) for females and 16.7% (95% CI, 15.4%–18.0%) for males.[75] 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.[76]

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 diabetes increased (consistent with increasing prevalence). Over time, the multivariable-adjusted hazards of stroke and mortality associated with AF declined by 74% and 25%, respectively.[77]
- Between 2000 and 2010 in Olmsted County, Minnesota, age- and sex-adjusted incidence rates and survival did not change over time.[78] 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.[70]
- In 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.[79]
- Between 1999 and 2013, among Medicare fee-for-service beneficiaries, rates of hospitalization for AF increased ≈1%/y. Although the median hospital length of stay, 3 days (IQR, 2.0–5.0 days), did not change, the mortality declined by 4%/y, and hospital readmissions at 30 days declined by 1%/y. During the same years, median Medicare inpatient costs per hospitalization increased substantially, from $2932 (IQR, $2232–$3870) to $4719 (IQR, $3124–$7209).[80]
- Similar trends have been observed globally. For instance, on the basis of data from a national health insurance database in Korea, between 2006 and 2015, the prevalence of AF increased 2.10-fold, and the incidence remained flat (1.8 per 1000 person-years), whereas the mortality rate (HR, 0.70 [95% CI, 0.68–0.93]) and ischemic stroke rate (HR, 0.91 [95% CI, 0.88–0.93]) after AF declined. Investigators projected that the adult prevalence of AF would reach 5.8% in 2060.[66]

Risk Factors (See Chart 17-6)

- The highest PAF for AF was hypertension, followed by BMI, smoking, cardiac disease, and diabetes in ARIC (Chart 17-6).

BP and Hypertension

- Hypertension accounted for ≈22%[81] of AF cases.
- In MESA, the PAF of AF attributable to hypertension appeared to be higher in US Chinese (46.3%), Hispanic (43.9%), and NH Black participants (33.1%) than in NH White participants (22.2%).[67]
- In a Korean health insurance administrative study, AF incidence increased with advancing hypertension stage; with stage 1 as reference, the HR for each stage was 1.1, 1.4, 1.9, and 2.3 and was observed for SBP and DBP and for all age groups. Each 5–mm Hg increase in SBP and DBP was associated with a 4.3% and 4.6%, respectively, increased risk incident AF.[82]

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.[83]
- Another meta-analysis of 29 studies examined various anthropometric components in relation to incident AF. A 5-kg/m^2 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/m^2 was still associated with excess risk compared with a BMI of 20 kg/m^2. WC, waist-hip ratio, fat mass, and weight gain were also associated with increased risk of AF.[84]
- In a meta-analysis of prospective studies, weight gain was associated with increased risk of AF (HR, 1.13 [95% CI, 1.04–1.23] per 5% weight gain). Nonsurgical loss of 5% body weight was not significantly related to AF risk (HR, 1.04 [95% CI, 0.94–1.16]).[85]
- A causal relationship between higher BMI and incident AF gained further support from a genetic mendelian randomization study, which observed that a BMI GRS that included 39 SNPs was associated with a higher risk of AF.[86]

Smoking

- A meta-analysis of 29 studies from 22 publications revealed that smoking was associated with an increased risk of AF. Compared with never

smokers, the RR of current smoking was 1.32 (95% CI, 1.12–1.56), former smoking was 1.09 (95% CI, 1.00–1.18), and ever smoking was 1.21 (95% CI, 1.12–1.31). There appeared to be a dose-response relationship such that the RR per 10 cigarettes per day was 1.14 (95% CI, 1.10–1.20) and the RR per 10 pack-years was 1.16 (95% CI, 1.09–1.25).[87]

Diabetes and HbA_{1c}

- In a meta-analysis restricted to prospective studies, HbA_{1c} was associated with an increased risk of AF when analyzed continuously (RR, 1.11 [95% CI, 1.06–1.16]) or categorically (RR, 1.09 [95% CI, 1.00–1.18]).[88]
- In a meta-analysis of observational studies (excluding a large outlier study), the RR of diabetes for incident AF was 1.28 (31 cohort studies [95% CI, 1.22–1.35]) and for prediabetes was 1.20 (4 studies [95% CI, 1.03–1.39]).[89]
- A machine learning meta-analysis reported similar risks of incident AF in individuals with type 1 and type 2 diabetes. However, compared with males with diabetes (RR, 1.11 [95% CI, 1.01–1.22]), females with diabetes appeared to have a higher risk of incident AF (RR, 1.38 [95% CI, 1.19–1.60]).[90]

Activity and Exercise

- A multiracial longitudinal study from Detroit, MI, reported a dose-response relation between objectively assessed exercise capacity and lower risk of new-onset AF.[91] 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.
- Whereas regular PA is associated with lower risk of AF, a meta-analysis of 9 studies supports that athletes have a higher risk of AF than the general population (OR, 2.34 [95% CI, 1.04–5.28]). However, the investigators reported substantial heterogeneity in the data, with the highest risks observed among males and individuals <60 years of age.[92]

HD as a Risk Factor

- In the CHARGE-AF consortium, pooling data from FHS, ARIC, and CHS, both a history of MI and HF were associated with risks of AF (HR, 1.64 [95% CI, 1.38–1.96] and 2.02 [95% CI, 1.64–2.48], respectively).[93]
- Among participants in the FHS, type of HF (HFrEF or HFpEF) was not differentially associated with the incidence of AF, but prevalent AF was marginally more strongly associated (P=0.06) with multivariable-adjusted incidence of HFpEF (HR, 2.34 [95% CI, 1.48–3.70]) than with HFrEF (HR, 1.32 [95% CI, 0.83–2.10]).[94]
- Individuals with congenital HD are at increased risk of AF. In an analysis in Sweden including 21 982 patients with congenital HD and 219 816 control subjects, risk of developing AF was 22 times higher (HR, 22.0 [95% CI, 19.3–25.1]) in those with congenital HD compared with referents without congenital HD.[95] By 42 years of age, ≈8% of patients with congenital HD had been diagnosed with AF.

Miscellaneous Risk Factors

- Other consistently reported risk factors for AF include clinical and subclinical hyperthyroidism,[96] CKD,[97,98] and moderate[99] or heavy alcohol consumption.[100]
- There is increasing evidence relating sleep features to AF:
  - In a meta-analysis of 8 studies, the sleep apnea-hypopnea syndrome was associated with an increased risk of AF after adjustment for confounders (RR, 1.40 [95% CI, 1.12–1.74]; P<0.001).[101]
  - The relation of sleep duration to AF has been less thoroughly studied, but a systematic review reported an increased risk of AF with long sleep duration (≥8 hours; 2 studies; HR, 1.13 [95% CI, 1.00–1.27]) and short sleep duration (<6 hours; 1 study; HR, 1.58 [95% CI, 1.18–2.13]).[102]
  - A meta-analysis of 3 studies of sleep quality also reported an association between insomnia and increased odds of AF (OR, 1.30 [95% CI, 1.26–1.35]).[103]
- Air pollution:
  - In a population-based cohort including >5 million residents of the province of Ontario, Canada, followed up between 2001 and 2015, higher levels of air pollutants were associated with increased risk of AF (HR per IQR, 1.03 [95% CI, 1.01–1.04] for fine particulate matter, 1.02 [95% CI, 1.01–1.03] for NO_2, and 1.01 [95% CI, 1.00–1.02] for ozone).[104]
  - Using the Korean National Health Insurance Service, investigators similarly reported that incident AF was associated with (per 10-μg/m^3 increments) both fine particles ($PM_{2.5}$, or those ≤2.5 μm in diameter; HR, 1.179 [95% CI, 1.176–1.183]) and coarse dust particles (PM_{10}, or those 2.5–10 μm in diameter; HR, 1.034 [95% CI, 1.033–1.036]).[105]
- Psychosocial factors have been associated with the risk of AF:

— Among close to 1 million individuals seeking care through the Veterans Health Administration between 2001 and 2014, a diagnosis of posttraumatic stress disorder was associated with a 13% increased risk of AF after adjustment for confounders (HR, 1.13 [95% CI, 1.02–1.24]).[106]
— In the MESA study, higher burden of depressive symptoms was associated with higher risk of AF (HR, 1.34 [95% CI, 1.04–1.74] when participants with a score ≥16 in the Center for Epidemiologic Studies Depression Scale were compared with those with a score <2. Anger, anxiety, and chronic stress were not associated with AF risk.[107]
— Similarly, in the ARIC study, higher levels of vital exhaustion were associated with increased AF risk (HR, 1.20 [95% CI, 1.06–1.35]). Neither anger nor social isolation was associated with the risk of AF.[108]
— A meta-analysis of 3 prospective studies evaluating the association between job strain (defined as high demands and low control in the occupational setting) and AF risk reported an HR of 1.37 (95% CI, 1.13–1.67) comparing those with job strain and those without.[109]

- 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.[110]
  — 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.[111] AF occurring in the context of sepsis is associated with an increased risk of stroke and death.[112]
  — A meta-analysis reported that new-onset AF has been observed in 10.9% of patients undergoing noncardiac general surgery.[113]
  — AF also occurs after CABG, with a risk-adjusted incidence of 33.1%, which has not varied over time.[114]
- With the increased interest in cardio-oncology, there are increasing reports that cancer and cancer medications are associated with increased risk of AF (e.g., ibrutinib; RR for AF, 4.69).[115] A study from the Danish national database reported that all major cancer subtypes were associated with increased risk of AF. Per 1000 person-years follow-up, the overall incidence was 17.4 (versus 3.7 in the general population), for an adjusted IRR of 1.46 (95% CI, 1.44–1.48), which appeared to decline with time since cancer diagnosis.[116]

Social Determinants of AF

- There is increasing research on the relation between social determinants of health and AF risk. In a study from REGARDS, involuntary unemployment was associated with increased risk of prevalent (OR, 1.60 [95% CI, 1.24–2.07]) and incident (OR, 1.54 [95% CI, 1.04–2.37]) AF.[117]

Risk Prediction of AF

- Life's Simple 7:
  — In the biracial REGARDS study, better CVH, as classified by Life's Simple 7, predicted decreased risk of AF similarly between sexes and in White and Black people. Individuals with optimal CVH (score, 10–14 points) had an adjusted 32% lower risk of AF (OR, 0.68 [95% CI, 0.47–0.99]).[118]
  — The ARIC study, which includes White and Black participants, also observed that patients with average (HR, 0.59 [95% CI, 0.51–0.67]) and optimal (HR, 0.38 [95% CI, 0.32–0.44]) CVH had a lower risk of incident AF. For every 1-point-higher Life's Simple 7 score, the risk of AF was 12% lower (HR, 0.88 [95% CI, 0.86–0.89]).[119]
  — A similar analysis in the MESA cohort reported a 27% lower risk of AF in participants with optimal CVH (HR, 0.73 [95% CI, 0.59–0.91]) compared with those with inadequate scores, without substantive differences by race/ethnicity.[120]
- ARIC,[121] the FHS,[122] and the WHS[123] 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), diabetes, BP (SBP and hypertension treatment), and presence of CVD (CHD, HF, valvular HD).
- The ARIC, CHS, and FHS investigators developed and validated a risk prediction model for AF in White and Black participants, which was replicated in 2 European cohorts.[93] The CHARGE-AF model has been validated in US multiethnic cohorts including Hispanic people,[124] in MESA,[125] in a UK cohort (EPIC Norfolk),[126] and in a post-CABG cohort.[127]

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 of

54.2 years of age was 2.19 for those with optimal risk, 3.68 for those with borderline risk, and 6.59 for those with elevated risk factors.[81]

Subclinical Atrial Tachyarrhythmias, Unrecognized AF, and 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.
- In a meta-analysis of 28 studies including patients with pacemakers or defibrillators followed up for a mean of 22 months, new-onset device-detected atrial tachyarrhythmias were observed in 23% of patients. In 9 studies, device-detected atrial tachyarrhythmias were associated with a 2.88 (95% CI, 1.79–4.64; *P*<0.001) RR of thromboembolism, which was higher with longer duration (≥5 minutes of RR, 3.86 versus <1 minute of RR, 1.77).[128]
- Another meta-analysis reported that high atrial rate episodes detected by cardiac implantable electronic devices were associated with higher risk of clinical AF (n=2 studies including 2892 participants; OR, 5.7 [95% CI, 4.0–8.0]; *P*<0.001) and a higher risk of stroke (n=7 studies including 17 247 participants; OR, 2.4 [95% CI, 1.8–3.3]; *P*<0.001). The annual stroke rate was 1.89 per 100 person-years with versus 0.93 per 100 person-years without high-atrial-rate episodes.[129]
- 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 health care system. The OR for an AIS 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.[130]

Community Screening

- The prevalence of undiagnosed AF in the community is unknown. Using Medicare and commercial 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 that 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 of age.[131]
- 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.[132]
- Methods vary in their sensitivity and specificity in the detection of undiagnosed AF, increasing from pulse palpation to devices such as handheld single-lead ECGs, modified BP devices, and plethysmographs.[132]
- In a community-based study in Sweden (STROKESTOP), of 7173 people 75 to 76 years of age who participated in an AF screening program, 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 initial 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.[133]
- There have been several systematic reviews of the effectiveness of screening to detect unknown AF.
  - A systematic review by the US Preventive Services Task Force of asymptomatic adults at least 65 years of age included 17 studies (135 300 individuals). Compared with no screening, systematic screening with ECG detected more new cases of AF (over 1 year, absolute increase from 0.6% [95% CI, 0.1%–0.9%] to 2.8% [95% CI, 0.9%–4.7%]). However, the systematic ECGs did not detect more cases than pulse palpation. Furthermore, none of the studies compared systematic screening versus usual care, and none examined health outcomes.[134]
  - A systematic review of 19 studies from 2007 to 2018 identified 24 single-time-point screening studies; 141 220 participants were included, of whom 1539 had newly detected AF. The detection rate adjusted for age and sex was 1.44% in those ≥65 years of age and 0.41% in individuals <65 years of age. The study included low- to middle- to high-income countries but did not identify geographic region variation in detection rates. The authors estimated that the number needed to screen to identify 1 treatable new AF case varied by age: 83 for ≥65 years of age, 926 for 60 to 64 years of age, and 1089 for <60 years of age.[135]
  - Another systematic review included 25 published studies involving 88 786 participants. The investigators reported that the incidence of newly detected AF was 1.5% (95% CI, 1.1%–1.8%) and was higher with systematic screening versus opportunistic screening (1.8% versus 1.1%) and with multiple (2.1%) versus single-time-point (1.2%) rhythm assessments.[136]

- There has been increasing interest in the use of wearable, commercially available technology to aid in community screening for AF.[137]
  - In the largest study to date, investigators recruited 419 297 Apple Watch owners to participate in a monitoring study to detect possible AF. The median follow-up was 117 days, during which 0.52% (n=2161) received irregular pulse warnings; 450 participants returned an electrocardiographic patch (on average 13 days after notification) that detected AF in 34%.[138]
  - At present, the detection of AF, even in an asymptomatic stage, is the basis for risk stratification for stroke and appropriate decision making for 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 history of AF. The findings from these studies will help to determine optimal strategies for subclinical AF screening and treatment.[132] To date, no studies have demonstrated that AF screening reduces mortality or incidence of thromboembolic complications.

Family History and Genetics

- Although unusual, early-onset lone AF has long been recognized to cluster in families.[13,139] The heritability of AF in the general community has been appreciated.
- In the FHS, 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 age at onset of the first-degree relative 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]).[140]
- A prospectively enrolled University of Illinois at Chicago AF Registry revealed that individuals with early-onset AF in the absence of structural HD had a 3-fold adjusted odds of having a first-degree relative with AF (aOR, 3.02 [95% CI, 1.82–4.95]; $P<0.001$) compared with individuals with AF without early-onset AF. Higher odds of having a proband with AF in the setting of early-onset AF were observed in individuals of African (OR, 2.69), Hispanic (OR, 9.25), and European (OR, 2.51) descent.[141]
- 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. Those investigators 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.[142]
- Racial variation in AF incidence is complex and not fully understood. One study of Black and White individuals from CHS and ARIC suggested that genetic markers of European ancestry were associated with an increased risk of incident AF.[143]
- Many common genetic variants have been identified as associated with AF: A GWAS that included >65 000 patients with AF reported 97 AF-associated loci, including the most consistent genetic locus *PITX2*, 67 of which were novel in combined-ancestry analyses.[144] Another GWAS of >1 000 000 individuals identified 111 independent genes associated with AF, many of which are near deleterious mutations that cause more serious heart defects or near genes important for striated muscle function and integrity.[145]
- Whole-exome/genome sequencing studies have identified rare mutations in additional genes associated with AF, including *MYL4*,[146] and loss-of-function mutations in *SCN4B* and *KCNA5*, a conserved gene that encodes the voltage-gated Kv1.5 potassium channel.[147,148] Loss-of-function variants in the titin gene have been associated with early-onset AF.[149,150]
- Combinations of these genetic variants for AF are predictive of lifetime risk of AF. Investigators in the FHS examined the lifetime risk of AF at 55 years of age using both clinical risk score and GRS (derived of thousands of variants 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 risk score and of GRS had a lifetime risk of AF of 22.3% (95% CI, 15.4%–29.1%), whereas those in the highest tertile of clinical risk score and GRS had a lifetime risk of 48.2% (95% CI, 41.3%–55.1%).[72]
- Some studies suggest that genetic markers of AF could improve risk prediction for AF over models that include clinical factors.[123]
- However, a study of 5 cohorts with 18 191 individuals found that a GRS associated with incident AF added only marginally to clinical risk prediction (maximum change in C statistic from clinical score alone, 0.009–0.017).[151]
- GRS could also identify patients at higher risk of cardioembolic stroke[152]; however, the utility of clinical genetic testing for AF-related genetic variants is currently unclear.
- SNPs associated with increased risk of AF are also associated with increased risk of AF recurrence after catheter ablation[153] and after CABG.[154]
- GWASs have also been conducted with variation in electrocardiographic traits used as a phenotype (i.e., QRS duration and area) and have identified novel genetic variants associated with these traits that also associate with cardiac conduction, arrhythmias, and other cardiovascular end points.[155]

Prevention: Observational Data

Primary Prevention of AF: Observational Data

- An observational prospective Swedish study revealed that individuals having bariatric surgery had a 29% lower risk (HR, 0.71 [95% CI, 0.60–0.83]; *P*<0.001) of developing AF in 19 years of median follow-up than matched referents.[156]

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).[157]
  - The same Australian investigators reported that overweight and obese individuals with 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.[158]
  - 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.[159]
  - 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 gained) 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 gained, 89% AF free).[160]
- Treatment of OSA has been noted to decrease risk of progression to permanent AF.[161] In a meta-analysis, CPAP was reported to be associated with a reduced risk of recurrent AF after ablation.[162] 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 SDB.
- 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 underuse of evidence-based preventive therapies for comorbid conditions in individuals with AF.[163]
- 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]).[164]
- 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 diabetes, 40.2% of those with HF, and 96.7% of those with hypertension.[165]

Prevention: Randomized Data

Primary Prevention of AF: Randomized Data

- Intensive glycemic control was not found to prevent incident AF in the ACCORD study (*P*=0.52).[166]
- In the Look AHEAD randomized trial of individuals with type 2 diabetes 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.[167]
- Meta-analyses have suggested that BP lowering might be useful in the prevention of AF in trials of hypertension, after MI, in HF, and after cardioversion.[168,169] However, the studies were primarily secondary or post hoc analyses, the intervention duration was modest, and the results were fairly heterogeneous.
- In an analysis of the EMPHASIS-HF trial, in 1 of many secondary outcomes, eplerenone reduced the incidence of new-onset AF (HR, 0.58 [95% CI, 0.35–0.96]). However, the number of AF events was modest (n=65).[170]
- A post hoc analysis of the PREDIMED randomized primary prevention study suggested a significant reduction in incident AF with the Mediterranean diet that included extravirgin olive oil (HR, 0.62 [95% CI, 0.45–0.86]).[171]

- 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.[172]

Secondary Prevention of AF: Randomized Data

- 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.[173]
- An Australian multisite open-label, controlled trial randomized 140 adults with a history of AF in sinus rhythm at baseline who consumed ≥10 drinks of alcohol per week either to alcohol abstinence or to continue their usual alcohol consumption.[174] AF recurred in 53% of the abstinence group and 73% of the control group. Compared with the control group, the abstinence group had a significantly longer duration without AF recurrence (HR, 0.55 [95% CI, 0.36–0.84]; *P*=0.005) and significantly lower AF burden (median percent time in AF, 0.5% versus1.2%; *P*=0.01).

Awareness

- In REGARDS, a US national biracial study, compared with White individuals, Black individuals had approximately one-third the likelihood (OR, 0.32 [95% CI, 0.20–0.52]) of being aware that they had AF.[175] 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.[176]
- A study from Kaiser Permanente in California examined the relationship between AF diagnosis (2006–2009) and self-report questionnaire data (2010). Of the >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 AF diagnosis (literacy prevalence ratio, 0.96 [95% CI, 0.94–0.98]).[177]

Treatment and Control

Anticoagulation Undertreatment

- Studies have demonstrated underuse 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 substance use disorder, noncompliance, warfarin contraindications, dementia, falls, both gastrointestinal and intracranial hemorrhage, renal impairment, and advancing age.[178] The underuse of anticoagulation in AF has been demonstrated to be a global problem.[179]
- The GWTG–Stroke program conducted a retrospective analysis consisting of 1622 hospitals and 94 474 patients with AIS in the setting of known AF from 2012 to 2015. In that analysis, 79 008 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, compared with patients receiving no antithrombotic medications, patients receiving antecedent therapeutic warfarin, non–vitamin K antagonist oral anticoagulant drugs, or antiplatelet therapy had lower odds of moderate or severe stroke (aOR, 0.56 [95% CI, 0.51–0.60], 0.65 [95% CI, 0.61–0.71], and 0.88 [95% CI, 0.84–0.92], respectively) and lower in-hospital mortality.[180]
- In the NCDR PINNACLE registry of outpatients with AF:
  - Fewer than half of high-risk patients, defined as those with a CHA_2DS_2-VASc score ≥4, were receiving an oral anticoagulant prescription.[181]
  - 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 the prevalence of oral anticoagulation treatment increased from 52.4% to 60.7% over the time period, substantive gaps remain.[182]
  - In the PINNACLE registry, females were significantly less likely to receive oral anticoagulant drugs at all levels of CHA_2DS_2-VASc scores (56.7% versus 61.3%; *P*<0.001).[183]
  - The PINNACLE registry investigators also reported that receipt of warfarin versus a DOAC 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.[184]
- The GLORIA-AF Registry reported North American anticoagulation patterns in 3320 patients with AF between 2011 and 2014, observing that factors associated with increased likelihood of receiving indicated oral anticoagulant prescription included nonparoxysmal AF (OR, 2.02), prior stroke/TIA (OR, 2.00), specialist care (OR, 1.50), more concomitant medications (OR, 1.47), commercial insurance (OR, 1.41), and HF (OR, 1.44), whereas factors inversely related were antiplatelet drugs (OR, 0.18), prior falls (OR, 0.41), and prior bleeding (OR, 0.50).[185]

Disparities in Treatment

- In the ORBIT-AF II US-based registry study of outpatients with nontransient AF, Black individuals

were less likely than their White counterparts to receive DOACs if an anticoagulant was prescribed, after adjustment for socioeconomic and clinical factors (aOR, 0.73 [95% CI, 0.55–0.95]); there were no significant differences in DOAC use for AF between groups of White and Hispanic patients. However, Black and Hispanic patients were more likely than their White counterparts to receive inappropriate doses of DOACs.[186]

- Disparities in treatment patterns also have 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]).[187]

Role of Coordinated Care

- A systematic review and meta-analysis identified 3 studies of coordinated systems of care that included 1383 patients.[188] The investigators reported that AF integrated care approaches were associated with reduced all-cause mortality (OR, 0.51 [95% CI, 0.32–0.80]; *P*=0.003) and cardiovascular hospitalizations (OR, 0.58 [95% CI, 0.44–0.77]; *P*=0.0002).

Mortality

2016 ICD-9 427.3; ICD-10 I48.

In 2018, AF was the underlying cause of death in 25 845 people and was listed on 175 326 US death certificates (any-mention mortality; unpublished NHLBI tabulation using NVSS[189] and CDC WONDER[190]).

- The age-adjusted mortality rate attributable to AF was 6.4 per 100 000 people in 2018 (unpublished NHLBI tabulation using CDC WONDER[190]).
- 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]).[191] 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 higher in females than in males with AF (RR, 1.12 [95% CI, 1.07–1.17]).[192]
- An observational study of Olmsted County, Minnesota, 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. Survival within the first 90 days did not change over time (aHR, 0.96 [95% CI, 0.85–1.31] for 2010 versus 2000).[78]
- 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.[193]
- AF is also associated with increased mortality in subgroups of individuals, including the following:
  - Individuals with other cardiovascular conditions and procedures, including HCM,[194] MI,[195,196] pre-CABG,[197] post-CABG[195,196,198,199] (both short term[198] and long term[198,199]), post–transcatheter aortic valve implantation,[200] PAD,[201] and stroke.[202]
  - Individuals with AF have increased mortality with concomitant HF,[203,204] including HFpEF[205,206] and HFrEF.[205] 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).[207]
  - AF is also associated with an increased risk of death in other conditions, including diabetes,[166,208] ESRD,[209] sepsis,[112,210] critically ill patients in the ICU,[211] after primary PCI,[212] and noncardiac surgery.[213]
- In a Medicare unadjusted analysis, Black and Hispanic people had a higher risk of death than their White counterparts with AF; however, after adjustment for comorbidities, Black (HR, 0.95 [95% CI, 0.93–0.96]; *P*<0.001) and Hispanic (HR, 0.82 [95% CI, 0.80–0.84]; *P*<0.001) people had a lower risk of death than White people with AF.[214] 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)[208] in Black participants, which was higher than the 55.9 (95% CI, 48.1–63.7) rate difference in mortality observed for White participants.[215]
- In a US-based study, there was substantial variation in mortality with AF in US counties from 1980 to 2014.[216] Investigators estimated that 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) YLL. In an examination of county-level data, the age-standardized AF 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.[216]

- In a study using the NIS for the period 2010 to 2015, adjusted in-hospital mortality in the setting of AF was higher (4.8% versus 4.3%; *P*=0.02) among Medicaid beneficiaries than among patients with private insurance.[217]
- 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]).[218]
- 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]).[219] In another study from the same group, unmarried and divorced males and males with lower educational levels with AF had a higher risk of mortality than their married and better-educated male counterparts.[220]

Complications (See Table 17-1)

- 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 17-1).

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.[221]
- 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 neither event.[222]

Stroke

- A systematic review of prospective studies found wide variability in stroke risk between studies and between patients with AF, ranging between 0.5%/y and 9.3%/y.[223]
- 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 (≈3- to 5-fold increased risk) did not vary 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.[224]
- In an observational study, at 5 years, of 177 patients with AF-related ischemic stroke, only 39.2% (95% CI, 31.5%–46.8%) were alive, and 21.5% (95% CI, 14.5%–31.3%) had experienced recurrent stroke.[225]
- In Medicare analyses that were adjusted for comorbidities, Black (HR, 1.46 [95% CI, 1.38–1.55]; *P*<0.001) and Hispanic (HR, 1.11 [95% CI, 1.03–1.18]; *P*<0.001) people had a higher risk of stroke than White people with AF.[214] The increased risk persisted in analyses adjusted for anticoagulant therapy status.[214] Additional analyses from the Medicare registry demonstrated that the addition of Black race to the CHA_2DS_2-VASc scoring system significantly improved the prediction of stroke events among patients with newly diagnosed AF ≥65 years of age.[226]
- In a University of Pennsylvania AF inception cohort without a history of remote stroke, compared with White participants, Black participants with AF were more likely to be younger and female and to have more cardiovascular risk factors. In addition, in adjusted analyses, compared with White participants with AF, Black participants with new-onset AF were more likely to have an ischemic stroke precede (OR, 1.37 [95% CI, 1.03–1.81]) or follow (HR, 1.67 [95% CI, 1.30–2.14]) the diagnosis of AF. The rate of ischemic stroke per year after AF diagnosis was 1.5% (95% CI, 1.3%–1.8%) in White participants and 2.5% (95% CI, 2.1%–2.9%) in Black participants.[227]
- 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 have significant heterogeneity.[192]

Cognition and Dementia

- 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.[228]
- A meta-analysis of 11 prospective studies including 112 876 participants with normal baseline cognition and without acute stroke reported an adjusted 34% (HR, 1.34 [95% CI, 1.24–1.44]) higher incidence of dementia in individuals with AF compared with those without AF.[229] Another meta-analysis included >2 million participants in 14 observational studies and 2 randomized studies and observed a similar increased risk of incident dementia (HR, 1.36 [95% CI, 1.23–1.51]; $P<0.0001$).[230]
- In a multicenter study of individuals with diagnosed AF (mean, 73 years of age) from Switzerland, among 1390 patients without a history of stroke or TIA, clinically silent infarcts were observed in 245 patients (18%) with small noncortical infarcts and 201 (15%) with large noncortical or cortical infarcts according to brain MRIs.[231] Furthermore, in adjusted analyses of all the vascular brain features, large noncortical or cortical infarcts had the strongest association with reduced Montreal Cognitive Assessment (β=–0.26 [95% CI, –0.40 to –0.13]; $P<0.001$), even when restricted to individuals with clinically silent infarcts.

Physical Disability and Subjective Health

- AF has been associated with physical disability, poor subjective health,[232,233] and diminished quality of life.[234] A systematic review suggested that among people with AF, moderate-intensity activity improved exercise capacity and quality of life.[235]

Falls

- In the REGARDS study, AF was significantly associated with an adjusted higher risk of falls (10%) compared with no 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]).[236]
- 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.[237]
- 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.[238]

Heart Failure
(See Chart 17-7)

- AF and HF share many antecedent risk factors, and ≈40% of people with either AF or HF will develop the other condition.[204]
- In the community, estimates of the incidence of HF in individuals with AF ranged from 3.3[204] to 5.8[239] per 100 person-years of follow-up. In Olmsted County, Minnesota, in individuals with AF, per 100 person-years of follow-up, the incidence of HFpEF was 3.3 (95% CI, 3.0–3.7), which was more common than HFrEF (2.1 [95% CI, 1.9–2.4]).[239]
- 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 17-7). Higher event rates after new-onset AF were associated with older age and higher mean $CHADS_2$ score.[240]
- Investigators examined the incidence rate of HFrEF versus HFpEF (<40% versus >50%, respectively) in a Netherlands community-based cohort study (PREVEND) by AF status. Per 1000 person-years, the incidence rate of HFrEF 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 HFpEF 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).[241]
- 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]).[242]

Myocardial Infarction

- 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.[242]
- 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.[243]

- Both REGARDS[243] and the ARIC study[244] observed that the risk of MI after AF was higher in females than in males.
- For individuals with AF in both REGARDS[243] and the CHS,[245] a higher risk of MI was observed in Black than White people. 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 White individuals (HR, 1.6 [95% CI, 1.2–2.1]; $P_{interaction}$=0.03).[245]
- 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, 0.18–1.34]; *P* for comparison of HR=0.004).[244]

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 diabetes 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.[246]
- 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 no AF (74 versus 64 per 1000 person-years of follow-up).[247]

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). The multivariable-adjusted HR associated with AF for sudden death was 2.47 (95% CI, 1.95–3.13).[248]
- 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 community control subjects without VF. 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 (aOR, 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.[249]
- In a meta-analysis of 27 studies, AF was associated with a doubling in risk of sudden death (pooled RR, 2.02 [95% CI, 1.77–2.35]; *P*<0.01). When the meta-analysis was restricted to 7 studies that conducted multivariable analyses, AF remained associated with an increased risk of sudden death (pooled RR, 2.22 [95% CI, 1.59–3.09]; *P*<0.01).[250]

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).[251]
- 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%, respectively, had progressed to persistent AF. Within 10 years, >50% of the patients had progressed to persistent AF or had died.[252]

Atrial Flutter Versus AF

- 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]).[253]
- 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 patients 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).[254]

Hospitalizations and Ambulatory Care Visits

- According to HCUP data,[255] in 2016, there were 465 000 hospital discharges with AF and atrial flutter as the principal diagnosis; ≈50.4% were males (unpublished NHLBI tabulation).
  - The rate per 100 000 discharges increased with advancing age, from 15.1 in those 18 to 44 years of age, 149.2 in those 45 to 64 years of age, and 577.5 in those 65 to 84 years of age to 1158.6 in individuals ≥85 years of age. However, 53.2% of all hospital discharges for AF occurred in patients 65 to 84 years of age.
- In 2016, there were 7 042 000 physician office visits and 647 000 ED visits for AF (NAMCS, NHAMCS, unpublished NHLBI tabulation).[256,257]
- Using cross-sectional data (2006–2014) from the HCUP's NEDS, the NIS, and the NVSS, 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. When AF listed as a comorbid condition was included, there were ≈4 million (3.6% of total) ED visits and 3.5 million (12.0% of total) hospitalizations.[258]

- A meta-analysis of prospective studies including 311 314 patients with AF reported an all-cause hospital admission rate of 43.7 (95% CI, 38.5–48.9) per 100 person-years. In studies (n=24) that reported admission causes (n=234 028 patients with AF), cardiovascular hospitalizations were more frequent than noncardiovascular hospitalizations (26.3 [95% CI, 22.7–29.9] versus 15.7 [95% CI, 12.5–18.9], respectively).[259]

Cost

- A study examining public and private health insurer records from 1996 to 2016 reported that AF was 33rd in spending for health conditions with an estimated $28.4 billion (95% CI, $24.6–$33.8 billion) in 2016 dollars.[260] The annualized rate of change standardized to the population for 2016 was 3.4%. The estimates varied by the following features:
  - Age group: <20 years, 0%; 20 to 64 years, 25%; and ≥65 years, 75%.
  - Type of payer: public insurance, 56.4%; private insurance, 36.9%; and out of pocket, 6.7%.
  - Type of care: ambulatory, 29.4%; inpatient, 29.8%; prescribed pharmaceuticals, 10.5%; nursing care facility, 15.3%; and ED, 5.1%.
- Investigators examined Medicare and Optum Touchstone databases (2004–2010) to estimate costs attributed to nonvalvular AF versus propensity-matched control subjects in 2014 USD[261]:
  - For patients 18 to 64 years of age, 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 of age were $25 322 for those with AF (95% CI, $25 049–$25 595) versus $21 706 (95% CI, $21 563–$21 849) for matched patients without AF.
  - 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 was 0.83% versus 0.07%, respectively, 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).
- Using cross-sectional data (2006–2014) from the HCUP's NEDS, the NIS, and the NVSS, 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 ≈$8819.[258]
- 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 health care costs were $8184, $12 895, and $41 420 for lower middle-, middle-, and high-income economies, respectively.[262]
- Costs of AF have been estimated for many other countries. Investigators estimated that the 3-year societal costs of AF were ≈€20 403 to €26 544 per person and €219 to 295 million for Denmark as a whole.[263]

Global Burden of AF (See Charts 17-8 and 17-9)

- The vast majority of research studies on the epidemiology of AF have 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.[264]
- The GBD 2019 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 369 diseases and injuries in 204 countries and territories.[265]
  - Total number of global deaths attributable to AF/atrial flutter was ≈300 000 in 2019 (200 000 females and 100 000 males).
  - Globally, 59.7 million individuals had prevalent AF/atrial flutter in 2019 (29.4 million females and 30.3 million males).
  - Age-standardized mortality attributable to AF is highest in parts of Western Europe, Central Asia, and Australasia (Chart 17-8).
  - Age-standardized prevalence of AF is highest in Central and Eastern Europe, Australasia, and parts of North America (Chart 17-9).
- Investigators conducted a prospective registry of >15 000 patients with AF 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%).[266]

Table 17-1. Cumulative Incidence Rate Over 5 Years After AF Diagnosis by Age,* United States, Diagnosed 1999 to 2007

Age group, y	Mortality	HF	MI	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; HF, heart failure; and MI, myocardial infarction.
*See Chart 17-7.
Source: Adapted from Piccini et al[240] by permission of the European Society of Cardiology. Copyright © 2013, The Authors.

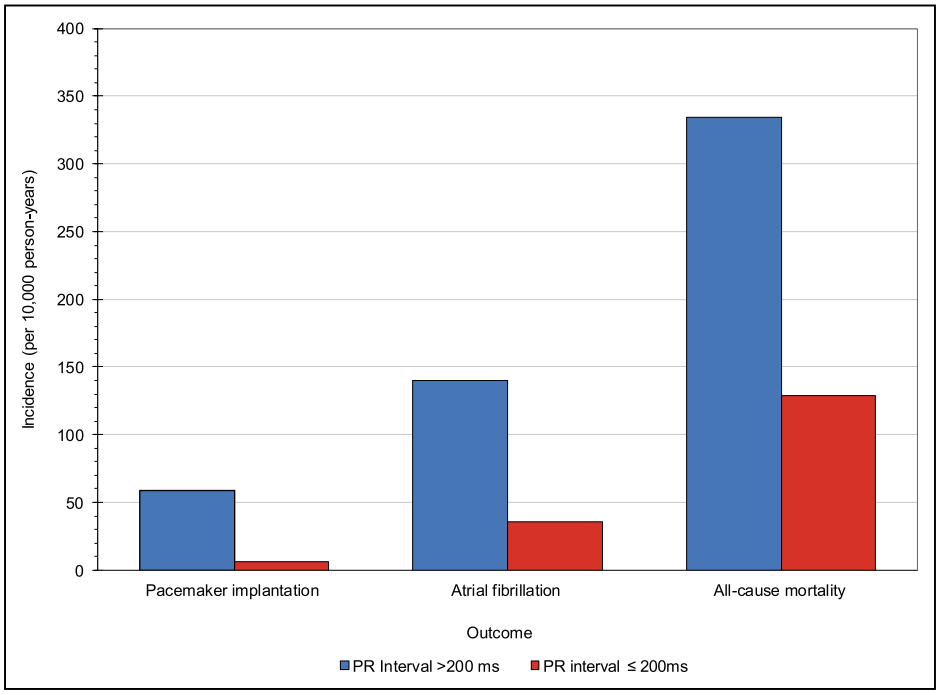

Chart 17-1. Long-term outcomes in individuals with prolonged PR interval (>200 milliseconds; first-degree atrioventricular block) compared with individuals with normal PR interval in the FHS, 1968 to 2007.
FHS indicates Framingham Heart Study.
Source: Data derived from Cheng et al.[15]

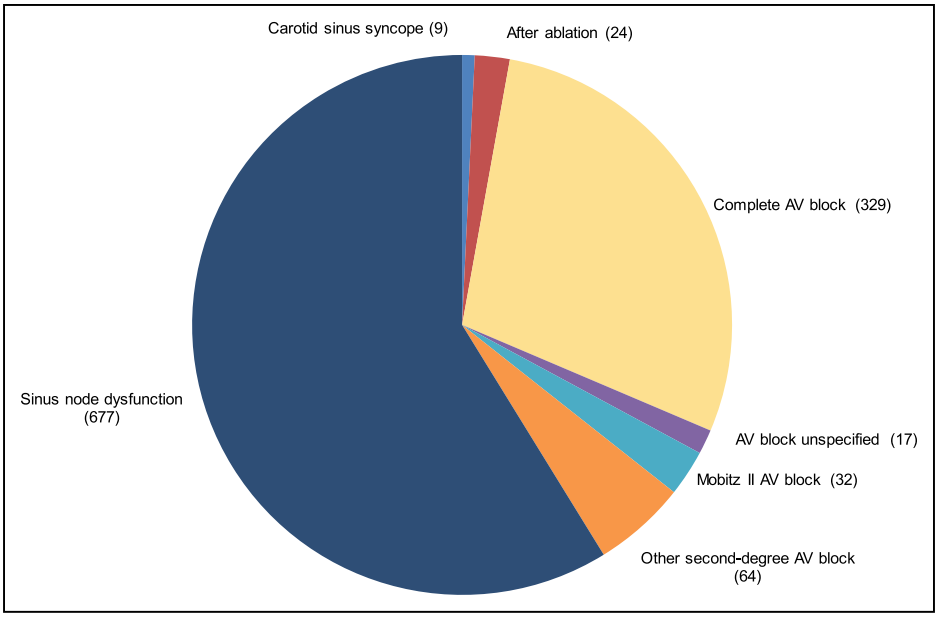

Chart 17-2. Primary indications (in thousands) for pacemaker placement between 1990 and 2002, United States (NHDS, NCHS).
AV indicates atrioventricular; NCHS, National Center for Health Statistics; and NHDS, National Hospital Discharge Survey.
Source: Data derived from Birnie et al.[33]

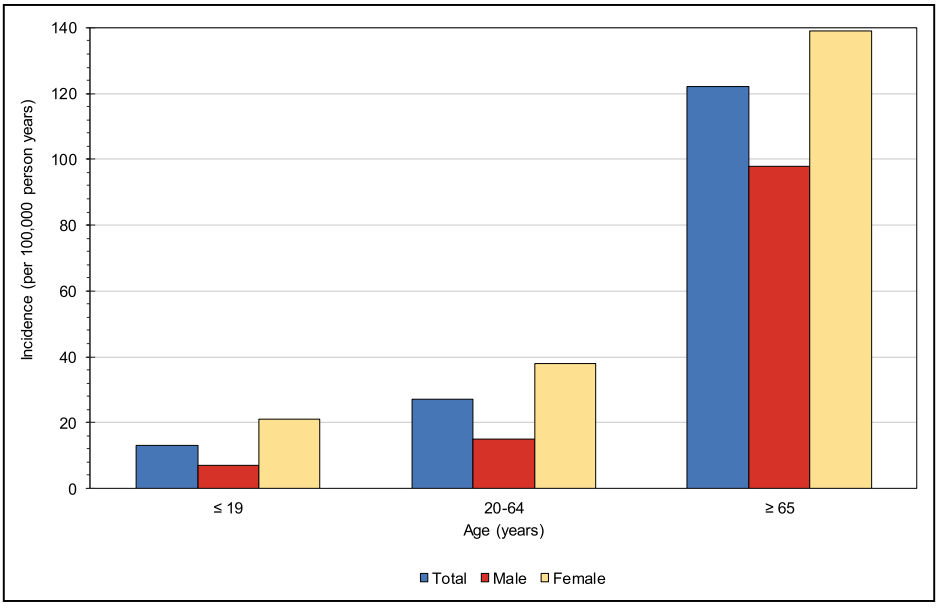

Chart 17-3. Incidence rate of paroxysmal supraventricular tachycardia per 100 000 person-years by age and sex, Marshfield Area, Wisconsin, July 1, 1991, to June 30, 1993.
Source: Data derived from Orejarena et al.[35]

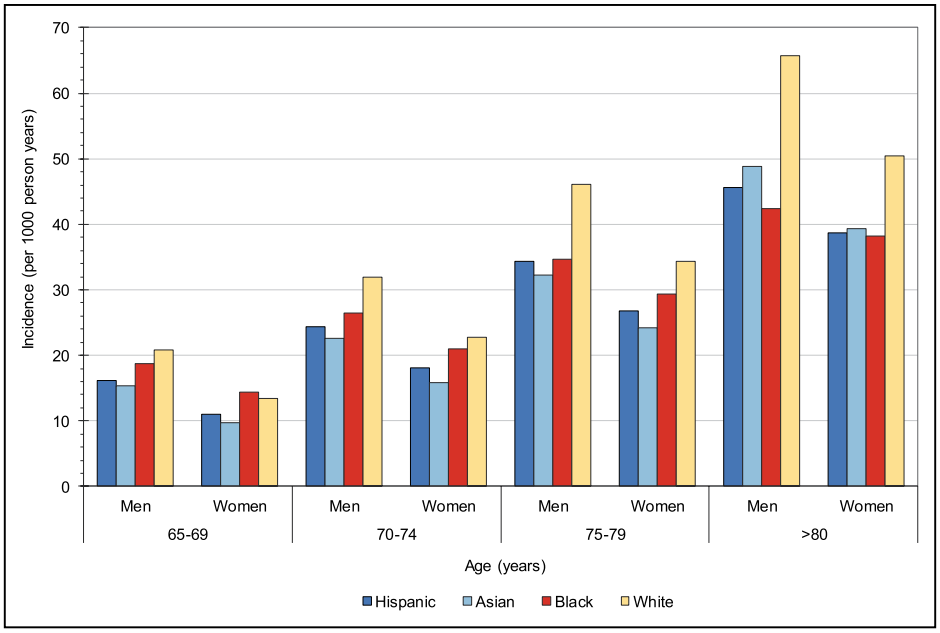

Chart 17-4. Atrial fibrillation incidence by race, 2005 to 2009.
Incidence increased with advancing age among different races and sexes in California.
Source: Data derived from Dewland et al.[68]

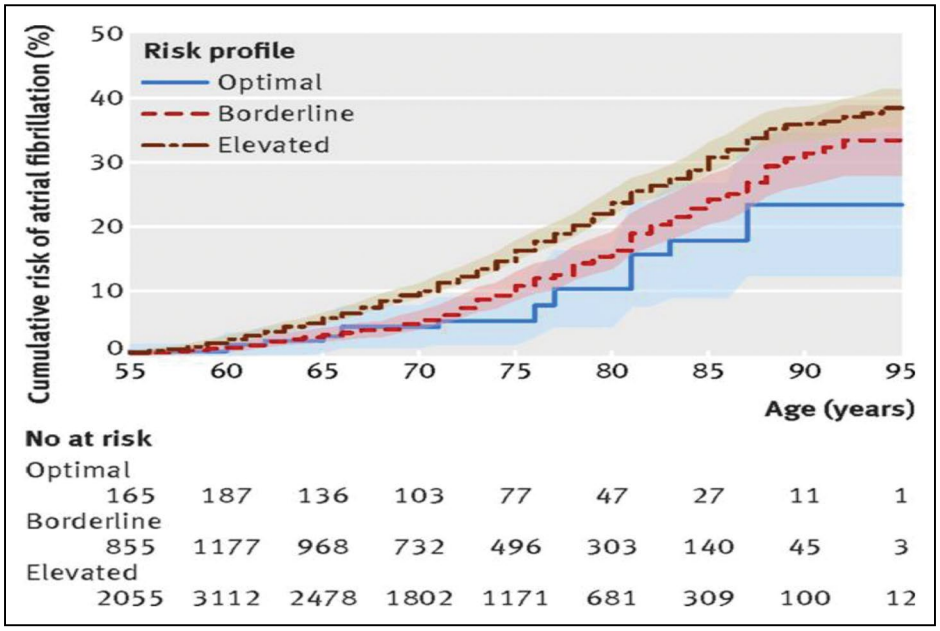

Chart 17-5. Lifetime risk (cumulative incidence at 95 years of age) for atrial fibrillation at different ages (through 94 years of age) by sex in the FHS, 1968 to 2014.
FHS indicates Framingham Heart Study.

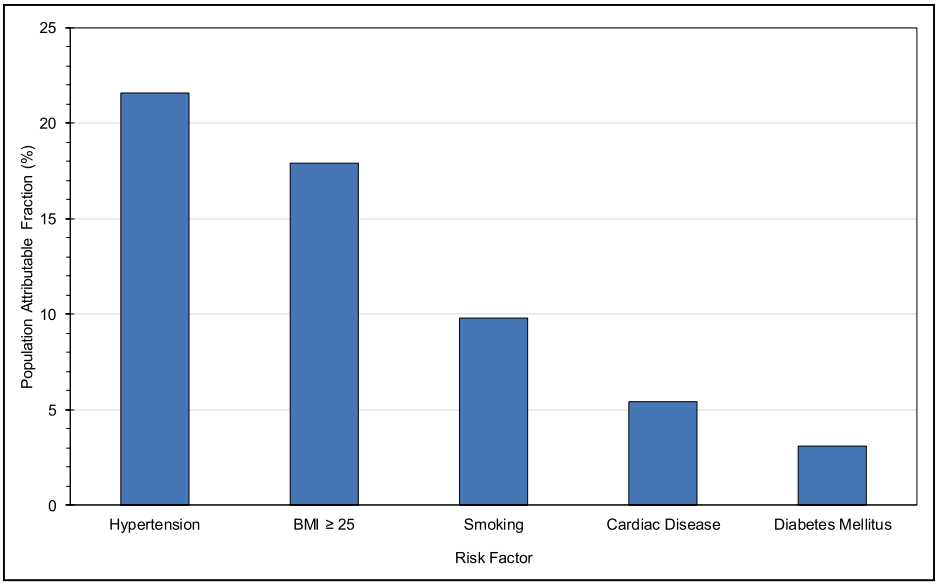

Chart 17-6. Population attributable fraction of major risk factors for atrial fibrillation in the ARIC study, 1987 to 2007.
ARIC indicates Atherosclerosis Risk in Communities; BMI, body mass index (in kg/m^2); cardiac disease, patients with history of coronary artery disease or heart failure; and smoking, current smoker.
Source: Data derived from Huxley et al.[81]

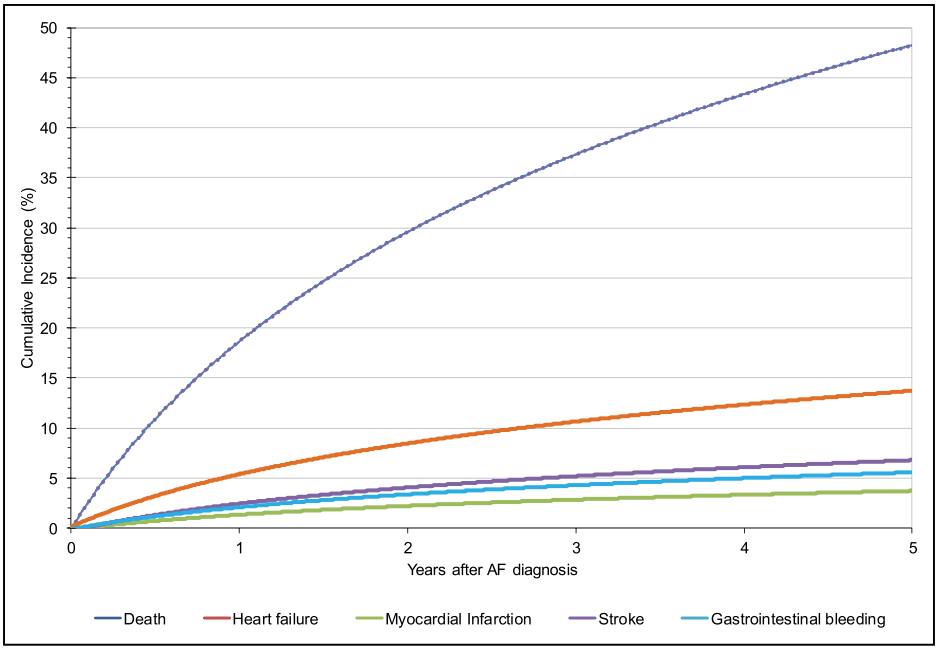

Chart 17-7. Cumulative incidence of events in the 5 years after diagnosis of incident AF in Medicare patients in the United States, diagnosed 1999 to 2007.
AF indicates atrial fibrillation.
Source: Reprinted from Piccini et al[240] by permission of the European Society of Cardiology. Copyright © 2013, The Authors.

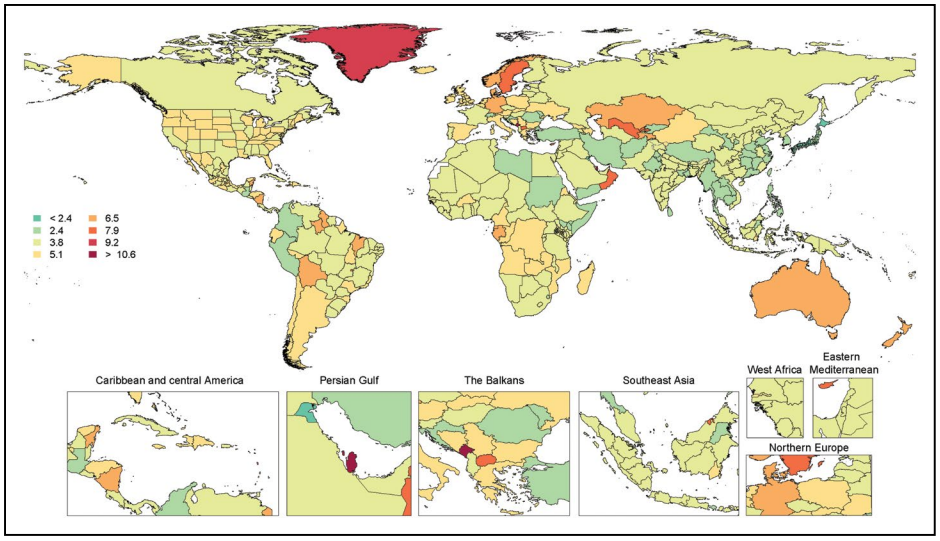

Chart 17-8. Age-standardized global mortality rates of atrial fibrillation and atrial flutter per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[265] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[267]

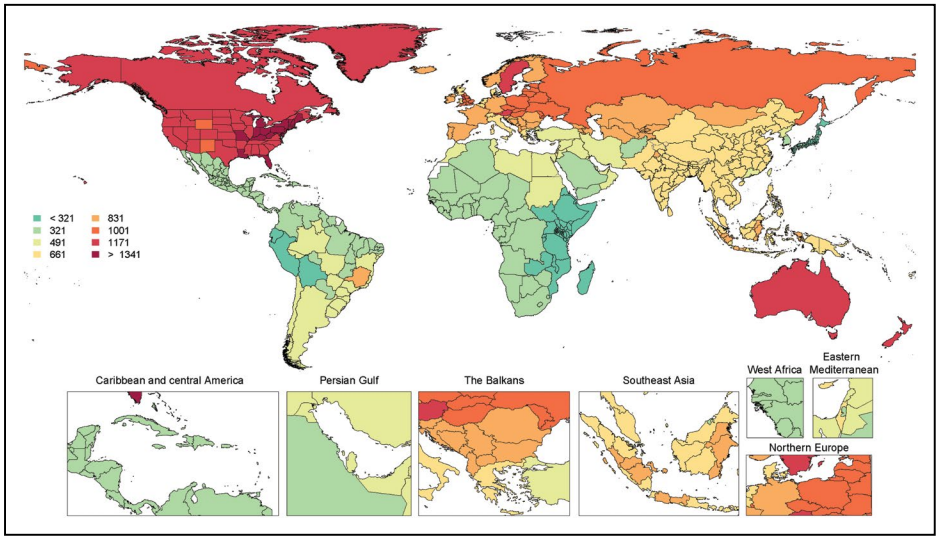

Chart 17-9. Age-standardized global prevalence rates of atrial fibrillation per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[265] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[267]

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18. SUDDEN CARDIAC ARREST, VENTRICULAR ARRHYTHMIAS, AND INHERITED CHANNELOPATHIES

See Tables 18-1 through 18-7 and Charts 18-1 through 18-4

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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.

2018: Mortality—18 989. Any-mention mortality—377 763.

Abbreviations Used in Chapter 18

ACS	acute coronary syndrome
ACTION	Acute Coronary Treatment and Intervention Outcomes Network
AED	automated external defibrillator
AF	atrial fibrillation
AHA	American Heart Association
aHR	adjusted hazard ratio
AMI	acute myocardial infarction
aOR	adjusted odds ratio
ARGEN-IAM-ST	National Survey of ST-Segment Elevation Acute Myocardial Infarction in Argentina
ARIC	Atherosclerosis Risk in Communities study
ARVC	arrhythmogenic right ventricular cardiomyopathy
AUC	area under the curve
CARES	Cardiac Arrest Registry to Enhance Survival
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CPC	Cerebral Performance Category
CPR	cardiopulmonary resuscitation
CPVT	catecholaminergic polymorphic ventricular tachycardia
CVD	cardiovascular disease
DCM	dilated cardiomyopathy
DVT	deep vein thrombosis

(*Continued*)

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Abbreviations Used in Chapter 18 Continued

ECG	electrocardiogram
ED	emergency department
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EMS	emergency medical services
ERP	early repolarization pattern
GWAS	genome-wide association study
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
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
ICU	intensive care unit
IHCA	in-hospital cardiac arrest
IHD	ischemic heart disease
IQR	interquartile range
LQTS	long-QT syndrome
LV	left ventricular
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MET	metabolic equivalent
MI	myocardial infarction
MUSIC	MUerte Subita en Insuficiencia Cardiaca
NCDR	National Cardiovascular Data Registry
NEDS	Nationwide Emergency Department Sample
NH	non-Hispanic
NIS	National (Nationwide) Inpatient Sample
NSTEMI	non–ST-segment–elevation myocardial infarction
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
PA	physical activity
PCI	percutaneous coronary intervention
PE	pulmonary embolism
PEDS	pediatrics
PEA	pulseless electric activity
PVC	premature ventricular contraction
QTc	corrected QT interval
REDINSCOR	Red Española de Insuficiencia Cardiaca
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
SES	socioeconomic status
STEMI	ST-segment–elevation myocardial infarction
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.

2018: Mortality—984. Any-mention mortality—8461.

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 (<1 year of age), children (1–18 years of age), 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 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 18-1 through 18-3)

- 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 18-1).
- The ongoing CARES registry[5] estimates the incidence of EMS-treated OHCA among individuals of any age in >1600 EMS agencies in the United States (Table 18-1).
- Incidence of EMS-assessed OHCA for 2015 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).[6]
- Incidence of EMS-treated OHCA in people of any age is 57 individuals per 100 000 population based on the 2013 CARES registry of EMS-treated OHCA and 63.8 individuals per 100 000 population based on the 2013 ROC registry.[7]
- Incidence of EMS-treated OHCA in people of any age is 76.5 individuals per 100 000 population based on the 2019 CARES registry, with >2-fold variation between states (range, 41.8–126.1; Table 18-2).
- Of the 3 686 296 hospital discharges from academic medical centers in 2012, 33 700 (0.91%) included a cardiac arrest diagnosis.[8]
- Incidence of maternal cardiovascular collapse requiring CPR during childbirth was 10 in 250 719 (4.0 per 100 000 births) in a registry of births in New York.[9]
- Incidence of IHCA among 15 953 rapid response team calls in Australia was 159 cases in 152 individuals or 0.62 IHCAs per 1000 multiday admissions (IQR, 0.50–1.19).[10]
- In the NIS for 2016:
  - Cardiac arrest or VF/flutter was included in 273 295 hospital discharges (rate of 84.6 per 100 000 people). For 9.5% (26 040), this was the principal diagnosis for hospital admission.
  - *ICD-10* codes for CPR or defibrillation were included in 286 945 hospital discharges (rate of 88.8 per 100 000 people).[11]
- In the NEDS for 2016:
  - The weighted national estimate of ED visits with a principal diagnosis of cardiac arrest or VF/flutter was 183 629 (rate of 56.8 per 100 000 people). Of these, 15.8% (29 096) were admitted to the same hospital or transferred to another hospital (Table 18-3).
  - Cardiac arrest or VF/flutter was estimated at 404 691 visits among all listed diagnoses, but this larger number may include patients with cardiac arrest after hospital admission (Table 18-3).
  - The weighted national estimate of ED visits including *ICD-10* codes for CPR or defibrillation was 187 097 (rate of 57.9 per 100 000 people; unpublished tabulation using HCUP,[11] 2016).

OHCA: Adults

(See Table 18-4)

- Incidence of EMS-assessed OHCA for 2015 in adults was 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).[6]

- Incidence of EMS-treated OHCA in adults for 2015 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 in adults 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).[12]
- In 2019, location of OHCA in adults was most often a home or residence (70.0%), followed by public settings (18.8%) and nursing homes (11.2%; Table 18-4). OHCA in adults was witnessed by a layperson in 38.3% of cases or by an EMS provider in 12.7% of cases. For 49.0% of cases, collapse was not witnessed.[5]
- Initial recorded cardiac rhythm was VF or VT or shockable by an automated external defibrillator in 19.2% of EMS-treated adult OHCAs in 2019 (Table 18-4).
- Of 4729 patients with STEMI in Los Angeles County, CA, from 2011 to 2014, 422 (9%) had OHCA.[13]
- Of 851 line-of-duty firefighter fatalities with adjudicated cause of death, 319 (37%) were cardiac in origin.[14]
- In a clinical trial of a wearable defibrillator in 2302 patients with reduced EF (<35%) after AMI, 44 patients (1.9%) had arrhythmic sudden death, 21 (0.9%) had appropriate defibrillator shock, and 86 (3.7%) had death attributable to any cause during the first 90 days.[15]

IHCA: Adults (See Table 18-4)

- Incidence of adult IHCA was a mean of 10.16 (SD, 26.08) per 1000 hospital admissions and 1.99 (SD, 1.57) per 1000 inpatient days in the 2019 GWTG data (GWTG–Resuscitation, unpublished data, 2019).
- 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]
- Incidence of IHCA was 1.7 per 1000 hospital admissions based on 18 069 patients with IHCA in the Swedish Register of CPR.[17]
- IHCA within the first 24 hours after admission for STEMI occurred in 7.8% (136) of 1754 patients in the ARGEN-IAM-ST. Features associated with IHCA were older age and cardiogenic shock.[18]
- MI with OHCA or cardiac arrest in the ED occurred in 9682 (3.8%) of 252 882 patients from 224 hospitals in the NCDR ACTION Registry (2594 or 1.6% of patients with NSTEMI and 7088 or 7.5% of patients with STEMI).[19]
- IHCA incidence was 320 (1.50%) of 21 337 patients with ACS admitted to 3 hospitals in China from 2012 to 2016.[20]
- According to 2019 GWTG data, location of adult IHCA was the ICU, operating room, or ED in 54.6% and noncritical care areas in 45.4% among 28 012 events at 332 hospitals (Table 18-4).
- Initial recorded cardiac rhythm was VF or VT or shockable in 15.4% of adult IHCAs in 2019 GWTG data (GWTG–Resuscitation, unpublished data, 2019; Table 18-4).

OHCA: Children

- Incidence of EMS-assessed OHCA in children in 2015 was 7037 (quasi CI, 6214–7861) in the United States based on extrapolation from ROC for individuals <18 years of age (ROC Investigators, unpublished data, July 7, 2016).
- In 2019, location of EMS-treated OHCA was home for 91.0% of children ≤1 year of age, 83.4% of children 1 to 12 years of age, and 76.2% of children 13 to 18 years of age in the CARES 2018 data. Location was a public place for 9.0% of children ≤1 year of age, 16.4% of children 1 to 12 years of age, and 22.9% of children 13 to 18 years of age.[5]
- Annual incidence of pediatric OHCA was 8.7 per 100 000 population in Western Australia from 2011 to 2014.[21]

Sports-Related SCA/SCD

- Sports-related SCA accounted for 39% of SCAs among those ≤18 years of age, 13% for those 19 to 25 years of age, and 7% for those 25 to 34 years of age in a prospective registry of 3775 SCAs in Portland, OR, between 2002 and 2015 that included 186 SCAs in young people (5–34 years of age).[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 of age was 0.76 per 100 000 athlete-years in a population-based registry of all

paramedic responses in Toronto, ON, Canada, from 2009 to 2014.[24]
- Incidence of SCD, estimated via LexisNexis and public media reports, during youth sport participation, estimated by the Sport and Fitness Industry Association, from 2007 to 2015 was 1.83 deaths per 10 million athlete-years.[25]
- Studies that included >14 million participants in long-distance or marathon running events from 1976 to 2009 reported race-related incidence of SCA or SCD ranging from 0.6 to 1.9 per 100 000 runners using various methods to ascertain events.[26] Only 2 deaths were reported among 1 156 271 participants in half-marathons or full marathons in Sweden from 2007 to 2016, yielding an estimated SCD incidence of 0.24 (95% CI, 0.04–0.79) per 100 000 runners.[27]
- 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]
- Among 55 patients admitted to 8 Spanish hospitals with SCA during or within 1 hour of vigorous sport activities between 2007 and 2016, 90.9% were male, mean (SD) age was 47 (15) years, and 96.4% presented with shockable rhythm. The cause of SCA varied by age: 25% cardiomyopathy, 63% idiopathic VF, and 13% AMI for those <35 years of age; and 9% cardiomyopathy, 18% idiopathic VF, 67% AMI, and 7% unknown for those ≥35 years of age.[28]
- Preparticipation screening of 5169 middle and high school students (mean [SD] age, 13.06 [1.78] years) from 2010 to 2017 revealed high-risk cardiovascular conditions in 1.47%.[29] Anatomic findings included DCM (n=11), nonobstructive HCM (n=3), and anomalous coronary artery origins (n=23). Electrocardiographic findings included WPW (n=4), prolonged QT intervals (n=34), and Brugada pattern (n=1).

IHCA: Children (See Table 18-4)

- Incidence of IHCA for children (30 days–18 years of age) was a mean 12.22 (SD, 42.13) per 1000 admissions and 1.78 (SD, 5.13) per 1000 inpatient days for 598 events from 80 hospitals per 2019 GWTG data (GWTG–Resuscitation, unpublished data, 2019).
- Of 598 events of IHCA in children (30 days–18 years of age) at 80 hospitals, 85.7% occurred in the ICU, operating room, or ED and 14.3% in noncritical care areas per 2019 GWTG data (Table 18-4).
- Incidence of IHCA was 1.8 CPR events per 100 pediatric (<18 years of age) ICU admissions (sites ranged from 0.6–2.3 per 100 ICU admissions) in the Collaborative Pediatric Critical Care Research Network data set of 10 078 pediatric ICU admissions from 2011 to 2013.[30]
- In a registry of 23 cardiac ICUs in the Pediatric Critical Care Consortium that included 15 908 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).[31]
- Initial recorded cardiac arrest rhythm was VF or VT or shockable in 8.1% of 598 events at 80 hospitals in GWTG–Resuscitation in 2018 (Table 18-4).

Lifetime Risk and Cumulative Incidence (See Table 18-5 and Chart 18-1)

- SCD appeared among the multiple causes of death on 13.3% of death certificates in 2018 (377 763 of 2 839 205), which suggests that 1 of every 7.5 people who died in the United States died of SCD (Table 18-5). Because some people survive SCA, the lifetime risk of cardiac arrest is even higher.
- In 2018, infants had a higher incidence of SCD (10.9 per 100 000) than older children (1.2–2.1 per 100 000). Among adults, risk of SCD increased exponentially with age, surpassing the risk for infants by 35 to 39 years of age (13.2 per 100 000; Chart 18-1).
- Of 2656 Finnish males 42 to 60 years of age randomly selected from 1984 to 1989 and prospectively followed up until 2008, a total of 193 (7.3%) had SCD.[32]

Secular Trends (See Table 18-1 and Charts 18-2 and 18-3)

- 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; Table 18-1).
- The annual rate of SCD among patients with HFrEF has declined from 6.5% to 3.3% based on analysis of 3583 cases of SCD among 40 195 patients

enrolled in 12 clinical trials in which enrollment started between 1995 and 2010.[33] This analysis estimates that the current cumulative incidence of SCD in patients with HFrEF is 1% by 3 months, <2% by 6 months, and 8.8% by 3 years.

- Incidence of pediatric OHCA declined from 1997 to 2014 in Perth, Western Australia, particularly among children <1 year of age.[21]
- Incidence of pediatric (<16 years of age) OHCA that was EMS attended (6.7 per 100 000) or EMS treated (4.9 per 100 000) did not change from 2000 to 2016 in Victoria, Australia.[34] Survival to hospital discharge increased from 9.4% to 17.7%.
- Rate of SCD (6.8% versus 11.4% over 4 years) and hazard of SCD in propensity-matched cohorts (subhazard ratio, 0.46 [95% CI, 0.30–0.70]) decreased over time in outpatients with HFrEF (<40%) based on 2 multicenter prospective registries (MUSIC (n=641, period: 2003–2004) and REDINSCOR I (n=1710, period: 2007–2011).[35] This reduction in SCD was associated with more frequent use of β-blockers (85% versus 71%), mineralocorticoid antagonists (64% versus 44%), implantable cardioverter-defibrillators (19% versus 2%), and resynchronization therapy (7.2% versus 4.8%).
- Age-adjusted death rates for any mention of SCD declined from 137.7 per 100 000 person-years in 1999 to 94.8 per 100 000 person-years by 2018 (Chart 18-2).
- Unadjusted survival to hospital discharge after EMS-treated OHCA increased from 10.2% in 2006 to 12.4% in 2015 in the ROC Epistry (Table 18-1).
- Crude incidence of OHCA significantly increased from 64.75 to 76.10 per 100 000 from 2002 to 2014 in a registry of 30 560 patients from Queensland, Australia.[36] Rates of return of spontaneous circulation also increased from 6.31 to 9.99 per 100 000.
- Survival after IHCA in children increased from 28.5% to 53.8% between 2000 and 2016 and then declined to 52.4% by 2019 in GWTG data (Chart 18-3).
- A national database of 120 365 adult, medical OHCAs in the Republic of Korea from 2006 to 2015 reported increases over time in layperson CPR (1.2% to 17.0%), age- and sex-adjusted survival (3.0% to 8.0%), and good functional recovery (0.9% to 5.8%).[37] Layperson CPR rates increased more in the highest socioeconomic quintile (1.6% to 32.5%) than in the lowest socioeconomic quintile (1.6% to 15.3%).

Risk Factors (See Chart 18-4)

- SCA and SCD result from many different disease processes, each of which can have different risk factors. Among patients with OHCA resuscitated and hospitalized from 2012 to 2016, ACS and other cardiac causes accounted for the largest proportion of causes. Among patients with IHCA, respiratory failure was the most common cause (Chart 18-4).[38]
- Among patients with DCM considered at low arrhythmic risk (LVEF >35% and New York Heart Association class I–III on optimal medical therapy), 14 (3.9%) of 360 had SCD and 16 (4.4%) had major ventricular arrhythmias (SCA or implantable cardioverter-defibrillator intervention) during a median follow-up of 152 months.[39] Events were associated with larger left atrial end-systolic area and arrhythmogenic profile (history of syncope, nonsustained VT, at least 1000 PVCs per 24 hours, or at least 50 ventricular couplets per 24 hours at Holter electrocardiographic monitoring).
- Of 2937 OHCA cases of SCA in people 2 to 45 years of age from 2009 to 2012 in Toronto, 1892 (64.4%) had presumed cardiac cause by Utstein definitions, but after detailed investigation, only 608 (20.7%) had an adjudicated pathology of cardiac cause.[40] Noncardiac causes comprised 130 (4.4%) blunt, penetrating, or burn injury traumas; 687 (23.4%) suicides; 521 (17.7%) drug overdoses; 288 (9.8%) acute noncardiac illnesses (eg, terminal illness); 218 (7.4%) motor vehicle collisions; 106 (3.6%) noncardiac vascular causes; 32 (1.1%) drownings; and 24 (0.82%) homicides.
- Among 608 OHCA cases of SCA with cardiac causes in people 2 to 45 years of age from 2009 to 2012 in Toronto, 243 (40%) were attributed to CHD, 174 (28.6%) were attributed to structural diseases of the myocardium, 98 (16.1%) were attributed to sudden unexplained death, 15 (2.5%) were attributed to other cardiac causes (anomalous coronary arteries, congenital HD, and tamponade), and 78 (12.8%) remained unspecified.
- Incidence of OHCA increased with daily atmospheric levels of particulate matter in 249 372 OHCAs in Japan from 2014 to 2015 (OR, 1.016 [95% CI, 1.009–1.023] per 10-μg/m^3 increase in $PM_{2.5}$).[41]
- Among 5869 autopsied subjects with SCD, after exclusion of cases with noncardiac causes of death, in Finland between 1998 and 2017, ischemic cardiac disease represented 4392 (74.8%) and nonischemic cardiac diseases represented 1477 (25.2%).[42] Over time, the proportion of ischemic SCD declined from 78.8% (1998–2002) to 72.4% (2013–2017).

Age (See Chart 18-1)

- In 2018, mortality rates for any mention of SCD decreased for those 0 to 9 years of age and increased from 10 years of age onward (Chart 18-1).

Sex

- According to multiple studies, females compared with males with OHCA are older, less likely to present with shockable rhythms, and less likely to collapse in public. Despite these factors that would reduce survival, females have equivalent or higher rates of survival to hospital discharge or to 30 days relative to males.[43]
- In a registry that included 40 159 OHCAs from 2009 to 2012 in Singapore, Japan, the Republic of Korea, Malaysia, Thailand, Taiwan, and the United Arab Emirates, OHCA was more common in males (60%) than females (40%).[44] Females were older, more often presented in a nonshockable rhythm, and more often received layperson CPR, but they less often collapsed in public. There was no difference between sexes in survival of the event or survival to hospital discharge after adjustment for these factors.
- In an EMS-based registry of 3862 OHCAs from 2013 to 2015 that includes 90% of the population of New Zealand, OHCA was more common in males (69%) than females (31%).[45] This study found the same differences between sexes in age, rhythm, location of arrest, and witnessed collapse, as well as the absence of any difference in survival of the event or 30-day survival after adjustment for these factors.

Race

- In the ARIC study, 215 of 3832 (5.61%) Black and 332 of 11 237 (2.95%) White participants experienced SCD during 27.4 years of follow-up.[46] The sex-adjusted HR for SCD comparing Black with White participants was 2.12 (95% CI, 1.79–2.51), and the fully adjusted HR was 1.38 (95% CI, 1.11–1.71).
- In patients with implanted defibrillators, the rate of first ventricular dysrhythmia or death within 4 years was higher among Black patients (42%) than White patients (34%; aHR, 1.60 [95% CI, 1.18–2.17]).[47]

Socioeconomic Factors

- OHCA incidence in 123 municipalities surrounding Paris has strong geographic variations (RR varies from 0.23–2) based on 3414 cases from 2013 to 2015. Municipalities with a high SCA incidence are characterized by a lower SES and more social deprivation as measured with the Human Development Index 2.[48]
- In King County, Washington, SCA was more common in census tracts with more pharmacies or other medical facilities (OR, 1.28 [95% CI, 1.03–1.59]).[49]
- In a national database of 120 365 adult, medical OHCAs in the Republic of Korea from 2006 to 2015, there were differences from the lowest to highest socioeconomic quintiles for layperson CPR (5.5% to 11.4%), survival to hospital discharge (3.8% to 6.1%), and good functional recovery (1.9% to 2.9%).[37]

HD, Cardiac Risk Factors, and Other Comorbidities

- Incidence of SCD was 0.10 per 100 patient-years (95% CI, 0.07–0.14) in a cohort of 33 of 3242 untreated hypertensive patients without evidence of coronary or cerebrovascular HD at entry and followed up for an average of 10.3 years.[50] For patients without and with electrocardiographic signs of LVH, rate of SCD was 0.07 versus 0.30 per 100 patient-years (aHR, 2.99 [95% CI, 1.47–6.09], adjusted for age, sex, diabetes, and 24-hour ambulatory pulse pressure).
- Among 2656 Finnish males 42 to 60 years of age randomly selected from 1984 to 1989 and prospectively followed up until 2008, the hazard for SCD increased with below-median (7.9 METs) baseline cardiopulmonary fitness (HR, 1.6 [95% CI, 1.1–2.3]) and below-median (191 kcal/d) leisure-time PA (HR, 1.4 [95% CI, 1.0–2.0]).[32]
- In a cohort of 233 970 patients from the United Kingdom, resting heart rate >90 bpm was associated an increased hazard of SCD or cardiac arrest as initial presentation of HD (aHR, 2.71 [95% CI, 1.90–3.83]).[51]
- In a cohort of 1 937 360 patients from the United Kingdom registered between 1997 and 2010, smoking was not associated with hazard of SCD or cardiac arrest as the initial presentation of HD (age-adjusted HR, 1.04 [95% CI, 0.91–1.09]), but it was associated with increased risk of unheralded death caused by CHD (age-adjusted HR, 2.70 [95% CI, 2.27–3.21]), a phenotype that may overlap with SCD.[52]
- In a cohort of 1 937 360 patients from the United Kingdom registered between 1997 and 2010, heavy drinking (aHR, 1.50 [95% CI, 1.26–1.77]) and former drinking (aHR, 1.37 [95% CI, 1.12–1.67]) were associated with increased hazard of SCD or cardiac arrest as the initial presentation of HD.[53]
- Among 7011 patients admitted to the hospital with acute HF, the 30-day rate of SCD, SCA, or VT/VF was 1.8% (n=121).[54] Events were associated with male sex (aOR, 1.73 [95% CI, 1.07–2.49]), history of VT (aOR, 2.11 [95% CI, 1.30–3.42]), chronic obstructive pulmonary disease (aOR, 1.63 [95% CI, 1.07–2.49]), or prolonged QRS interval (aOR, 1.10 [95% CI, 1.03–1.17] per 10% increase from baseline).

- Analysis of 76 009 patients including 8401 with AF from 21 studies between 1991 and 2017 found that patients with AF had higher risk of incident SCD/SCA or VF/VT (RR, 2.04 [95% CI, 1.77–2.35]).[55]
- Among 21 105 patients with AF followed up for a median of 2.8 years, SCD accounted for 31.7% of all deaths, with an incidence of 12.9 per 1000 patient-years.[56]
- 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, diabetes, current smoking, and SBP.[57]
- A logistic model incorporating age, sex, race, current smoking, SBP, use of antihypertensive medication, diabetes, 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).[57]
- 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]).[58]
- In a registry of 2119 SCAs in Portland, OR, from 2002 to 2015, prior syncope was present in 6.8% of 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]).[59]
- In a cohort of 5211 Finnish people >30 years of age 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]).[60]
- 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]).[61]

Risk Prediction

Prodromal Symptoms

- 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.[62]
- Early warning score systems using both clinical criteria and vital signs identified hospital patients with a higher risk of IHCA.[63]
- A comparison using receiver-operating curves of early warning score accuracy for predicting risk of IHCA and other serious events for individual patients in the hospital had AUCs of 0.663 to 0.801.[64]
- Among 1352 surgical patients with postoperative IHCA within 30 days, 746 (55%) had developed a postoperative complication (acute kidney injury, acute respiratory failure, DVT/PE, MI, sepsis/septic shock, stroke, transfusion) before the arrest.[65]

Electrocardiographic Abnormalities

- Age- and sex-adjusted prevalence of electrocardiographic abnormalities associated with SCD was 0.6% to 1.1% in a sample of 7889 Spanish citizens ≥40 years of age, including Brugada syndrome in 0.13%, QTc <340 milliseconds in 0.18%, and QTc ≥480 milliseconds in 0.42%.[66]
- 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.[67]
- 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.[68]

Genetics and Family History Associated With SCD

- Exome sequencing in younger (<51 years of age) decedents who had sudden unexplained death or suspected arrhythmic death revealed likely pathogenic variants in channelopathy- or cardiomyopathy-related genes for 29% to 34% of cases.[69,70] Among children with exertion-related deaths, pathogenic mutations were present in 10 of 11 decedents (91%) 1 to 10 years of age and 4 of 21 decedents (19%) 11 to 19 years of age.[71]
- 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%).[72]
- 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%).[73]
- Screening of 292 relatives of 56 probands with SCD revealed a diagnosis in 47 (16.1%) relatives: LQTS (12.7%), CPVT (0.3%), DCM (0.7%), ARVC (0.3%), and thoracic aortic dilation (0.3%). Among relatives completing follow-up, 3.3% had a cardiac event within 3 years and 7.2% within 5 years.[74]

- Prevalence of genetic HD declines with increasing age according to a screening of 180 survivors of SCA, who represented 5.9% of 3037 referrals to a genetic heart rhythm clinic from 1999 to 2017.[75] Among 127 adults, diagnoses included idiopathic VF (44.1%), arrhythmogenic bileaflet mitral valve (14.2%), acquired LQTS (9.4%), LQTS (7.9%), and J-wave syndromes such as Brugada (3.9%). Among 53 children, diagnoses included LQTS (28.3%), CPVT (20.8%), idiopathic VF (20.8%), HCM (5.7%), and triadin knockout syndrome (5.7%).
- Screening of 60 SCA survivors by targeted exome sequencing for 185 clinically relevant cardiac genes revealed a pathogenic variant in 45% of patients, with a 28% yield in patients without any clear cardiac phenotype.[76]

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. For example, a GWAS of 3939 cases with SCA found no variants associated with SCD at genome-wide significance, which suggests that common genetic variation is not a significant risk factor for SCD.[77]
- GWASs have also been conducted using variation in electrocardiographic traits as a phenotype (ie, QRS, QT duration), which have identified novel genetic variants associated with these traits that also associate with cardiac conduction, arrhythmias, and other cardiovascular end points.[78]

Long-QT Syndrome

- Hereditary LQTS is a genetic channelopathy characterized by prolongation of the QT interval (QTc typically >460 milliseconds) and susceptibility to ventricular tachyarrhythmias that lead to syncope and SCD. Investigators have identified rare mutations in 15 genes leading to 17 different subtypes of LQTS phenotype.[79,80] There is variability in presentation, therapeutic approach, and prognosis by subtype.
- Approximately 5% of sudden infant death syndrome and some cases of intrauterine fetal death could be attributable to LQTS.[81]
- Acquired prolongation of the QT interval is common. Prevalence of prolonged QTc was 115 of 412 (27.9%) among adults admitted to an ICU from 2014 to 2016 in Brazil.[82] At least 1 drug known to prolong QT interval was present in 70.4% of these cases.
- Prevalence of prolonged QTc interval was 50 of 712 patients (7%) admitted to a short-stay medical unit in the United Kingdom.[83]
- Prevalence of prolonged QTc interval was 95 of 7522 patients (1.9%) with ECG in the ED from 2010 to 2011, and these prolongations were attributable individually or in combination to electrolyte disturbances (51%), QT-prolonging medical conditions (56%), or QT-prolonging medications (77%).[84]
- Among 65 654 patients on hemodialysis, initiation of a selective serotonin reuptake inhibitor with higher (47.1% of patients) versus lower (52.9% of patients) QT-prolonging potential was associated with higher risk of SCD (aHR, 1.18; 95% CI, 1.05–1.31).[85]
- Genetic testing for LQTS among 281 families had a diagnostic yield for genetic mutations of 47%.[86]
- However, some studies have called into question whether previously identified LQTS genes are truly causative.[87,88] The ClinGen Channelopathy Clinical Domain Working Group, leveraging large publicly available genetic databases, has shown that only 3 genes (*KCNQ1*, *KCNH2*, *SCN5A*) have definitive gene-disease association for typical LQTS, with another 4 having definitive evidence for association with disease onset in childhood (*CALM1*, *CALM2*, *CALM3*, *TRDN*). That group has found that *KCNE1* and *KCNE2*, which are commonly clinically tested, had limited or disputed evidence for typical LQTS but showed strong evidence for association with acquired LQTS.
- GWASs have identified additional rare and common variants in genes associated with QT interval,[87] suggesting that individuals with long QT who are mutation negative could have a polygenic inheritance.

Short-QT Syndrome

Prevalence and Incidence

- Short-QT syndrome is an inherited mendelian condition characterized by shortening of the QT interval (typically QT <320 milliseconds) and predisposition to AF, ventricular tachyarrhythmias, and sudden death. Mutations in 5 ion channel genes (*SQT1–SQT5*) have been described.[89]
- Prevalence of a QTc interval <320 milliseconds in a population of 41 767 young, predominantly male Swiss conscripts was 0.02%,[90] which was identical to prevalence from a Portugal sudden death registry.[91]
- Prevalence of QT interval ≤320 milliseconds in 18 825 apparently healthy people from the United Kingdom 14 to 35 years of age between 2005 and 2013 was 0.1%.[92] Short QT intervals were associated with male sex and Afro-Caribbean ethnicity.

- Prevalence of QT interval ≤340 milliseconds in 99 380 unique patients ≤21 years of age at Cincinnati Children's Hospital between 1993 and 2013 was 0.05%.[93] Of these children, 15 of 45 (33%) were symptomatic.[93]

Genetics

- The genes that have been associated with short-QT syndrome are many of the same ones involved in LQTS, but with opposite effects on channel function, and include potassium channel genes and calcium channel genes. The yield of genetic testing in short-QT syndrome is only 23% of 53 probands.[94]

Brugada Syndrome

Prevalence and Incidence

- Brugada syndrome is an acquired or inherited channelopathy characterized by persistent ST-segment elevation in the right precordial leads (V_1–V_2), either at rest or with provocative testing, and susceptibility to ventricular arrhythmias and SCD.[95] Brugada syndrome is associated with mutations in at least 12 ion channel–related genes.
- In a meta-analysis of 24 studies, the 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.[96] Prevalence was higher in males (0.9%) than in females (0.1%).[97]
- Among 678 patients with Brugada syndrome from 23 centers in 14 countries, patients whose first documented arrhythmic event was SCA had a mean (SD) age of 39 (15) years, whereas age at the first documented arrhythmic event in patients with prophylactic defibrillator implantation was 46 (13) years.[98]

Genetics

- Rare genetic variants in *SCN5A* account for disease in 20% of patients with Brugada syndrome. Variants in additional genes have been reported but remain unclear.[99]
- The large proportion of sporadic cases and variable penetrance in *SCN5A* carriers have suggested a more complex pattern of penetrance, supported by a GWAS of 312 individuals with Brugada syndrome that identified common variants in novel genes as associated with the disease.[100]

Catecholaminergic Polymorphic Ventricular Tachycardia

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 polymorphic VT 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.[101] 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*.[101]
- Prevalence of CPVT is estimated at 1:5000 to 1:10 000, but this could be an underestimate because childhood cases were excluded.[101]
- Analysis of 171 probands with CPVT who were <19 years of age and 65 adult relatives described clinical presentations and prevalence of genotypes.[102] The presenting symptom was cardiac arrest for 28% of cases and syncope/seizure in 58%. Genetic testing of 194 subjects identified variants in *RYR2* (60%), CASQ2 (calsequestrin 2; 5%), *KCNJ2* (1%), and >1 gene in 17 cases (9%). For 23 cases (12%), no genetic variant was identified.

Complications

- In a cohort of 34 patients with CPVT, 20.6% developed fatal cardiac events during 7.4 years of follow up.[103]
- Incidence of SCA in children with ≥2 CPVT gene variants was 11 of 15 (73%).[104] VT or exertional syncope occurred in 3 of the children (20%), and only 1 (7%) was asymptomatic.

Arrhythmogenic RV Dysplasia/ Cardiomyopathy

- 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).[105]

Complications

- 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.[106]
- In a cohort of 502 patients with ARVC, younger patients (<50 years of age versus >50 years of age) were more likely to present with SCA (5% versus 2%) or SCD (7% versus 6%).[107]

Hypertrophic Cardiomyopathy

(Please refer to Chapter 21, Cardiomyopathy and Heart Failure, for statistics on the general epidemiology of HCM.)

Complications

- SCA rates were 2.7%/y in a retrospective cohort of 106 patients with HCM treated medically and followed up for a mean of 7.7 years.[108]
- Hospitalizations related to arrhythmias among patients with HCM increased 10.5% from 7784 in 2003 to 8380 in 2014 in the NIS.[109] Reported arrythmias were AF (34.1%), VT (6.7%), and atrial flutter (4.4%). Mortality declined in patients with HCM with arrhythmia from 6.2% in 2003 to 3.4% in 2014.
- Among 1436 SCA cases in individuals 5 to 59 years of age between 2002 and 2015, HCM was present in 3.2% of those 5 to 34 years of age and 2.2% of those 35 to 59 years of age. This study noted the difficulty of distinguishing HCM from secondary LVH in older patients, who were excluded from the analysis.[110]

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-segment elevation, terminal QRS slurring, terminal QRS notching, J-point elevation, J waves, and other variations. Although the Brugada electrocardiographic pattern is considered an early repolarization variant, it is generally not included in epidemiology assessments of ERP or early repolarization syndrome.[111]
- ERP was observed in 4% to 19% of the population (more commonly in young males and in athletes) and conventionally has been considered a benign finding.[111]
- Among 6631 adults >30 years of age recruited into the Mini-Finland Health Survey, a representative sample of the Finnish population in 1978 to 1980, 793 (12.0%) had ERP.[112]
- Among 11 956 residents of rural Liaoning Province, China, who were ≥35 years of age, 1.3% had ERP, with higher prevalence in males (2.6%) than females (0.2%).[113]
- In an Italian public health screening project, 24% of 13 016 students 16 to 19 years of age had at least 1 of the following electrocardiographic abnormalities: ventricular ectopic beats, atrioventricular block, Brugada-like electrocardiographic pattern, left anterior/posterior fascicular block, LVH/RV hypertrophy, long/short QT interval, left atrial enlargement, right atrial enlargement, short PQ interval, and ventricular preexcitation WPW syndrome.[114]

Complications

- ERP was associated with increased age- and sex-adjusted hazard of SCD among people 30 to 50 years of age in the Mini-Finland Health Survey (HR 1.72 [95% CI, 1.05–2.80]).[112]
- Shocks from an automatic implantable cardioverter-defibrillator occur more often and earlier in survivors of idiopathic VF with inferolateral early repolarization syndrome.[115]

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 electrocardiographic 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]).[116] 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.
- Among 698 patients with cardiac resynchronization therapy, 3-year risk of VT/VF was higher in patients with >10 PVCs per hour (24%) than in patients with <10 PVCs per hour (8%; aHR, 2.79 [95% CI, 1.69–4.58]).[117]

Monomorphic VT

Prevalence and Incidence

- Monomorphic VT occurred in 9 of 342 (2.6%) patients at a median of 1 (IQR, 0.25–4.75) day after PCI for chronic total occlusion of a coronary artery.[118]
- During a mean follow-up period of 85 months, sustained VT was observed in 13 of 250 (5.2%) and monomorphic VT in 9 of 250 (3.6%) patients with congenital LV aneurysms or diverticula.[119]

Polymorphic VT

Prevalence and Incidence

- In the setting of AMI, the prevalence of polymorphic VT was 4.4%.[120]

Complications

- In the setting of AMI, polymorphic VT is associated with increased mortality (17.8%).[120]

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 torsade de pointes.[121]

Risk Factors

- An up-to-date list of drugs with the potential to cause torsade de pointes is available at a website maintained by the University of Arizona Center for Education and Research on Therapeutics.[122]

Awareness and Treatment (See Table 18-1)

- Median annual CPR training rate for US counties was 2.39% (25th–75th percentiles, 0.88%–5.31%) 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.[123] 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.[124] 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,[125] 68% of citizens in Victoria, Australia,[126] 61.1% of laypeople in the United Kingdom,[127] and 49% of people in the Republic of Korea,[128] according to surveys.
- Prevalence of prior CPR training among 1076 adults in all states and territories in Australia was 540 (55.7%). The majority of respondents replied "unsure" (n=404, 37.6%) or "no" (n=316, 29.4%) when asked if they knew the difference between a cardiac arrest and a heart attack. Of respondents with CPR training, 227 (42%) received training >5 years ago.[129]
- Laypeople with knowledge of automated external defibrillators include 69.3% of people in the United Kingdom, 66% in Philadelphia, PA, and 32.6% in the Republic of Korea.[127,128,130] A total of 58% of Philadelphia respondents[130] but only 2.1% of UK respondents[127] reported that they would actually use an automated external defibrillator during a cardiac arrest.
- A survey of 5456 households in Beijing, China, Shanghai, China, and Bangalore, India, found that 26%, 15%, and 3% of respondents, respectively, were trained in CPR.[131]
- A survey of 501 inhabitants of Vienna, Austria, found that 52% would recognize cardiac arrest, 50% were willing to use an automated external defibrillator, and 33% were willing to do CPR.[132]
- Laypeople in the United States initiated CPR in 41.6% of OHCAs in CARES 2019 data (Table 18-1).
- Layperson CPR rates in Asian countries range from 10.5% to 40.9%.[133]
- Layperson CPR among 4525 witnessed pediatric OHCAs was 831 of 1669 (36.9%) for female patients versus 1336 of 2856 (46.8%) for male patients.[134]
- Laypeople in the United States were less likely to initiate CPR for people with OHCA in low-income Black neighborhoods (OR, 0.49 [95% CI, 0.41–0.58])[135] or in predominantly Hispanic neighborhoods (OR, 0.62 [95% CI, 0.44–0.89]) than in high-income White neighborhoods.[136]
- Laypeople from Hispanic and Latino neighborhoods in Denver, CO, reported 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.[137]

Mortality (See Tables 18-1, 18-2, and 18-5 and Chart 18-1)

- In 2018, primary-cause SCD mortality was 18 989, and any-mention SCD mortality in the United States was 377 763 (Table 18-5). The any-mention age-adjusted annual rate is 94.8 (95% CI, 94.5–95.1) SCDs per 100 000 population.[138]
- 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.[8]
- Survival after OHCA varied between US regions (4.2%–19.8%) in the ROC Epistry from 2011 to 2015.[139] This variation was more marked at the level of EMS agencies (0%–28.9%) and persisted after adjustment for multiple patient, resuscitation, and hospital variables.[140]
- Survival after EMS-treated OHCA was 10.6% in the 2019 CARES registry, with variation between states reporting data (range, 6.0%–16.0%; Tables 18-1 and 18-2).
- Of 1 452 808 death certificates from 1999 to 2015 for US residents 1 to 34 years of age, 31 492 listed SCD (2%) as the cause of death, for an SCD rate of 1.32 per 100 000 individuals.[141]
  - SCD rate varied by age, from 0.49 per 100 000 (1–10 years of age) to 2.76 per 100 000 (26–34 years of age).
  - The rate of SCD declined from 1999 to 2015, from 1.48 to 1.13 per 100 000 individuals.

- Mortality rates for any mention of SCD by age are provided in Chart 18-1.

OHCA: Adults (See Tables 18-4 and 18-6)

- Survival to hospital discharge after EMS-treated OHCA was 10.5% and survival with good functional status was 8.5% based on 98002 adult cases in CARES for 2019 (Table 18-4).[5]
- Survival to hospital admission after EMS-treated nontraumatic OHCA in 2019 was 28.0% for all presentations, with higher survival rates in public places (40.7%) and lower survival rates in homes/residences (26.1%) and nursing homes (18.3%) in the 2019 CARES registry (Table 18-6).
- Survival to hospital discharge varied between regions of the United States, being higher in the Midwest (aOR, 1.16 [95% CI, 1.02–1.32]) and the South (aOR, 1.24 [95% CI, 1.09–1.40]) relative to the Northeast, in 154177 patients hospitalized after OHCA in the NIS (2002–2013).[142]
- Survival at 1, 5, 10, and 15 years was 92.2%, 81.4%, 70.1%, and 62.3%, respectively, among 3449 patients surviving to hospital discharge after OHCA from 2000 to 2014 in Victoria, Australia.[143]
- Patients with STEMI who had OHCA had higher in-hospital mortality (38%) than patients with STEMI without OHCA (6%) in a Los Angeles, CA, registry of 4729 patients with STEMI from 2011 to 2014.[13]
- Survival to 30 days was lower for 2516 patients in nursing homes (1.7% [95% CI, 1.2%–2.2%]) than for 24483 patients in private homes (4.9% [95% CI, 4.6%–5.2%]) in a national database in Denmark from 2001 to 2014.[144]

Sports-Related SCA/SCD

- 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 18-4 and Chart 18-3)

- Survival to hospital discharge was 26.7% of 28012 adult IHCAs at 332 hospitals in GWTG 2019 data (Table 18-4 and Chart 18-3). Among survivors, 80.3% 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.[145]
- Unadjusted survival to 30 days after IHCA was 28.3% and survival to 1 year was 25.0% in 18069 patients from 66 hospitals between 2006 and 2015 in the Swedish Register of CPR.[17]
- Survival to hospital discharge after IHCA was lower for males than for females (aOR, 0.90 [95% CI, 0.83–0.99]) in a Swedish registry of 14933 cases of IHCA from 2007 to 2014.[146]
- Mortality was lower among 348368 patients with IHCA managed in teaching hospitals (55.3%) than among 376035 managed in nonteaching hospitals (58.8%), even after adjustment for baseline patient and hospital characteristics (aOR, 0.92 [95% CI, 0.90–0.94]).[147]

OHCA: Children (See Table 18-7)

- Survival to hospital discharge after EMS-treated nontraumatic cardiac arrest in 2015 was 13.2% (95% CI, 7.0%–19.4%) for children in the ROC Epistry (ROC Investigators, unpublished data, July 7, 2016).
- Survival to hospital discharge was 6.8% for 1299 children ≤1 year of age, 15.0% for 835 children 1 to 12 years of age, and 16.2% for 550 children 13 to 18 years of age in CARES 2019 data (Table 18-7).
- In a registry including 974 children with OHCA from 2009 to 2012 in Singapore, Japan, the Republic of Korea, Malaysia, Thailand, Taiwan, and the United Arab Emirates, 8.6% (range, 0%–9.7%) of children survived to hospital discharge.[148]

IHCA: Children (See Table 18-4)

- Survival to hospital discharge after pulseless IHCA was 42.3% in 598 children 0 to 18 years of age and 27.4% in 166 neonates (0–30 days old) per 2019 GWTG data (GWTG–Resuscitation, unpublished data, 2019; Table 18-4).
- 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.[30]

Complications (See Tables 18-6 and 18-7)

- Survivors of cardiac arrest experience multiple medical problems related to critical illness, including impaired consciousness and cognitive deficits (Tables 18-6 and 18-7).
- Functional impairments are associated with reduced function, reduced quality of life, and shortened life span.[149,150]
- 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.[151,152]

- 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.[153]
- 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%).[154] Subjective symptoms declined over time after SCA, although 10% to 22% had cognitive impairments at 12 months, with executive functioning being most affected.[155]
- Of 141 individuals who survived hospitalization after SCA, 41 (72%) returned to work by 12 months.[154]
- 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.[156]
- Of 153 survivors of OHCA 18 to 65 years of age in Paris, France, between 2000 and 2013, 96 (63%) returned to work after a mean (SD) of 714 (1013) days.[157] Younger patients with a higher-level job and for whom cardiac arrest occurred in the workplace were more likely to return to work.
- Of 206 patients who survived to 1 year after OHCA in Finland, 188 (91.3%) were living at home.[158] Among 95 patients who were employed before the arrest, 69 (72.6%) had returned to work, whereas 23 (24.2) had stopped work specifically because of their medical condition.
- Among 195 family caregivers of cardiac arrest survivors, anxiety was present in 33 caregivers (25%) and depression in 18 caregivers (14%) at 12 months.[159]
- Among 7321 patients with OHCA in Taiwan who survived to ICU admission, 281 (3.84%) had new-onset HF.[160] Strong predictors of new-onset HF were age (60–75 years; HR, 11.4 [95% CI, 9–14.4]), history of MI (HR, 2.47 [95% CI, 2.05–2.98]), history of cardiomyopathy (HR, 2.94 [95% CI, 1.45–5.94]), or new-onset IHD during admission (HR, 4.5 [95% CI, 3.46–5.86]).
- Among 57 437 patients discharged from the hospital after cardiac arrest identified from 2008 to 2015 Medicare claims data, unadjusted annual incidence of seizures was 1.26% (95% CI, 1.20%–1.33%), which is higher than for other Medicare patients (0.61% [95% CI, 0.61%–0.62%]).[161] Cardiac arrest survivors had no increased hazard for seizures after adjustment for demographics and comorbidities (HR, 0.9 [95% CI, 0.9–1.0]).

Health Care Use and Cost

- Among 138 children surviving IHCA, caregiver burden increased at baseline and at 3 and 12 months as measured by the Infant Toddler Quality of Life Questionnaire (<5 years of age) or the Child Health Questionnaire (children >5 years of age).[162]

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.[163]
- 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.[164] 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.
- A cohort of 400 000 people in Xinjiang, China, reports SCD incidences of 37.94 and 36.2 per 100 000 for Han and Kazakh people, respectively.[165] After standardization for age, the incidence in these populations was 29.36 and 51.85 per 100 000.
- Hospitals in Beijing, China, reported IHCA incidence of 17.5 events per 1000 admissions.[166]
- Among 353 adults after IHCA in 6 Kenyan hospitals in 2014 to 2016, 16 (4.2%) survived to hospital discharge.[167]

Table 18-1. Trends in Layperson Response and Outcomes for EMS-Treated OHCA, 2006 to 2018

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
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	10.4	10.6
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	29.5	29.1
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	18.4	18.9
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	39.2	41.6
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	7.3	7.4
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	1.7	1.7

Values are percentages.

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.[5]

Table 18-2. Regional Variation in EMS-Treated OHCA, 2018

	Percent of population reporting data	EMS-treated OHCA cases	Rate per 100 000 people	Layperson-initiated CPR, %	Public use of AED, %	Survival to hospital discharge if witnessed collapse and shockable rhythm, %	Overall survival to hospital discharge, %
United States	40.1	100 956	76.5	41.2	12.2	33.2	10.5
Alaska	83.6	394	64.4	73.3	2.7	44.1	16.0
California	62.5	16 100	65.2	43.5	12.0	32.1	9.0
Colorado	62.8	2074	57.4	41.7	15.1	39.4	12.3
Delaware	99.3	1165	120.5	36.2	6.5	30.4	11.8
Hawaii	100.0	1321	93.3	49.2	13.2	31.4	11.3
Michigan	79.1	7727	97.9	40.2	13.9	30.3	8.7
Minnesota	86.7	2537	51.9	37.5	14.1	38.5	13.5
Mississippi	59.8	1825	102.6	36.5	10.1	22.1	6.0
Montana	60.1	507	78.9	48.5	5.2	36.8	11.2
New Hampshire	100.0	1059	77.9	53.5	14.4	28.2	10.2
North Carolina	67.8	5965	83.8	37.1	13.6	32.4	12.6
Oregon	92.4	2410	61.9	57.4	13.9	35.6	14.7
Pennsylvania	77.9	8013	80.3	36.4	10.0	31.4	9.5
South Carolina	53.6	2551	92.4	37.4	10.9	28.2	11.8
Utah	98.6	1321	41.8	36.9	10.2	26.8	8.6
Vermont	100.0	481	77.1	43.0	6.6	36.0	10.2
Washington	95.5	4210	57.9	57.3	12.2	42.5	15.0
District of Columbia	99.5	886	126.1	33.6	6.9	31.0	7.7

Population reporting data indicates percentage of region's population within geographic footprint of EMS agencies contributing data. Layperson CPR rate excludes EMS-witnessed, nursing home, and health care facility events. Public AED use rate excludes EMS-witnessed, home/residence, nursing home, and health care facility events.

AED indicates automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; and OHCA, out-of-hospital cardiac arrest.

Source: Cardiac Arrest Registry to Enhance Survival 2019 data from states with ≥50% population reporting data and voluntarily sharing data.[5]

Table 18-3. SCA Diagnoses Among ED Visits in the United States, 2016

	Adult (≥18 y)	Child (1–17 y)	Infant (<1 y)	Total	Rate per 100 000 people
Any listed diagnosis, n	393 872	6510	3961	404 691	125.2
CPR or defibrillation procedure code, n	185 509	969	559	187 097	88.8
Principal diagnosis, n	177 052	3406	3027	183 629	56.8
Died in ED, %	77.1	70.0	80.8	77.0	…
Transferred to another hospital, %	5.1	15.0	8.4	5.3	…
Admitted to same hospital, %	10.8	5.2	2.1	10.5	…
Died in same hospital, %	5.6	2.1	1.9	5.5	…
Discharged from same hospital, %	4.9	2.7	…	5.0	…

CPR indicates cardiopulmonary resuscitation; ED, emergency department; ellipses (…), data not reported; and SCA, sudden cardiac arrest.
Source: Unpublished tabulation using Healthcare Cost and Utilization Project, 2016.[11]

Table 18-4. Characteristics of and Outcomes for OHCA and IHCA, 2019

	OHCA		IHCA	
	Adults	Children	Adults	Children
Survival to hospital discharge	10.5	11.3	26.7	42.3
Good functional status at hospital discharge	8.5	8.6	18.0	15.9
VF/VT/shockable	19.2	7.0	15.4	8.1
PEA	…	…	54.6	48.1
Asystole	…	…	22.0	28.1
Unknown	…	…	8.1	15.8
Public setting	18.8	14.2	…	…
Home	70.0	85.6	…	…
Nursing home	11.2	0.3	…	…
Arrest in ICU, operating room, or ED	…	…	54.6	85.7
Noncritical care area	…	…	45.4	14.3

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 electric activity; VF, ventricular fibrillation; and VT, ventricular tachycardia.
Source: OHCA data derived from the Cardiac Arrest Registry to Enhance Survival,[5] based on 98 002 emergency medical services (EMS)-treated OHCA adult cases and 2684 EMS-treated OHCA child cases in 2019. IHCA data are from Get With The Guidelines (unpublished AHA tabulation) 2019 based on 28 012 pulseless adult IHCAs in 332 hospitals and 598 pulseless child IHCAs in 80 hospitals.

Table 18-5. SCA Mortality, 2018 (*ICD-10* Codes I46.0, I46.1, I46.9, I49.0)

Population group	Number of deaths as underlying cause, 2018, all ages	Number of deaths as any-mention cause, 2018, all ages
Both sexes	18 989	377 763
Males	10 273	195 723
Females	8716	182 040
NH White males	7679	139 570
NH White females	6461	128 009
NH Black males	1814	26 975
NH Black females	1653	27 286
Hispanic males	504	18 973
Hispanic females	365	17 667
NH Asian/Pacific Islander males	194	8072
NH Asian/Pacific Islander females	170	7428
NH American Indian/ Alaska Native	108	2456

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.
ICD-10 indicates *International Classification of Diseases, 10th Revision*; NH, non-Hispanic; and SCA, sudden cardiac arrest.
Sources: Any-mention cause and underlying cause data derived from Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research database, 2018.[138]

Table 18-6. Outcomes of EMS-Treated Nontraumatic OHCA in Adults (≥18 Years of Age), CARES, 2019

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 (98002)	28.0	10.5	8.5	62.3
Home/residence (66636)	26.1	8.6	6.8	67.1
Nursing home (10977)	18.3	4.7	2.4	74.5
Public setting (18388)	40.7	21.3	18.5	47.7
Unwitnessed (48046)	17.6	4.4	3.2	75.1
Bystander witnessed (37521)	36.8	15.9	13.2	56.9
EMS provider witnessed (12434)	41.2	18.2	15.1	55.8
Shockable presenting rhythm (18835)	48.0	29.0	25.8	39.6
Nonshockable presenting rhythm (79157)	23.2	6.1	4.4	73.5
Layperson CPR (29586)	30.3	13.2	11.3	56.7
No layperson CPR (42827)	24.4	7.4	5.7	69.5

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 died before hospital discharge.

Source: Data from 98002 adults in CARES.[5]

Table 18-7. Outcomes of EMS-Treated Nontraumatic OHCA in Children, CARES, 2019

Age group (n)	Survival to hospital admission	Survival to hospital discharge	Survival with good neurological function (CPC 1 or 2)	In-hospital mortality*
<1 y (1299)	17.8	6.8	4.9	61.9
1–12 y (835)	37.0	15.0	10.4	59.5
13–18 y (550)	37.1	16.2	14.5	56.4

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 died before hospital discharge.

Source: Data derived from CARES.[5]

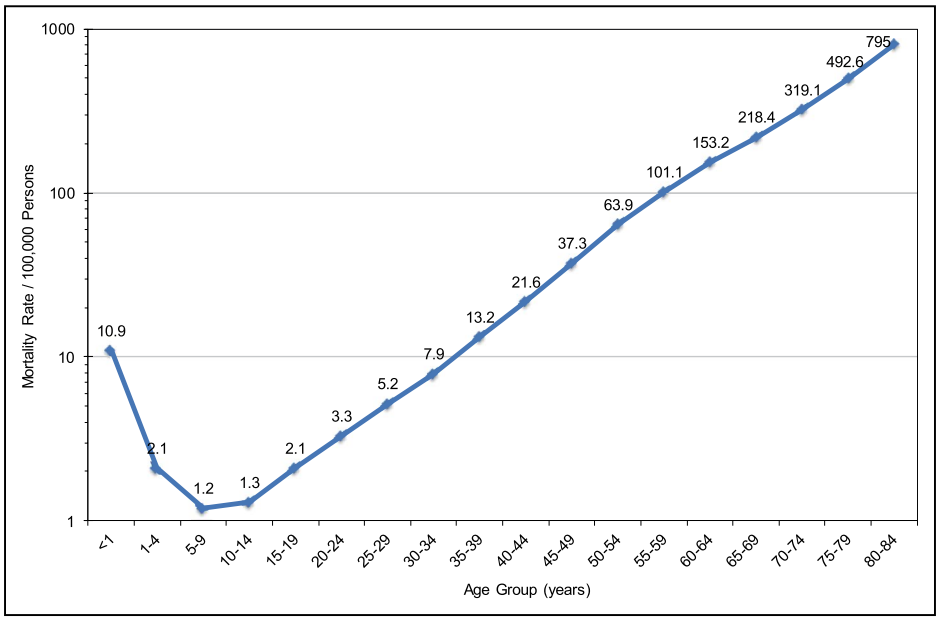

Chart 18-1. Age-specific mortality rates for any mention of sudden cardiac death by age, United States, 2018.

Source: Data derived from Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research database. Accessed May 25, 2020.[138]

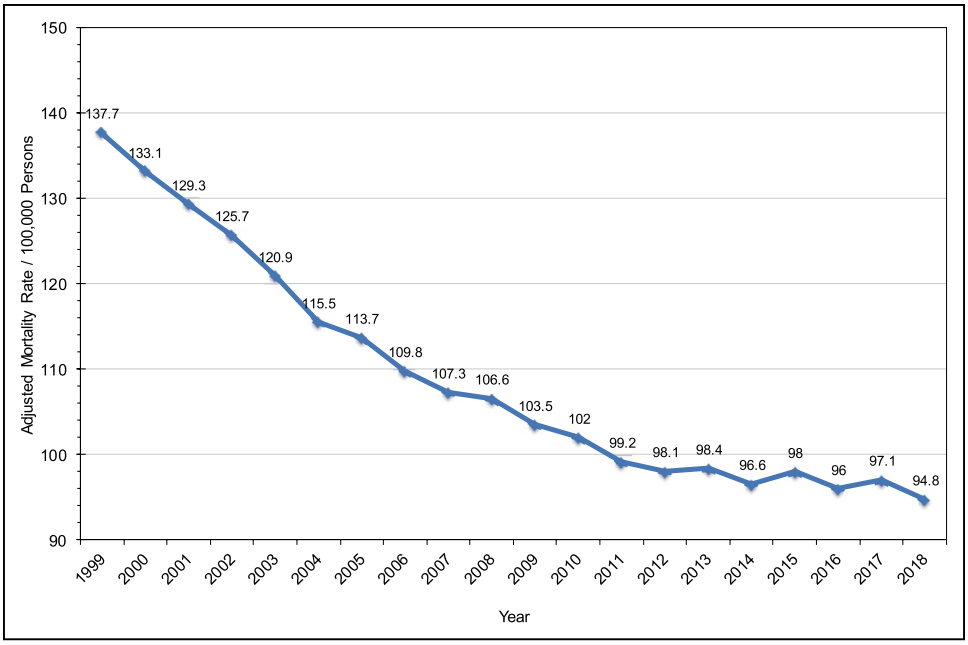

Chart 18-2. Age-adjusted mortality rates for any mention of sudden cardiac death, United States, 1999 to 2018.
Source: Data derived from Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[138]

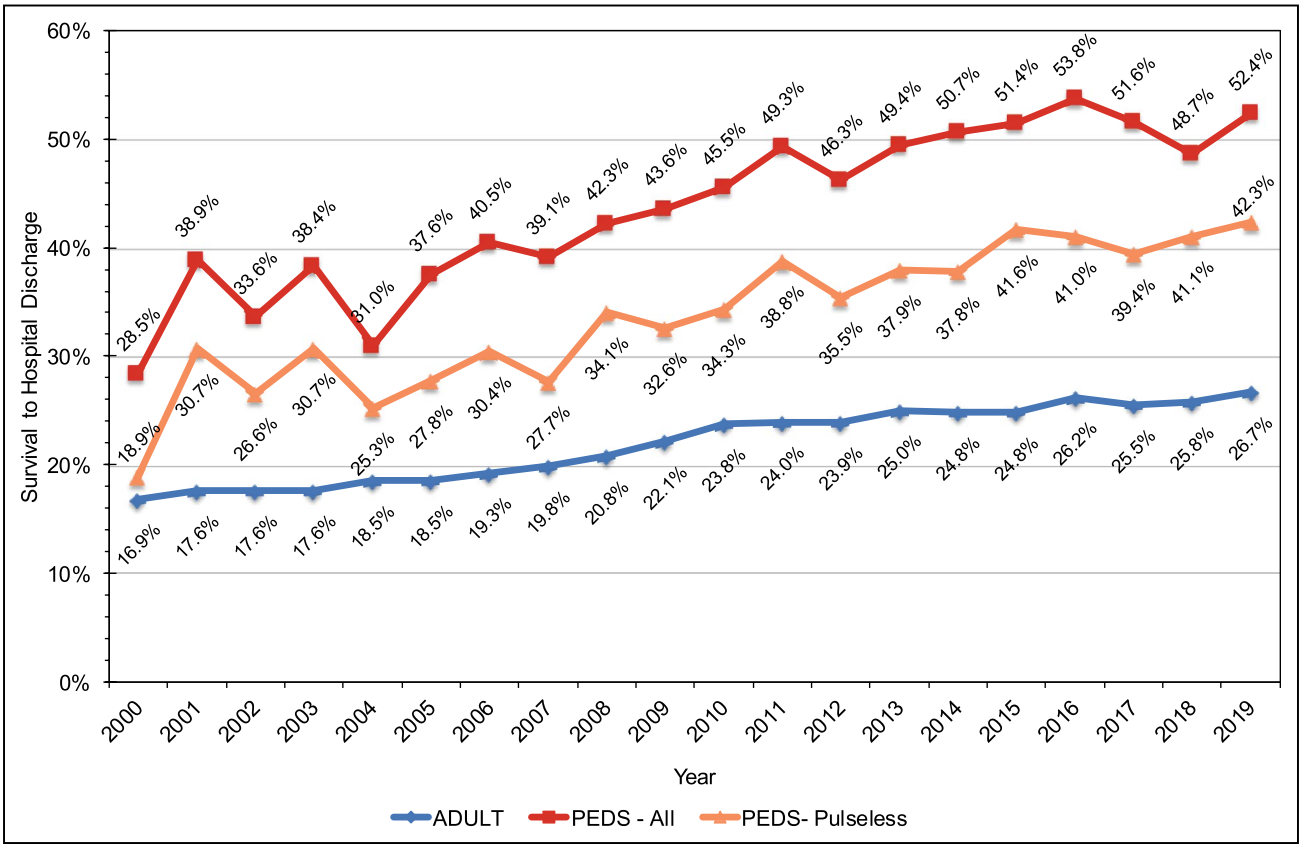

Chart 18-3. Temporal trends in survival to hospital discharge after in-hospital cardiac arrest in adults and children in GWTG–Resuscitation from 2000 to 2019, United States.
GWTG indicates Get With The Guidelines; and PEDS, pediatrics.
Source: GWTG–Resuscitation; unpublished American Heart Association data.

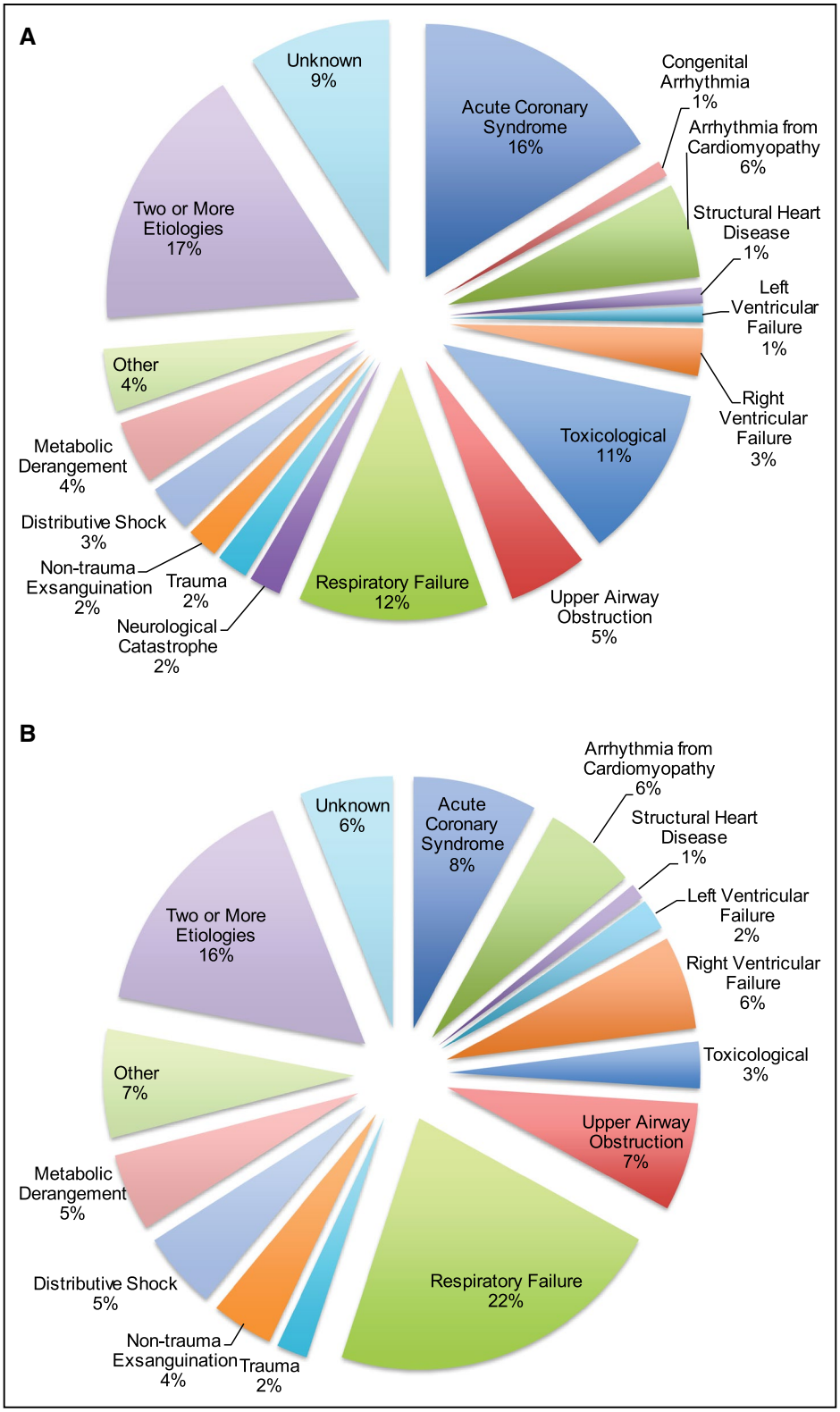

Chart 18-4. Detailed causes of out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA) among patients surviving to hospital admission in 1 US center.

A, Proportion of hospitalized patients with each cause after OHCA. **B**, Proportion of hospitalized patients with each cause after IHCA. Pathogenesis based on testing and evaluation in the hospital. "Other" corresponds to all other causes.

Source: Data derived from Chen et al.[38]

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19. SUBCLINICAL ATHEROSCLEROSIS

See Charts 19-1 through 19-4

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Multiple complementary imaging modalities allow detection and quantification of atherosclerosis through its stages in 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. Several modalities can be used for imaging atherosclerosis, including CT of the chest for evaluation of CAC, B-mode ultrasound of the neck for evaluation of carotid artery IMT or plaque, brachial artery reactivity testing, aortic and carotid MRI, and tonometric methods of measuring vascular compliance or microvascular reactivity. Among these modalities, the role of CAC in cardiovascular risk assessment is particularly well defined. According to the 2018 Cholesterol Clinical Practice Guideline[1] and the 2019 CVD Primary Prevention Clinical Practice Guidelines,[2] in intermediate-risk or selected borderline-risk adults, if the decision about statin therapy remains uncertain after 10-year ASCVD risk calculation and after accounting for risk enhancers,

Abbreviations Used in Chapter 19

ABI	ankle-brachial index
AF	atrial fibrillation
aHR	adjusted hazard ratio
ARIC	Atherosclerosis Risk in Communities study
ASCVD	atherosclerotic cardiovascular disease
AUC	area under the curve
AWHS	Aragon Workers' Health Study
BMI	body mass index
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
CI	confidence interval
CKD	chronic kidney disease
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
EPA	eicosapentaenoic acid
ESRD	end-stage renal disease
FHS	Framingham Heart Study
FMD	flow-mediated dilation

(*Continued*)

Abbreviations Used in Chapter 19 Continued

FRS	Framingham Risk Score
GRS	genetic risk score
HANDLS	Healthy Aging in Neighborhoods of Diversity Across the Life Span
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HR	hazard ratio
IMPROVE	Carotid Intima Media Thickness (IMT) and IMT Progression as Predictors of Vascular Events in a High Risk European Population
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
Lp(a)	lipoprotein(a)
LV	left ventricular
LVH	left ventricular hypertrophy
MACE	major adverse cardiovascular event
MESA	Multi-Ethnic Study of Atherosclerosis
MetS	metabolic syndrome
MI	myocardial infarction
MRI	magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease
NHLBI	National Heart, Lung, and Blood Institute
NNT_5	5-year number needed to treat
OR	odds ratio
PA	physical activity
PAD	peripheral artery disease
PESA	Progression of Early Subclinical Atherosclerosis
PWV	pulse-wave velocity
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SES	socioeconomic status
SNP	single-nucleotide polymorphism
SWAN	Study of Women's Health Across the Nation
TC	total cholesterol
TIA	transient ischemic attack
WC	waist circumference
WMH	white matter hyperintensity

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

it is reasonable to use a CAC score in the decision to withhold, postpone, or initiate statin therapy.[1]

Coronary Artery Calcification

Background

- CAC measures atherosclerotic burden in the coronary arteries 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.

•*Prevalence and Risk Factors (See Charts 19-1 through 19-3)*

- The NHLBI's FHS reported CAC measured in 3238 White adults in groups ranging from <45 to ≥75 years of age.[4]
  - — Overall, 32.0% of females and 52.9% of males had prevalent CAC.
  - — Among participants at intermediate risk according to the 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).[5]
  - — 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 Agatston scores >100.
- Chart 19-1 shows the prevalence of CAC by ethnicity and sex in adults 33 to 45 years of age. The prevalence of CAC was lower in African American versus White males but was similar in African American versus White females at these ages.
- The NHLBI's MESA, a study of White, Black, Chinese, and Hispanic adults, measured CAC in 6814 participants 45 to 84 years of age (mean, 63 years), including White (n=2619), Black (n=1898), Hispanic (n=1494), and Chinese (n=803) males and females.[6]
  - — The overall prevalence of CAC in these 4 ethnic groups was 70.4%, 52.1%, 56.5%, and 59.2%, respectively, among males and was 44.6%, 36.5%, 34.9%, and 41.9%, respectively, among females.
  - — The prevalence and 75th percentile levels of CAC were highest in White males and lowest in Black and Hispanic females. Ethnic differences persisted after adjustment for risk factors, with the prevalence of coronary calcium being 22% lower in Black people, 15% lower in Hispanic people, and 8% lower in Chinese people than in White people.
- Illustrating the variability of CAC by 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.[7]
  - — 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 typically be avoided by maintaining a low lifetime burden of CAD risk factors.[7]
- The prevalence of CAC varies according to baseline traditional risk factor profile. In MESA, the prevalence of CAC in those with no lipid abnormalities was 42% versus 50% in those with 3 lipid abnormalities,[8] 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.[9]
- The duration of risk factor exposure is associated with CAC, as exemplified in an analysis of exposure to diabetes and prediabetes in 3628 participants in CARDIA.[10]
  - — For each additional 5 years of exposure to diabetes and prediabetes, the aHR for CAC was 1.15 (95% CI, 1.06–1.25) and 1.07 (95% CI, 1.01–1.13), respectively.
- Beyond traditional cardiovascular risk factors, studies have identified obesity, NAFLD, and elevated Lp(a) as being associated with CAC.
  - — Considering 1585 participants free of CHD and free of MetS, those who were obese had a higher prevalence of CAC than individuals with a normal weight, with a prevalence ratio of 1.59 (95% CI, 1.38–1.84).[11]
  - — In a meta-analysis of 42 410 individuals, including 16 883 with NAFLD, CAC scores were higher in those with NAFLD (OR, 1.64 [95% CI, 1.42–1.89]).[12]
  - — In 937 apparently healthy asymptomatic family members of individuals with premature ASCVD, high Lp(a) levels were associated with CAC ≥100 (OR, 1.79 [95% CI, 1.13–2.83]).[13]
  - — In 140 patients with a CAC score of 1 to 999 who were treated with pitavastatin with/without EPA and followed up for 1 year, a decrease in oxidized HDL was independently associated with less CAC progression (OR, 0.95 per 10 U/mL [95% CI, 0.90–0.99]; *P*=0.04).[14]
- The 10-year trends in CAC among individuals without clinical CVD in MESA were assessed (Chart 19-2).
  - — The mean age at the baseline examination was 67 years, with 47.4% male. Detectable CAC was evaluated in White, African American, Hispanic, and Chinese participants, with >50% prevalence at baseline.

— Ten-year trends in CAC prevalence among the 4 racial/ethnic groups revealed a significant trend toward increased prevalence of CAC in African American participants but not in any other group (Chart 19-2). Among African American participants, the CAC prevalence ratio (year 10 versus baseline) was 1.27 (P<0.001 for test for trend).[15]

— CAC severity was also evaluated at baseline and 10 years (Chart 19-3). 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 CAC 1 to 99 and from 14.7% to 17.7% (P=0.14) for those with CAC 100 to 399, whereas the proportion with CAC ≥400 decreased from 9.1% to 7.2% (P=0.11).

CAC and Incidence of ASCVD Events (CHD and Stroke)

(See Chart 19-4)

- The NHLBI's MESA reported the association of CAC 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 participants).[16]
  — Chart 19-4 shows the HRs associated with CAC scores of 1 to 100, 101 to 300, and >300 compared with CAC=0, after adjustment for standard risk factors. People with CAC 1 to 100 had ≈4 times greater risk and those with CAC scores >100 were 7 to 10 times more likely to experience a CHD event than those without CAC.
  — CAC provided similar predictive value for CHD events in White, Chinese, Black, and Hispanic individuals (HRs ranging from 1.15–1.39 for each doubling of CAC).
- In another 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]
- CAC was highly predictive of CHD event risk in both young and elderly MESA participants in a follow-up that extended to 8.5 years, suggesting that once CAC is known, chronological age has less importance.[18]
  — 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 of age), 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).
- A meta-analysis pooling data from 3 studies examined the association of CAC with stroke in 13 262 asymptomatic individuals (mean age, 60 years; 50% males) without apparent CVD.[19]
  — 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%/y for CAC=0, 0.26%/y for CAC 1 to 99, 0.41%/y for CAC 100 to 399, and 0.70%/y for CAC ≥400).

CAC and Incidence of HF, AF, and Noncardiovascular Outcomes

- An analysis from the MESA study found that CAC >300 was significantly associated with HF in females (HR, 2.82 [95% CI, 1.32–6.00]) but not in males (HR, 0.91 [95% CI, 0.46–1.82]).[20]
- 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]).[21] The addition of CAC to a risk score yielded relative integrated discrimination improvement of 0.10 (95% CI, 0.061–0.15).
- A MESA analysis also showed that a higher CAC burden was associated with noncardiovascular outcomes.[22]
  — 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.

CAC Progression and Risk

- 6778 MESA participants showed annual CAC progression averaging 25±65 Agatston units. Among those without CAC at baseline, a 5-unit annual change in CAC was associated with HRs of 1.4 and 1.5 for total and hard CHD events, respectively.[23]
- In a MESA study of 2759 postmenopausal females, despite no association between sex hormones and prevalent CAC, an association emerged between sex hormones and CAC progression over a median of 4.7 years.[24]

Social Determinants of CAC

- In a Chinese study of 8867 patients 25 to 92 years of age with suspected CHD, long-term exposure to higher levels of air pollution was associated greater presence of any CAC and severe CAC.[25]
- Schmidt et al[26] examined the interaction of SES and a common variant in chromosome 9p21.3 in association with CAC and incident events in the Heinz Nixdorf Recall Study. In the 4116 participants in the analysis, SES was examined by education and income.
  - Genotype-income interaction, but not genotype-education interaction, was observed for CAC and events.
  - The lowest tertile of income had the strongest genetic effect, a 53.1% (95% CI, 30.6%–79.6%; P=1.8×10^{-7}) increase in CAC and an HR of 1.44 (95% CI, 1.01–2.07; P=0.049) for incident coronary events per additional risk allele.
  - This suggests that lower income may be a determinant of increased expression of genetic susceptibility to CAD.

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 earlier manifestation of atherosclerosis than CAC because thickening precedes the development of frank atherosclerotic plaque. Carotid IMT methods may vary by part of the artery measured (common carotid, internal carotid, or bulb), measurement of near and far walls, and reporting of average (more common) or maximum thickness.
- Carotid IMT is greater with age and in 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. Carotid ultrasound can also detect plaques and percent stenosis, although primary prevention guidelines have not recommended screening of asymptomatic people with either the presence of atherosclerotic plaque or carotid IMT used to quantify atherosclerosis or to predict risk.[2]

Risk Factors

- In participants in the Bogalusa Heart Study (mean age, 32±3 years), 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.[27]
- In a meta-analysis of 7645 individuals, carotid IMT increased from 723±39 μm in participants with normal BP to 779±45 μm in those with prehypertension and 858±82 μm in individuals with hypertension.[28]
- Adverse risk factor levels in early childhood and young adulthood are implicated in the early development of atherosclerosis. In the Bogalusa Heart Study, higher BMI and LDL-C levels measured at 4 to 7 years of age were associated with increased risk for carotid IMT >75th percentile in young adulthood.[29] Higher SBP and LDL-C and lower HDL-C in young adulthood were also associated with having high carotid IMT. A large Finnish cohort study showed similar findings.[30]
- In the Cardiovascular Risk in Young Finns Study, childhood oral infections, including periodontal disease or caries, were associated with greater carotid IMT, particularly in boys.[31]
- Two large, population-based prospective studies demonstrated the shared pathogenesis of atherosclerosis[32,33]:
  - In 1243 FHS participants (57±9 years of age; 53% females), carotid stenosis ≥25% was associated with a 2.2-fold (95% CI, 1.10–4.40) increased risk of cerebral microbleed, a marker of stroke and dementia. No association was noted with carotid IMT.[32]
  - Among 13 197 individuals 45 to 64 years of age (26% Black participants, 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.[33]
- Sleep patterns and duration, which are associated with CVD, are associated with subclinical atherosclerosis.[34] In nearly 4000 asymptomatic middle-aged individuals in the PESA study, individuals who slept <6 hours per night had a 1.27 greater odds of noncoronary atherosclerosis defined by carotid and femoral ultrasound imaging, even with adjustment for conventional risk factors.[34]
- The Bogalusa Heart Study highlights sex and race differences in carotid IMT.[27] In 518 healthy Black and White males and females (32±3 years of age), males had significantly higher carotid IMT in all segments than females, and Black participants had higher common carotid and carotid bulb IMT than White participants.
- Updates from an individual-participant meta-analysis involving 15 population-based cohorts worldwide that included 60 211 individuals (46 788 White, 7200 Black, 3816 Asian, and 2407 Hispanic participants) demonstrated differing associations

between risk factors and burden of carotid IMT according to racial/ethnic groups.[35] Specifically, the association between age and carotid IMT was weaker in Black and Hispanic individuals, SBP was more strongly associated with carotid IMT in Asian individuals, and HDL-C and smoking were less associated with carotid IMT in Black individuals.

- In MESA, carotid IMT and CAC were found to be commonly associated, but patterns of association differed somewhat by sex and race.[36]
  - Common IMT 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 Black people than in other ethnic groups.
  - In general, Black people had the thickest carotid IMT (particularly common carotid) of all 4 ethnic groups, regardless of the presence of CAC.
  - Chinese participants had the lowest carotid IMT, in particular in the internal carotid, of the 4 ethnic groups.

Social Determinants of Carotid IMT and Vascular Disease

- The IMPROVE study cohort of 3703 European people studied the relationship between SES and carotid IMT. Manual laborers had higher carotid IMT than white collar workers, a finding that was independent of sex, age groups, and education and was only partially mediated by risk factors.[37]
- In the biracial HANDLS study of 2270 adults, interaction analyses demonstrated a race×SES effect whereby Black people with high (rather than low) SES had higher carotid IMT and aortic stiffness than other groups, suggesting a group with greater subclinical CVD.[38]
- In the Young Finns Study of 1813 adults 27 to 39 years of age followed up for >20 years, individuals with higher education had lower progression in IMT in follow-up.[39]

Risk Prediction

- A study 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 the presence of carotid plaque were independently associated with an increased risk of incident AF.[40] In this study, a 1-SD increase in carotid IMT and the presence of carotid plaque were associated with a meta-analyzed HR for AF of 1.12 (95% CI, 1.08–1.16) and 1.30 (95% CI, 1.19–1.42), respectively.
- Among 13 590 participants in ARIC who were 45 to 64 years of age, 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.[41]
- In MESA, during a median follow-up of 3.3 years, an IMT rate of change of 0.5 mm/y was associated with an HR of 1.23 (95% CI, 1.02–1.48) for incident stroke.[42] 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.
- 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.[43] After a mean follow-up of 6.2 years and with multivariable adjustment, those with maximal combined carotid IMT in the highest quintile had a 3-fold greater risk for incident MI or stroke than those in the bottom quintile.
- ARIC investigators found that the addition of carotid IMT and plaque to traditional risk factors improved prediction of CHD risk[44]: among 13 145 participants (5682 males, 7463 females), ≈23% were reclassified by adding carotid IMT and plaque data to traditional risk factors. The AUC improved from 0.742 to 0.755 (95% CI for difference in adjusted AUC, 0.008–0.017).
- However, conflicting data have been reported on the contribution of carotid IMT alone to risk prediction. 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 to discriminate and reclassify incident MI and stroke (95% CI, 2.7%–4.6%).[45] The C statistics of the model with FRS alone (0.757 [95% CI, 0.749–0.764]) and with the 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.
- The ability of carotid IMT to predict incident CVD events might also depend on data modeling. In MESA, the use of an age-, sex-, and race-adjusted carotid IMT score that combined data from both the internal and common carotid arteries 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%.[46]
- In the BioImage Study of 5808 asymptomatic US adults (mean age, 69 years; 56.5% females), increasing 3-dimensional carotid ultrasound plaque burden tertile was associated with HRs for MACEs

(cardiovascular death, MI, and ischemic stroke) of 1.45 (95% CI, 0.67–3.14) and 2.36 (95% CI, 1.13–4.92), respectively. Net reclassification improved significantly with carotid plaque burden (0.23).[47]

CAC, Carotid IMT, CT Angiography, and Risk Prediction

- In MESA, the investigators reported the 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).[48]
  - For CVD and CHD prediction: 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, C=0.776; CHD, C=0.784; $P<0.001$), followed by carotid plaque presence (CVD, C=0.760; CHD, C=0.757; $P<0.05$). Mean IMT ≥75th percentile (for age, sex, and race) alone did not predict events.
  - For stroke/TIA prediction: Compared with risk factors (C=0.782), carotid plaque presence (C=0.787; $P=0.045$), but not CAC (C=0.785; $P=0.438$), added to risk prediction.
- The CARDIA and MESA studies of adults <50 years of age confirm the importance of early exposure to risk factors for the onset and progression of subclinical atherosclerosis: those with low short-term/high lifetime predicted risk had significantly greater burden and progression of CAC and significantly greater burden of carotid IMT than those with low short-term/low lifetime predicted risk.[49]
- Despite promise for examination of coronary anatomy, CT angiography has limited impact on the prediction of outcomes in asymptomatic individuals. Thus, guidelines have not recommended its use as a screening tool for assessment of cardiovascular risk in asymptomatic individuals.[2,50–52] In the CONFIRM study, although CT angiography presence, extent, and severity of CAD improved risk prediction over traditional risk factors, no additional prognostic value for all-cause death was conferred once traditional risk factors and CAC scores were included in the model.[53]

Genetics/Family History

- There is evidence for genetic control of subclinical atherosclerosis, with several loci identified that associate with CAC and carotid artery IMT in multiethnic and racial populations.[54–57] 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.
- Investigators identified 8 unique genetic loci that contribute to carotid IMT in 71 128 individuals and 1 novel locus for carotid plaque in 48 434 individuals.[58] Genetic correlations with CHD and stroke using linkage disequilibrium score regression analysis were observed, which suggests the connection between genetic susceptibility to subclinical atherosclerosis and overt CVD.
- A 48-SNP GRS for type 2 diabetes was associated with carotid plaque and ASCVD events in ≈160 000 individuals, suggesting a causal role between genetic predisposition to type 2 diabetes and ASCVD.[59]

Treatment: Healthy Lifestyle and Preventive Medications

- In overweight and obese children 6 to 13 years of age, greater nut consumption was associated with lower carotid IMT (β=0.135 mm; $P=0.009$) when controlled for confounders.[60]
- A study examining the relation of different vegetables to carotid IMT in a cohort of older females showed that a diet high in vegetables, particularly cruciferous vegetables, was associated with lower carotid IMT.[61] Consuming ≥3 servings of vegetables each day was associated with a ≈5% lower amount of carotid atherosclerosis compared with consuming <2 servings of vegetables.
- Optimal lifestyle habits influence subclinical atherosclerosis: In SWAN, healthier lifestyle, including self-reported abstinence from smoking, healthy diet, and PA in females during midlife, was associated with lower carotid IMT.[62] Similar results of lifestyle habits, including Mediterranean diet, abstinence from smoking, and moderate alcohol intake, were associated with lower subclinical atherosclerosis in nearly 2000 individuals in the Spanish AWHS.[63]
- In 3393 participants from the MESA study with prevalent CAC, recreational PA was associated with higher CAC density, whereas nonrecreational PA appeared to be associated with lower CAC density.[64] In terms of CVD risk, 520 CVD events occurred over a 13.7-year median follow-up, and recreational PA was linked to lower CVD risk (HR, 0.88 per 1-SD increase [95% CI, 0.79–0.98]), without effect modification by CAC. Therefore, PA seems to be associated with CAC composition, but the association of PA with lower CVD risk appears to be independent of CAC.
- 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.

- When the benefit found in the JUPITER trial is applied to the event rates in each of 3 CAC groups in MESA (0, 1–100, or >100), the predicted NNT_5 for CHD was 549 for those with CAC of 0, 94 for scores of 1 to 100, and 24 for scores >100.[65]
- 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%).[8,66]
  - The estimated NNT_5 for preventing 1 CVD event across dyslipidemia categories in the MESA cohort ranged from 23 to 30 in those with CAC ≥100.[8] 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. A very high NNT_5 of 186 and 222 was estimated to prevent 1 CHD event in the absence of CAC among those with 10-year FRS of 11% to 20% and >20%, respectively. 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. 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 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.[66] Conversely, individuals with CAC=0 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.

Measures of Vascular Function and Incident CVD Events

- Background BP and its variability are related to CVD events. Greater home BP variability was associated with higher carotid IMT, aortic calcification, and lower ABI in 1033 Japanese males and females.[67] 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.
- Because of the absence of significant prospective data relating these measures to outcomes, the guidelines do not recommend measuring either FMD or arterial stiffness for cardiovascular risk assessment in asymptomatic adults.[52]

Arterial Stiffness and CVD

- The association of arterial stiffness measured by PWV with CHD was assessed in the Rotterdam Study of 2835 elderly participants (mean age, 71 years).[68] PWV tertiles were associated with CHD (RR, 1.72 and 2.45 for second and third versus first tertile, respectively). Results remained robust even after accounting for carotid IMT, ABI, and pulse pressure.
- A study from Denmark of 1678 individuals 40 to 70 years of age found that each 1-SD increment in aortic PWV (3.4 m/s) increased CVD risk by 16% to 20%.[69]
- In the FHS, higher PWV was associated with a 48% increased risk of incident CVD events, and PWV improved CVD risk prediction (integrated discrimination improvement of 0.7%; $P<0.05$).[70]
- An analysis from the JHS suggested that peripheral arterial tonometry is associated with LVH.[71] A total of 440 Black 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, diabetes, hypertension, ratio of TC and HDL-C, smoking, and history of CVD.
- Evidence suggests that arterial stiffness has negative impacts on brain health across the life spectrum. In 5853 children in the Generation R study, DBP was related to nonverbal intelligence, and in 5187 adults in the Rotterdam study, cognition was linearly related to SBP, PWV, and pulse pressure and nonlinearly related to DBP.[72] In the ARIC–Neurocognitive and positron emission tomography study, higher arterial stiffness measured by heart-carotid PWV was associated with

greater β-amyloid deposition in the brain defined by positron emission tomography imaging, and carotid femoral PWV was associated with lower brain volumes and with higher WMH burden.[73] FHS investigators also previously demonstrated findings of arterial stiffness with brain aging and similar brain structural abnormalities and progression of these abnormalities in regions implicated in Alzheimer disease.[74–78]

FMD and CVD

- In a meta-analysis of 13 studies involving 11516 individuals without established CVD, with a mean follow-up duration of 2 to 7.2 years and adjusted for age, sex, and risk factors, a multivariate RR of 0.93 (95% CI, 0.90–0.96) for CVD per 1% increase in brachial FMD was observed.[79]

Comparison of Measures

- In 1330 intermediate-risk individuals in MESA, the clinical utility of 6 risk markers—CAC, ABI, high-sensitivity CRP, carotid IMT, brachial FMD, and family history of CHD—were compared.[80] 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, 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). 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.[81]
- In addition, in MESA, the values of 12 negative markers were compared for all and hard CHD and for all CVD events over the 10-year follow-up.[82] After accounting for CVD risk factors, 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).The Pooled Cohort ASCVD Risk Estimator was compared against the FRS for prediction of subclinical atherosclerosis measured by carotid IMT and vascular dysfunction measured by carotid femoral PWV, central pulse pressure, and augmentation index in a cohort of 1231 individuals free of prevalent CVD.[83] Not surprisingly, given that the FRS was based on individuals of Northern European descent, the Pooled Cohort Risk Equations were suggested to better identify the significance of race in subclinical atherosclerosis and vascular dysfunction.

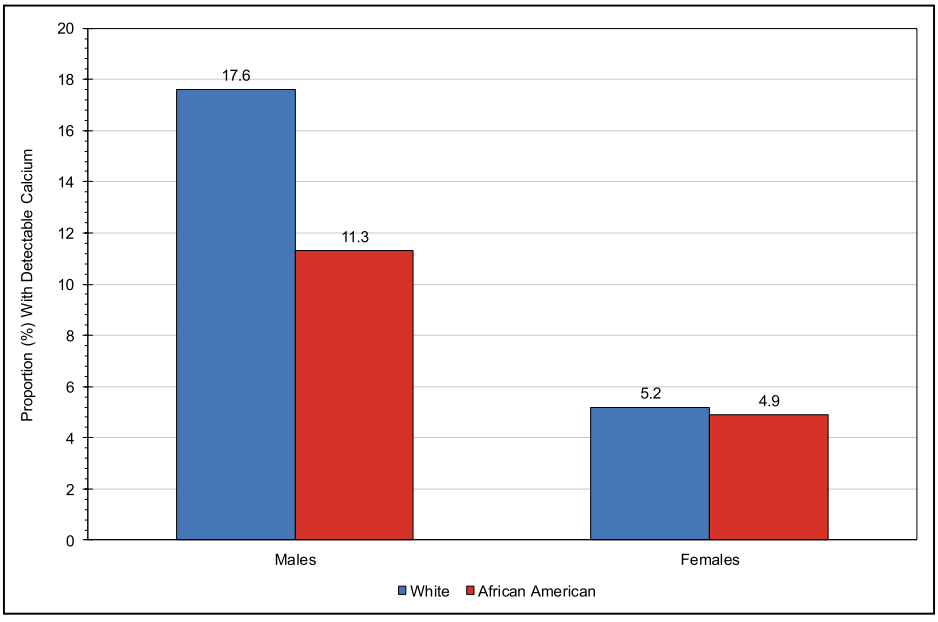

Chart 19-1. Prevalence (percent) of detectable coronary calcium in the CARDIA study: US adults 33 to 45 years of age (2000–2001).
P<0.0001 across race-sex groups.
CARDIA indicates Coronary Artery Risk Development in Young Adults.
Source: Data derived from Loria et al.[5]

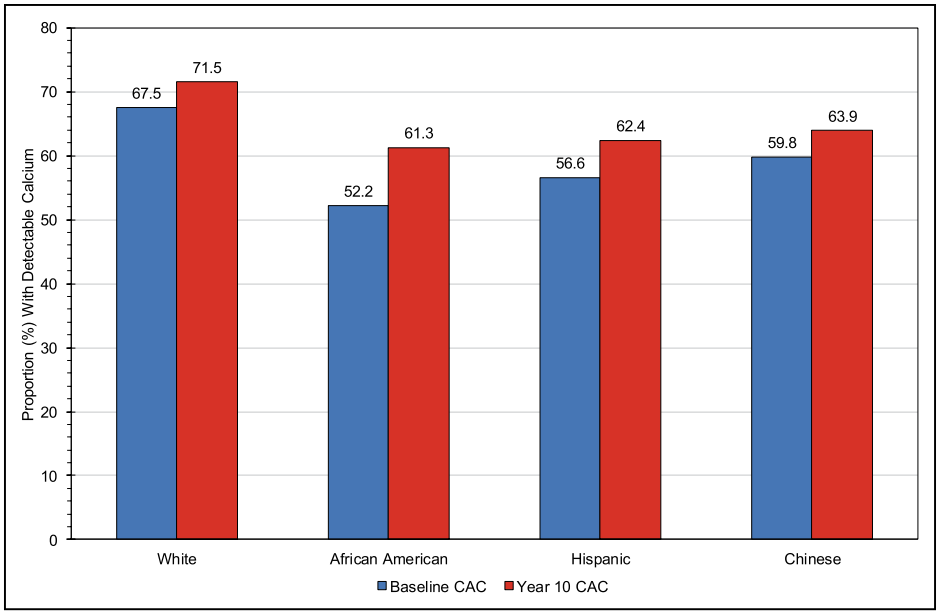

Chart 19-2. Prevalence by ethnicity of detectable CAC at baseline (2000–2002) and year 10 (2010–2012) among US adults 55 to 84 years of age without cardiovascular disease in MESA.

CAC indicates coronary artery calcification; and MESA, Multi-Ethnic Study of Atherosclerosis.

Source: Data derived from Bild et al.[6,15]

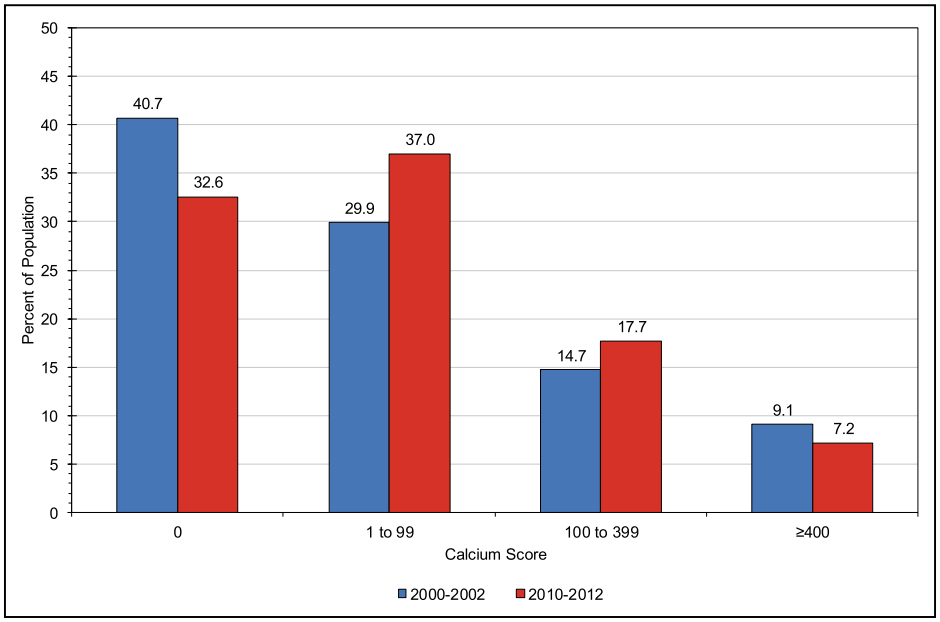

Chart 19-3. Ten-year trends in severity of coronary artery calcification in US individuals without clinical cardiovascular disease in MESA, baseline examination 2000 to 2002.

Data adjusted to the average baseline age (67 years), sex (47% male), race/ethnicity (39% White, 28% African American, 21% Hispanic, and 12% Chinese), and scanner (electron-beam computed tomography vs other).

MESA indicates Multi-Ethnic Study of Atherosclerosis.

Source: Adapted from Bild et al.[15]

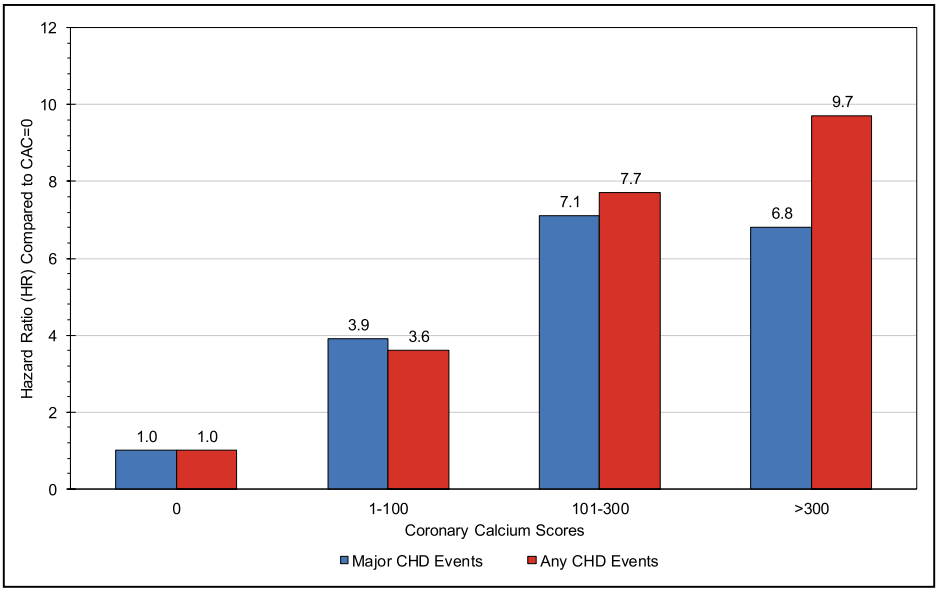

Chart 19-4. HRs for CHD events associated with CAC scores: US adults 45 to 84 years of age (reference group, CAC=0) in MESA, baseline examination 2000 to 2002.

Baseline examination 2000 to 2002 with median of 3.9 years of follow-up (maximum, 5.3 years). 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; HR, hazard ratio; and MESA, Multi-Ethnic Study of Atherosclerosis.
Source: Data derived from Detrano et al.[16]

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20. CORONARY HEART DISEASE, ACUTE CORONARY SYNDROME, AND ANGINA PECTORIS

See Tables 20-1 through 20-3 and Charts 20-1 through 20-11

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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 20-1 and 20-2 and Charts 20-1 through 20-4)

- On the basis of data from NHANES 2015 to 2018,[1] an estimated 20.1 million Americans ≥20 years of age have CHD (Table 20-1). The prevalence of CHD was higher for males than females ≥60 years of age (Chart 20-1).

Abbreviations Used in Chapter 20

ACS	acute coronary syndrome
ACTION	Acute Coronary Treatment and Intervention Outcomes Network
AHA	American Heart Association
AMI	acute myocardial infarction
ARIC	Atherosclerosis Risk in Communities study
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ASCVD	atherosclerotic cardiovascular disease
AUC	area under curve
BEST	Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease
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

(*Continued*)

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Abbreviations Used in Chapter 20 Continued

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
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CMS	Centers for Medicare & Medicaid Services
CRUSADE	Can Rapid Risk Stratification of Unstable Angina Patient Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines
CVD	cardiovascular disease
ED	emergency department
EMS	emergency medical services
FH	familial hypercholesterolemia
FHS	Framingham Heart Study
FINRISK	Finnish Population Survey on Risk Factors for Chronic, Noncommunicable Diseases
FOURIER	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk
FRS	Framingham Risk Score
GBD	Global Burden of Disease Study
GRS	genetic risk score
GWAS	genome-wide association study
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
IQR	interquartile range
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

(*Continued*)

Abbreviations Used in Chapter 20 Continued

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
PHS	Physicians' Health Study
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
SAGE	Study on Global Ageing and Adult Health
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SES	socioeconomic status
SHS	Strong Heart Study
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
UI	uncertainty interval
VTE	venous thromboembolism
WHI	Women's Health Initiative
WHO	World Health Organization
WHS	Women's Health Study
YLL	years of life lost

- Total CHD prevalence is 7.2% in US adults ≥20 years of age. CHD prevalence is 8.3% for males and 6.2% for females. CHD prevalence by sex and ethnicity is shown in Table 20-1.
- On the basis of data from the 2018 NHIS, the CHD prevalence estimates are 5.7% among White people, 5.4% among Black people, 8.6% among American Indian/Alaska Native people, and 4.4% among Asian people ≥18 years of age.[2]
- According to data from NHANES 2015 to 2018 (unpublished NHLBI tabulation),[1] the overall prevalence for MI is 3.1% 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 of age (Chart 20-2). MI prevalence is 4.3% for males and 2.1% for females. MI prevalence by sex and ethnicity is shown in Table 20-1.
- According to data from NHANES 2015 to 2018,[1] the overall prevalence of angina is 4.1% in US adults ≥20 years of age (Table 20-2).
- Data from the BRFSS 2018 survey indicated that 4.6% of respondents had been told that they had had an MI. The highest prevalence was in West Virginia (7.2%), and the lowest was in the District of Columbia (2.6%) and California (2.8%; age adjusted; Chart 20-3).[3]
- In the same survey, 4.3% of respondents had been told that they had angina or CHD. The highest prevalence was in Puerto Rico (7.3%) and West Virginia (6.8%), and the lowest was in Colorado, Hawaii, and Utah (2.5% in each state; age adjusted; Chart 20-4).[3]

Incidence
(See Charts 20-5 through 20-7)

- Approximately every 40 seconds, an American will have an MI (AHA computation based on incidence data from the ARIC study of the NHLBI[4]).
- On the basis of data tabulated by the NHLBI from the 2005 to 2014 ARIC study[4]:
  - Approximately 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.
- Annual numbers for MI or fatal CHD in the NHLBI-sponsored ARIC study and the CHS stratified by age and sex are displayed in Chart 20-5. Incidence of heart attacks or fatal CHD stratified by age, race, and sex is displayed in Chart 20-6.
- Incidence of MI by age, sex, and race in the NHLBI-sponsored ARIC study is displayed in Chart 20-7. 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 45 to 65 years of age (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.[5]
- In 9498 participants in the ARIC study, White participants had a higher rate of clinically recognized MI than Black participants (5.04 versus 3.24 per 1000 person-years; P=0.002).[6]

Secular Trends

- Among Medicare beneficiaries between 2002 and 2011, the rates of MI hospitalization declined from 1485 to 1122 per 100 000 person-years. The rates 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 rates of MI 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%.[7]
- Among Medicare beneficiaries, the rates of primary hospitalization for MI between 2002 and 2011 declined by 36.6% among NH White individuals (from 1057 to 670 per 100 000 person-years between 2002 and 2011) and by 26.4% among NH Black individuals (from 966 to 711 per 100 000 person-years between 2002 and 2011).[8]
- In Olmsted County, Minnesota, between 2003 and 2012, the annual incidence declined for both type 1 MI (from 202 to 84 per 100 000; $P<0.001$) and type 2 MI (from 130 to 78 per 100 000; $P=0.02$).[9]

Social Determinants

- In an analysis of nationally representative longitudinal register data in Finnish adults (N=94 501) for the period 1988 to 2010, household crowding during childhood increased the risk of MI incidence in adulthood 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.[10]
- Among US adults 45 to 74 years of age 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 use, features of the environment, and health indicators (6%).[11]
- In 3635 patients who underwent left-sided heart catheterization for CAD at Emory University between 2004 and 2014, low neighborhood SES (a composite measure using 6 census measures capturing income, housing, education, and occupation) was associated with increased risk of cardiovascular death or MI in patients without a prior MI (HR, 2.72 [95% CI, 1.73–4.28] for the lowest versus highest quartile of neighborhood SES), but no association was observed for those with a prior MI (HR, 1.02 [95% CI, 0.58–1.81]; P interaction=0.02).[12]
- Data from the NCHS on trends in CHD death rates from 1999 to 2009 indicate disparities in the trends by rural-urban status. An overall 40% decline in the rate of CHD death was observed; however, the decline was greater in urban areas (large metro: 42% decline; from 284 to 164 per 100 000 from 1999–2009; medium metro: 40% decline; from 244 to 147 per 100 000) compared with rural areas (35% decline; from 266 to 173 per 100 000).[13]
- According to the CMS Hospital Inpatient Quality Reporting Program data on 2363 hospitals in 2018, the average 30-day mortality after AMI was 13.6% (IQR, 12.8%–14.3%), with higher mortality observed in rural hospitals (from 13.4% to 13.8% for the most urban to most rural hospitals).[14]

Risk Prediction

- The percentage of US adults with a 10-year predicted ASCVD risk (using the 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.[15]
- 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 diabetes, and not a smoker), 10-year CVD risk ≥7.5% will occur at 65 years of age for White males, 70 years of age for Black males and females, and 75 years of age for White females.[16]
- The ASCVD tool might overestimate risk across all strata of risk compared with external contemporary cohorts (PHS, WHS, and WHI Observational Study), as well as in reanalysis of the original validation cohorts. However, some of the subsequent analyses were not conducted in populations comparable to the original study cohorts.[17]
- In 9066 participants 45 to 79 years of age from the REGARDS study, the observed and predicted ASCVD risks using the Pooled Cohort Risk Equations were similar in people with high social deprivation, although ASCVD risk was overestimated in those with low social deprivation.[18]
- In the WHI, although the risk of ASCVD was overestimated with the Pooled Cohort Risk Equations, adding ASCVD events identified through linkage with CMS claims that were not self-reported resulted in alignment of the observed and predicted risks.[19]
- In 14 169 patients with ASCVD risk <5% and self-reported family history of CHD from the multicenter Coronary Artery Calcium Consortium, increasing CHD mortality over a mean follow-up of 11.6 years was observed for increasing CAC scores. Those with CAC scores >100 had a >10-fold higher risk of CHD mortality than patients with CAC=0 (HR, 10.4

[95% CI, 3.2–33.7]). Furthermore, addition of CAC to a model with traditional risk factors (age, sex, race, hypertension, hyperlipidemia, diabetes, and smoking status) improved the prediction for CHD mortality (AUC, 0.72 for model with traditional risk factors and 0.82 for model adding CAC; *P*=0.03).[20]

Genetics and Family History

Family History as a Risk Factor

- Among adults ≥20 years of age, 12.9% (SE, 0.5%) reported having a parent or sibling with a heart attack or angina before 50 years of age. The racial/ethnic breakdown from NHANES 2015 to 2018 is as follows (unpublished NHLBI tabulation)[1]:
  - For NH White people, 12.4% (SE, 0.9%) for males and 15.3% (SE, 1.0%) for females.
  - For NH Black people, 8.9% (SE, 1.1%) for males and15.6% (SE, 1.2%) for females.
  - For Hispanic people, 7.8% (SE, 0.8%) for males and 11.2% (SE, 0.8%) for females.
  - For NH Asian people, 6.0% (SE, 0.7%) for males and 7.1% (SE, 1.4%) 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 2015 to 2018 is as follows (unpublished NHLBI tabulation)[1]:
  - 20 to 39 years of age, 7.9% (SE, 0.9%) for males and 10.2% (SE, 0.7%) for females.
  - 40 to 59 years of age, 12.9% (SE, 1.2%) for males and 16.8% (SE, 1.3%) for females.
  - 60 to 79 years of age, 14.8% (SE, 1.8%) for males and 18.7% (SE, 2.0%) for females.
  - ≥80 years of age, 13.2% (SE, 2.6%) for males and 14.1% (SE, 2.2%) 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%).[21]
- In premature ACS (≤55 years of age), 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.[22]
- 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).[23]

Genetic Predictors of CHD

- The application of GWASs to large cohorts of subjects with CHD has identified many consistent genetic variants associated with CHD, with associations related to atherosclerosis and traditional risk factors but also highlighting the importance of key biological process in the arterial wall.[24]
- The first GWAS identified the now most consistently replicated genetic marker for CHD and MI in European-derived populations, on chromosome 9p21.3.[25] 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).[26]
  - 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%.[26]
- A large-scale GWAS of CAD in >60 000 cases and >123 000 controls identified 2213 genetic variants as genome-wide significantly associated with CAD, grouping in 44 loci across the genome.[27] More recent GWASs have identified at least 13 additional loci across the genome, implicating pathways in blood vessel morphogenesis, lipid metabolism, nitric oxide signaling, and inflammation.[28]
- 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 Black individuals. Effect sizes were greater for those ≤55 years of age and in females.[29]
- 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 *ANGPTL4* (angiopoietin-like 4), which is an inhibitor of lipoprotein lipase. These mutations are associated with low plasma triglycerides and high HDL-C.[30]
- 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.[31]
- In the DiscovEHR study, loss-of-function variants in *ANGPTL3* (angiopoietin-like 3) 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.[32]
- 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]; $P=5.1\times10^{-3}$).[33]

- In 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.[34]
- Whole-genome sequencing studies, which offer a deeper and more comprehensive coverage of the genome, have identified 13 variants with large effects on blood lipids. Five variants within *PCSK9*, *APOA1*, *ANGPTL4*, and *LDLR* are associated with CHD.[35]
- Hematopoietic somatic mutations (clonal hematopoiesis of indeterminate potential) that accumulate with age have also been shown to be independent predictors of CHD events. Carriers of clonal hematopoiesis of indeterminate potential had a risk of CHD 1.9 times greater than noncarriers (95% CI, 1.4–2.7) and a risk of MI 4.0 times greater than noncarriers (95% CI, 2.4–6.7).[36]

Clinical Utility of Genetic Markers

- Studies demonstrated the utility of genetics in CAD risk prediction. In 48421 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-TIMI 22), a GRS consisting of 27 variants of genetic risk for CAD improved risk prediction above models that incorporated traditional risk factors and family history.[37] 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).[38]
- In the FINRISK and FHS cohorts, with a sample size of 16082 individuals, a GRS incorporating 49310 SNPs based on the CARDIoGRAMplusC4D Consortium data showed that the combination of GRS with the FRS improved 10-year cardiac risk prediction, particularly in those ≥60 years of age.[39]
- Studies have also shown that patients with early-onset MI have a higher proportion of very high polygenic GRS than of FH mutations; for example, ≈2% carry a rare FH genetic mutation, whereas ≈17% have a high polygenic risk score.[40]
- In the MI-GENES trial of intermediate-risk patients, patient knowledge of their GRS resulted in lower levels of LDL-C than in a control group managed by conventional risk factors alone, which suggests the influence of GRS in risk prevention.[41]
- Even in individuals with high genetic risk, prevention strategies have added benefit. For example, in 4 studies across 55685 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.[42]
- A novel genomic risk score for CAD including 1.7 million genetic variants was associated with increased risk of CAD in the UK Biobank (HR, 1.71 [95% CI, 1.68–1.73] per 1-SD increase in the score). Compared with individuals in the bottom quintile of the score, the HR of CAD for those in the top quintile was 4.17 (95% CI, 3.97–4.38). However, adding the genetic score to conventional risk factors resulted in only a small increase in predictive ability (C statistic changing from 0.670 to 0.696).[43]
- In the FOURIER study, patients without multiple clinical risk factors or high genetic risk as defined by a 27-CHD-variant GRS did not derive benefit from evolocumab, whereas patients with high genetic risk, regardless of clinical risk, derived the greatest benefit from the drug (HR, 0.69 [95% CI, 0.55–0.86]; *P*=0.0012), suggesting that GRSs have clinical utility.[44]
- Studies suggest that addition of a GRS to a clinical model has only modest clinical utility. In the UK Biobank with >350000 subjects, the change in C statistic for incident CAD prediction between a Pooled Cohort Equation and GRS model was 0.02 (95% CI, 0.01–0.03) with an overall net reclassification improvement of 4.0% (95% CI, 3.1%–4.9%).[45] In the ARIC and MESA studies, addition of a GRS to the Pooled Cohort Equation did not significantly increase the C statistic in either cohort for prediction of incident CHD events (ARIC: change in C statistic, –0.001 [95% CI, –0.009 to 0.006]; MESA: 0.021 [95% CI, –0.0004 to 0.043]).[46]

Awareness, Treatment, Control

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.[47]
- 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%.[47]
- Among female online survey participants, 21% responded that their doctor had talked to them about HD risk. Rates were lower among Hispanic females (12%) than White (22%) or Black (22%) females and increased with age from 6% (25–34 years of age) to 33% (≥65 years of age).[47]

- Among 2009 females and 976 males <55 years of age hospitalized for MI, only 48.7% of females and 52.9% of males reported having been told that they were at risk for HD or a heart problem. In addition, 50.3% of females and 59.7% of males reported that their health care provider had discussed HD and things they could do to take care of their heart.[48]
- Data from the NHIS indicate that awareness of 5 common heart attack symptoms (jaw, neck, or back discomfort; weakness or lightheadedness; chest discomfort; arm or shoulder discomfort; and shortness of breath) increased from 39.6% in 2008 to 50.0% in 2014 and 50.2% in 2017. In 2017, knowledge of the 5 symptoms was higher in females than in males (54.4% versus 45.6%) and differed by race/ethnicity (White participants, 54.8%; Black participants, 43.1%; Asian participants, 33.5%; Hispanic participants, 38.9%).[49]
- Data from the 2017 NHIS indicate that being unaware of all 5 MI symptoms was more common in males (OR, 1.23 [95% CI, 1.05–1.44]), Hispanic individuals (OR, 1.89 [95% CI, 1.47–2.43]), those not born in the United States (OR, 1.85 [95% CI, 1.47–2.33]), and those with a high school or lower education (OR, 1.31 [95% CI, 1.09–1.58]).[50]

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.[51]
- A retrospective analysis of the NHAMCS data from 2004 to 2011 that reviewed 15438 hospital visits related to ACS symptoms suggested that Black patients have a 30% longer waiting time than White patients, the reasons for which are unclear.[52]
- 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), resulting in greater mortality.[53]
- 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.[54]
- 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 105 minutes for patients transferred from another facility for therapy.[55]
- In a meta-analysis including 57136 patients from 10 studies, door-to-balloon time of >90 minutes versus ≤90 minutes was associated with higher in-hospital or 30-day mortality (OR, 1.52 [95% CI, 1.40–1.65]). An increased risk of 6-month to 12-month mortality was also observed for >90 minute door-to-balloon delay in 14261 patients from 8 studies (OR, 1.53 [95% CI, 1.13–2.06]).[56]

Operations and Procedures

- In 2014, an estimated 480000 percutaneous transluminal coronary angioplasties, 371000 inpatient bypass procedures, 1016000 inpatient diagnostic cardiac catheterizations, 86000 carotid endarterectomies, and 351000 pacemaker procedures were performed for inpatients in the United States (unpublished NHLBI tabulation using HCUP[57]).

Comparison of Outcomes.

- In an analysis of the BEST, PRECOMBAT, and SYNTAX trials comparing individuals with MI who had left main or multivessel CAD, CABG (versus PCI) was associated with a lower risk of recurrent MI and repeat revascularizations.[58] CABG was associated with lower all-cause and cardiovascular mortality in patients with multivessel CAD but not among patients with multivessel plus left main CAD.[59]
- 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 and those treated with CABG. However, PCI was associated with a lower risk of the composite outcome within the first 30 days of follow-up (OR, 0.62 [95% CI, 0.45–0.86]).[60]
- At 5 years of follow-up in the SYNTAX and BEST randomized trials, among patients with multivessel CAD involving the proximal left anterior descending coronary artery, PCI (versus CABG) was associated with greater 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).[61] At 10 years of follow-up in the SYNTAX trial, no difference in all-cause death was observed between PCI and CABG overall and among the subgroup of patients with left main CAD; however, for patients with 3-vessel disease, a greater risk of death was observed for those treated with PCI (HR, 1.42 [95% CI, 1.11–1.81]).[62]
- In patients with left main CAD with low or intermediate complexity (SYNTAX scores ≤32), no difference in the composite outcome of MI, stroke, or death was observed between PCI and CABG at 5 years of follow-up, although ischemia-driven

revascularization (OR, 1.84 [95% CI, 1.39–2.44]) and all-cause death (OR, 1.39 [95% CI, 1.03–1.85]) were more common after PCI.[63]
- In the NCDR CathPCI registry, 1% of PCI procedures were for unprotected left main coronary lesions. A composite end point of in-hospital MI, stroke, emergency CABG, or death was more frequent in unprotected left main PCI (OR, 1.46 [95% CI, 1.39–1.53]) compared with all other PCIs.[64]
- In 4041 patients with STEMI with multivessel CAD randomized to complete revascularization versus culprit lesion–only PCI, those with complete revascularization experienced lower rates of a composite end point of cardiovascular death or MI (HR, 0.74 [95% CI, 0.60–0.91]; *P*=0.004) and a composite end point of cardiovascular death, MI, or ischemia-driven revascularization (HR, 0.51 [95% CI, 0.43–0.61]; *P*<0.001) at a median follow-up of 3 years.[65]
- In 27 840 patients with STEMI transported via EMS to 744 hospitals in the ACTION registry, preactivation of the catheterization laboratory >10 minutes before hospital arrival compared with no preactivation was associated with shorter times to the catheterization laboratory (median, 17 minutes versus 28 minutes), shorter door-to-device time (median, 40 minutes versus 52 minutes), and lower in-hospital mortality (2.8% versus 3.4%; *P*=0.01).[66]
- The importance of adherence to optimal medical therapy was highlighted in an 8-hospital study of patients with NSTEMI 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 outcomes in patients nonadherent to medical therapy (*P*=0.001), but outcomes were similar in medicine-adherent patients (*P*=0.574).[67]

Secular Trends in Procedures.

- In the NIS, isolated CABG procedures decreased by 25.4% from 2007 to 2011 (326 to 243 cases per 1 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).[68]
- 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.[69]
- 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.[70]
- In an analysis of the NIS, among patients ≥70 years of age with non–ST-segment–elevation ACS or STEMI, the proportion of patients undergoing PCI increased from 7.3% in 1998 to 24.9% in 2013 in those with non–ST-segment–elevation ACS and from 11% in 1998 to 35.7% in 2013 in those with STEMI.[71]
- Among Medicare fee-for-service beneficiaries, the total number of revascularization procedures performed peaked in 2010 and declined by >4%/y 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.[72]
- 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%).[55]
- 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.[73]

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.[74]
- In the NCDR between 2009 and 2012, 59% of individuals were referred to cardiac rehabilitation after PCI, with significant site-specific variation.[75]
- 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.[76]
- In a randomized trial in patients undergoing cardiac rehabilitation after ACS with PCI, patients receiving digital health interventions (consisting of an online and smartphone-based platform by which

patients reported dietary and exercise habits and received educational information geared toward a healthy lifestyle) had more weight loss at 90 days than the control group (mean±SD, −5.1±6.5 kg versus −0.8±3.8 kg; *P*=0.02) and reduced cardiovascular-related rehospitalizations and ED visits at 180 days (8.1% versus 26.6%; RR, 0.30 [95% CI, 0.08–1.10]; *P*=0.054).[77]

- Among 366 103 Medicare fee-for-service beneficiaries eligible for cardiac rehabilitation in 2016, only 24.4% participated in cardiac rehabilitation; among those who participated, the mean number of days to initiation was 47.0 (SD, 38.6), and 26.9% completed cardiac rehabilitation with ≥36 sessions. Participation decreased with increasing age and was lower in females, Hispanic people, Asian people, those eligible for dual Medicare/Medicaid coverage, and those with ≥5 comorbidities.[78]

Mortality (See Table 20-1)

- On the basis of 2018 mortality data[79]:
  - CHD mortality was 365 744, and CHD any-mention mortality was 544 270 (Table 20-1).
  - MI mortality was 108 610. MI any-mention mortality was 147 965 (Table 20-1).
- From 2008 to 2018, the annual death rate attributable to CHD declined 27.9% and the actual number of deaths declined 9.8% (unpublished NHLBI tabulation using CDC WONDER[80]).
- In 2018, CHD age-adjusted death rates per 100 000 were 128.6 for NH White males, 141.4 for NH Black males, and 92.9 for Hispanic males; for NH White females, the rate was 64.9; for NH Black females, it was 79.7; and for Hispanic females, it was 50.3 (unpublished NHLBI tabulation using CDC WONDER[80]).
- In 2018, 78% of CHD deaths occurred out of the hospital. According to US mortality data, 283 565 CHD deaths occurred out of the hospital or in hospital EDs in 2018 (unpublished NHLBI tabulation using CDC WONDER[80]).
- The estimated average number of YLL because of an MI death was 16.1 in 2018 (unpublished NHLBI tabulation using CDC WONDER[80]).
- 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 (unpublished NHLBI tabulation using ARIC Community Surveillance [2005–2014]).[4]
- 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.[81]
- In the CRUSADE study including 22 295 patients ≥65 years of age treated for STEMI or NSTEMI at 344 hospitals in the United States between 2004 and 2006, in-hospital mortality was 7%. Mortality was 24% at 1 year, 51% at 5 years, and 65% at 8 years. Eight-year mortality was higher for NSTEMI (67%) than for STEMI (53%), although the difference was attenuated after adjustment for demographics and comorbidities (HR, 0.94 [95% CI, 0.88–1.00]).[82]
- Among Medicare fee-for-service beneficiaries, between 1999 and 2011, the 30-day mortality rate after hospitalized MI declined by 29.4%.[83]
- In a community-based study in 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.[84]
- 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%).[85]
- According to data on >4 million Medicare fee-for-service beneficiaries with AMI, 30-day mortality declined from 1995 through 2014 (20.0% to 12.4%). Mortality was higher in females, but over time, the difference in 30-day mortality between males and females reduced.[86]
- Other data, however, indicate that the rapid increase in the population ≥65 years of age has resulted in a slowing of HD mortality. From CDC WONDER data from 2011 through 2017, a deceleration in the decline in HD mortality was observed with a <1% annualized decrease. Taking into account the increase in the growth of the population ≥65 years of age, combined with the slowing of the decrease in HD mortality, resulted in an increase in the absolute number of HD deaths since 2011 (50 880 deaths; 8.5% total increase). However, the age-adjusted mortality for CHD continued to decline (2.7% annualized decrease) and the absolute number of CHD deaths declined (2.5% total decrease over the time period) between 2011 and 2017.[87]

Age, Sex, Race, and Social Determinants of Mortality

- In-hospital mortality is higher in females than in males with STEMI (7.4% versus 4.6%) and NSTEMI (4.8% versus 3.9%).[88,89] Females experience longer door-to-balloon times and lower rates

of guideline-directed medical therapy than males; however, a 4-step systems-based approach to minimize STEMI care variability at the Cleveland Clinic resulted in reduced sex disparities and improved care and outcomes in females.[90]

- 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 of age), in-hospital mortality was 8.0% for White females and between 6% and 8% for other race-sex groups.[91]
- Among patients hospitalized for STEMI between 2003 and 2014 in the NIS database, lack of health insurance (OR, 1.77 [95% CI, 1.72–1.82]; *P*<0.001) and below-median income (OR, 1.08 [95% CI, 1.07–1.09]; *P*<0.001) were independent predictors of in-hospital mortality.[92]
- Compared with nonparticipants, participants in the Supplemental Nutrition Assistance Program have twice the risk of CVD mortality, which likely reflects differences in socioeconomic, environmental, and behavioral characteristics.[93]
- 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.

Complications

- From the NCDR CathPCI registry, in 2014, the unadjusted rates of various events were as follows: acute kidney injury, 2.6% (versus 2.3% in 2011); blood transfusion, 1.4% (versus 1.9% in 2011); postprocedural stroke, 0.2% (versus 0.2% in 2011); emergency CABG surgery, 0.2% (versus 0.3% in 2011); and vascular access site injury, 1.3% (versus 1.2% in 2011).[55]
- 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).[55] In the NCDR ACTION Registry–GWTG, a measure of neighborhood SES was associated with in-hospital deaths and major bleeding in patients with AMI. Compared with those in the highest quintile of neighborhood SES, those residing in the most disadvantaged quintile experienced higher rates of in-hospital death (OR, 1.10 [95% CI, 1.02–1.18]) and major bleeding (OR, 1.10 [95% CI, 1.05–1.15]).[94]
- 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).[95]
- 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).[96]
- Patients with LV thrombosis complicating anterior STEMI had longer hospital stays, higher hospitalization-related costs, and higher risk of thromboembolic events than those without LV thrombosis (7.3% versus 2.1%; OR, 3.65 [95% CI, 1.95–6.84]; *P*<0.001).[97]
- In a propensity score–matched analysis from the NIS HCUP that included discharges with MI as the principal diagnosis from 2012 to 2014, patients with delirium had higher rates of in-hospital mortality than those without delirium (10.5% versus 7.6%; RR, 1.39 [95% CI, 1.2–1.6]; *P*<0.001).[98]
- Individuals with HF symptoms (New York Heart Association functional class ≥2) within 30 days after PCI for STEMI experience increased risk of death or hospitalization for HF within 1 year compared with those without HF symptoms (HR, 3.78 [95% CI, 1.16–12.22]; *P*=0.03).[99]

- 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.[100]
- 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 for 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.[101]
- 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.[102] Crude 30-day rehospitalization rates decreased from 20.5% in 2001 to 2003 to 15.8% in 2009 to 2011.[103]
- In 3863 patients ≥65 years of age hospitalized for AMI at 1 of 3 medical centers in Worcester, MA, between 2001 and 2011, those with ≥3 cardiac conditions plus ≥1 noncardiac condition experienced worse outcomes compared with those with ≤2 cardiac conditions and no noncardiac condition (in-hospital mortality: OR, 1.78 [95% CI, 1.32–2.39]; 7-day any-cause rehospitalization: OR, 1.62 [95% CI, 1.10–2.37]; 30-day any-cause rehospitalization: OR, 1.67 [95% CI, 1.32–2.11]).[104]
- In the NIS from 2003 to 2013, patients who developed VTE during their hospitalization for STEMI (1% of hospitalizations) had longer length of stay (median, 9 days for those with versus 3 days for those without VTE; *P*<0.001) and increased risk of gastrointestinal bleeding (OR, 2.13 [95% CI, 2.02–2.25]; *P*<0.001), intracranial hemorrhage (OR, 2.14 [95% CI, 1.84–2.49]; *P*<0.001), blood transfusions (OR, 1.94 [95% CI, 1.87–2.02]; *P*<0.001), and death (OR, 1.39 [95% CI, 1.34–1.44]; *P*<0.001) during the hospitalization.[105]

Age, Sex, Race, and Complications

- On the basis of pooled data from the FHS, ARIC, CHS, MESA, CARDIA, and JHS studies of the NHLBI (1995–2012; unpublished NHLBI tabulation), 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.

Hospital Discharges and Ambulatory Care Visits (See Table 20-1 and Chart 20-8)

- From 2006 to 2016, the number of inpatient discharges from short-stay hospitals with CHD as the first-listed diagnosis decreased from 1 857 000 to 1 045 000 (Table 20-1).
- From 1997 through 2016, the number of hospital discharges for CHD was higher for males than females (Chart 20-8).
- In 2016, there were 11 072 000 physician office visits for CHD (unpublished NHLBI tabulation using NAMCS[106]). In 2016, there were 469 000 ED visits with a primary diagnosis of CHD (unpublished NHLBI tabulation using NHAMCS[107]).
- In the NIS, the mean length of hospital stay for patients with STEMI with primary PCI declined from 3.3 days in 2005 to 2.7 days in 2014; the proportion of hospitalizations with length of stay >3 days declined from 31.9% in 2005 to 16.9% in 2014.[108]
- In the CathPCI registry, a composite of use of evidence-based medical therapies, including aspirin,

$P2Y_{12}$ inhibitors, and statins, was high (89.1% in 2011 and 93.5% in 2014). However, in the ACTION-GWTG registry, metrics shown to need improvement were defect-free care (median hospital performance rate, 78.4% in 2014), $P2Y_{12}$ 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 diabetes or HF (12.8%).[55]

Cost

- The estimated direct cost of HD in 2016 to 2017 (average annual) was $103.2 billion (MEPS,[109] unpublished NHLBI tabulation).
- The estimated direct and indirect cost of HD in 2016 to 2017 (average annual) was $219.6 billion (MEPS,[109] unpublished NHLBI tabulation).
- MI ($12.1 billion) and CHD ($9.0 billion) were 2 of the 10 most expensive conditions treated in US hospitals in 2013.[110]
- In 642 105 Medicare beneficiaries hospitalized for AMI between 2011 and 2014, 30-day episode payments averaged $22 128 but varied 2-fold across hospitals. Median costs were $20 207 in the lowest quartile versus $24 174 in the highest quartile of hospitals.[111]
- In Medicare beneficiaries hospitalized with AMI, the 180-day expenditures increased from an average of $32 182 per person in 1999 to 2000 to $36 836 in 2008 and remained relatively stable thereafter, with expenditures of $36 668 in 2013 to 2014.[112]
- 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 than for 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.[113]
- In 11 969 patients with AMI from 233 US hospitals who underwent PCI from 2010 to 2013, average hospital costs were higher for patients with STEMI ($19 327) compared with patients with NSTEMI ($18 465; $P=0.002$) and higher among elderly patients ($19 575 for those ≥65 years of age versus $18 652 for those <65 years of age; $P=0.004$). Forty-five percent of costs were related to the catheterization laboratory, 22% to room and board, 14% to supplies, and 9% to pharmacy costs. At 1 year after discharge, hospital and ED costs averaged $8037, with three-quarters attributable to hospitalizations ($6116 for hospitalizations, $1334 for outpatient hospital stays, and $587 for ED visits).[114]
- In 2016, total health care spending related to IHD was $89.3 billion, of which nearly half was for inpatient care (49.5%) and almost one-quarter was for ambulatory care expenses (23.8%). An estimated 54% of spending was paid by public insurance and 42% by private insurance; the remaining 4% was out-of-pocket costs.[115]

Global Burden (See Table 20-3 and Charts 20-9 and 20-10)

- The GBD 2019 study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 369 diseases and injuries in 204 countries and territories.[116] Globally, it is estimated that, in 2019, 197.2 million people lived with IHD, and it was more prevalent in males than in females (113.7 and 83.6 million people, respectively). The number of people with IHD increased by 103.5% from 1990 to 2019, although the age-standardized rate per 100 000 decreased 4.6% over the same time period (Table 20-3).
  - IHD mortality rates are highest in parts of North Africa and the Middle East, Eastern Europe, and Central Asia (Chart 20-9).
  - North Africa and the Middle East, Central Asia, and Eastern Europe have the highest prevalence rates of IHD in the world (Chart 20-10).
- Among 31 443 respondents ≥50 years of age from 6 low- and middle-income countries participating in the WHO SAGE Wave 1, prevalence of angina ranged between 8% in China and 39% in Russia and was higher in females than males.[117]

Acute Coronary Syndrome

ICD-9 410, 411; *ICD-10* I20.0, I21, I22.

- In 2016, there were 661 000 ACS principal diagnosis discharges. Of these, an estimated 409 000 were males, and 252 000 were females. This estimate was derived by adding the principal diagnoses for MI (651 000) to those for UA (10 000; unpublished NHLBI tabulation using HCUP[57]).
- When all listed discharge diagnoses in 2016 were included, the corresponding number of inpatient hospital discharges was 1 045 000 unique hospitalizations for ACS; 615 000 were males, and 430 000 were females. Of the total, 1 022 000 were for MI alone, and 23 000 were for UA alone (HCUP,[57] unpublished NHLBI tabulation).
- 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).[118]

- 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.[119]
- According to data from the NIS, between 2001 and 2011, the use of PCI for patients with ACS declined by 15%.[69]
- In a report from the TRACE-CORE study, people 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 individuals with a first ACS.[120]
- In the NIS from 2012 to 2013, females with non–ST-segment–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.[121]
- 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 patients with non–ST-segment–elevation ACS treated with a routine strategy (coronary angiography within 24–96 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.[122]

Stable Angina Pectoris

ICD-9 413; *ICD-10* I20.1 to I20.9.

Prevalence

(See Table 20-2 and Chart 20-11)

- According to data from NHANES 2015 to 2018, the prevalence of angina pectoris among adults (≥20 years of age) is 4.1% (11.0 million adults; Table 20-2).
- On the basis of NHANES 2015 to 2018, the prevalence of angina pectoris 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 20-11).
- On the basis of data from NHANES in 2009 to 2012, an average of 3.4 million people ≥40 years of age in the United States had angina each year compared with 4 million in 1988 to 1994. Declines in angina symptoms have occurred for NH White but not for NH Black people.[123]
- In Americans ≥40 years of age with health insurance, age-adjusted angina prevalence declined from 7.6% in 2001 to 2002 to 5.2% 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% (*P* for trend=0.4).[124]
- 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.[125]

Table 20-1. CHD in the United States

Population group	Prevalence, CHD, 2015–2018, age ≥20 y	Prevalence, MI, 2015–2018, age ≥20 y	New and recurrent MI and fatal CHD, 2005–2014, age ≥35 y	New and recurrent MI, 2005–2014, age ≥35 y	Mortality,* CHD, 2018 all ages	Mortality,* MI, 2018 all ages	Hospital discharges: CHD, 2016 all ages
Both sexes	20 100 000 (7.2%) [95% CI, 6.5%–7.9%]	8 800 000 (3.1%) [95% CI, 2.7%–3.6%]	1 055 000	805 000	365 744	108 610	1 045 000
Males	11 000 000 (8.3%)	5 800 000 (4.3%)	610 000	470 000	215 032 (58.8%)†	64 079 (59.0%)†	664 000
Females	9 100 000 (6.2%)	3 000 000 (2.1%)	445 000	335 000	150 712 (41.2%)†	44 531 (41.0%)†	381 000
NH White males	8.7%	4.4%	520 000‡	…	169 211	50 465	…
NH White females	6.0%	2.0%	370 000‡	…	117 194	34 447	…
NH Black males	6.7%	3.9%	90 000‡	…	22 699	6650	…
NH Black females	7.2%	2.3%	75 000‡	…	18 118	5476	…
Hispanic males	6.8%	3.7%	…	…	14 755	4584	…
Hispanic females	6.4%	2.1%	…	…	10 105	3099	…
NH Asian males	5.0%	2.7%	…	…	6084	1835§	…
NH Asian females	3.2%	0.7%	…	…	4054	1166§	…
NH American Indian or Alaska Native	…	…	…	…	2058	612	…

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 CHD, angina or angina pectoris, heart attack, or MI?" Those who answered "no" but were diagnosed with Rose angina are also included (the Rose questionnaire is administered only to survey participants >40 years of age). CIs have been added for overall prevalence estimates in key chapters. CIs have not been included in this table for all subcategories of prevalence for ease of reading.

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 Hispanic and non-Hispanic people. Estimates for White people include other non-Black races.

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

Sources: Prevalence: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey 2015 to 2018.[1] Percentages for racial/ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2018 US population estimates. These data are based on self-reports. Incidence: Atherosclerosis Risk in Communities study (2005–2014),[4] unpublished tabulation by NHLBI, extrapolated to the 2014 US population. Mortality: unpublished NHLBI tabulation using National Vital Statistics System, 2018.[79] Mortality for NH Asian people includes Pacific Islander people. Hospital discharges: unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2016[57] (data include those inpatients discharged alive, dead, or status unknown).

Table 20-2. Angina Pectoris* in the United States

Population group	Prevalence, 2015–2018, age ≥20 y	Hospital discharges, 2016, all ages
Both sexes	11 000 000 (4.1%)	18 000
Males	5 300 000 (4.2%)	9000
Females	5 700 000 (4.0%)	9000
NH White males	4.5%	…
NH White females	4.0%	…
NH Black males	3.3%	…
NH Black females	4.7%	…
Hispanic males	3.5%	…
Hispanic females	4.3%	…
NH Asian or Pacific Islander males	2.1%	…
NH Asian or Pacific Islander females	2.2%	…

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 (the Rose questionnaire is administered only to survey participants >40 years of age).

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

*Angina pectoris is chest pain or discomfort that results from insufficient blood flow to the heart muscle. Stable angina pectoris is predictable chest pain on exertion or under mental or emotional stress. The incidence estimate is for angina pectoris without myocardial infarction.

Sources: Prevalence: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES (National Health and Nutrition Examination Survey), 2015 to 2018.[1] Percentages for racial/ethnic groups are age adjusted for US adults ≥20 years of age. Estimates from NHANES 2015 to 2018 were applied to 2018 population estimates (≥20 years of age). Hospital discharges: unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2016[57]; data include those inpatients discharged alive, dead, or status unknown.

Table 20-3. Global Burden of IHD and Trends, 2019

	Both sexes		Male		Female	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions)	9.1 (8.4 to 9.7)	197.2 (177.7 to 219.5)	5.0 (4.6 to 5.3)	113.7 (102.3 to 126.0)	4.2 (3.7 to 4.5)	83.6 (74.7 to 93.6)
Percent change in total number 1990 to 2019	60.4 (50.2 to 69.1)	103.5 (101.6 to 105.6)	64.4 (51.6 to 76.8)	104.3 (102.1 to 106.6)	56.0 (44.0 to 67.0)	102.5 (100.4 to 104.8)
Percent change in total number 2010 to 2019	19.4 (13.6 to 24.9)	29.1 (28.4 to 29.8)	18.6 (11.0 to 25.9)	28.8 (28.1 to 29.5)	20.3 (12.5 to 27.8)	29.5 (28.7 to 30.4)
Rate per 100 000, age standardized	118.0 (107.8 to 125.9)	2421.0 (2180.5 to 2692.6)	144.6 (132.9 to 155.0)	3007.5 (2717.4 to 3328.9)	95.1 (83.9 to 103.1)	1911.5 (1708.9 to 2140.3)
Percent change in rate, age standardized 1990 to 2019	−30.8 (−34.8 to −27.2)	−4.6 (−5.7 to −3.6)	−29.5 (−34.7 to −24.8)	−6.8 (−7.8 to −5.7)	−32.9 (−38.0 to −28.4)	−3.5 (−4.7 to −2.3)
Percent change in rate, age standardized 2010 to 2019	−9.7 (−13.9 to −5.7)	0.1 (−0.3 to 0.5)	−9.8 (−15.2 to −4.8)	−0.7 (−1.2 to −0.2)	−9.6 (−15.4 to −4.0)	0.7 (0.2 to 1.3)

IHD indicates ischemic heart disease; and UI, uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[116] Printed with permission. Copyright © 2020, University of Washington.

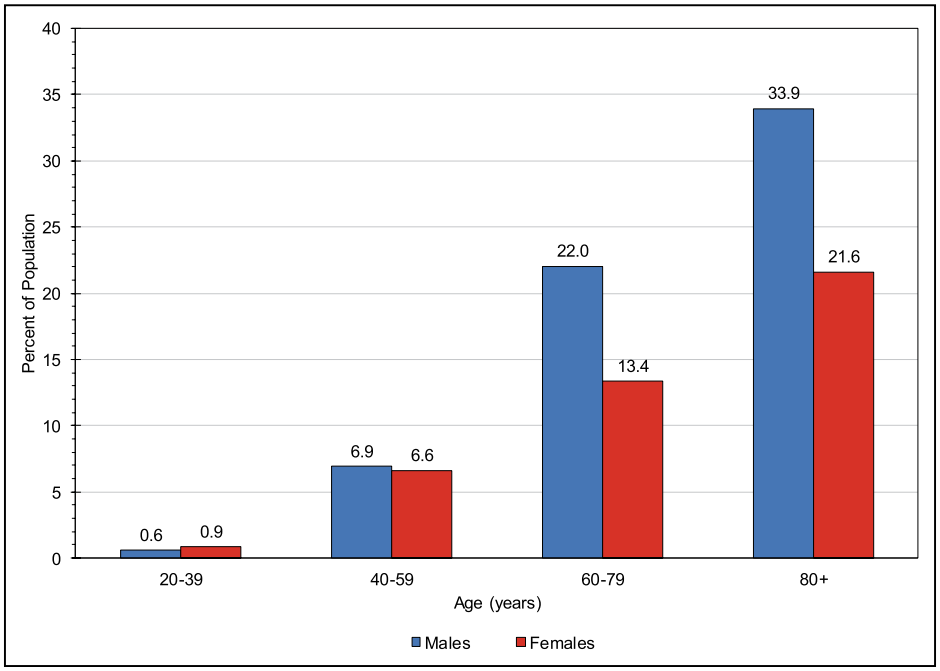

Chart 20-1. Prevalence of coronary heart disease by age and sex, United States (NHANES, 2015–2018).

NHANES indicates National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2015 to 2018.[1]

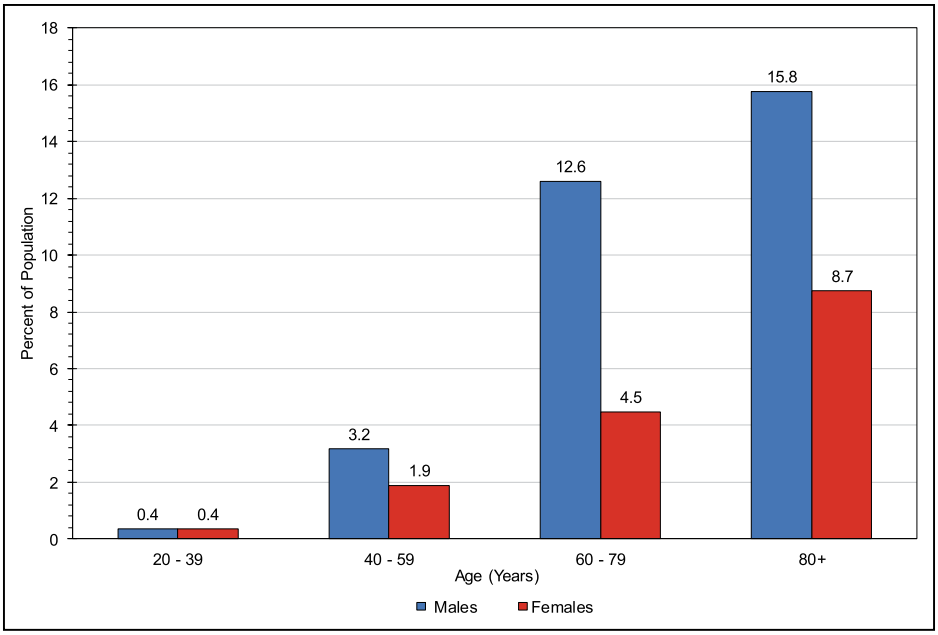

Chart 20-2. Prevalence of myocardial infarction (MI) by age and sex, United States (NHANES, 2015–2018).
MI includes people who answered "yes" to the question of ever having had a heart attack or MI.
NHANES indicates National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2015 to 2018.[1]

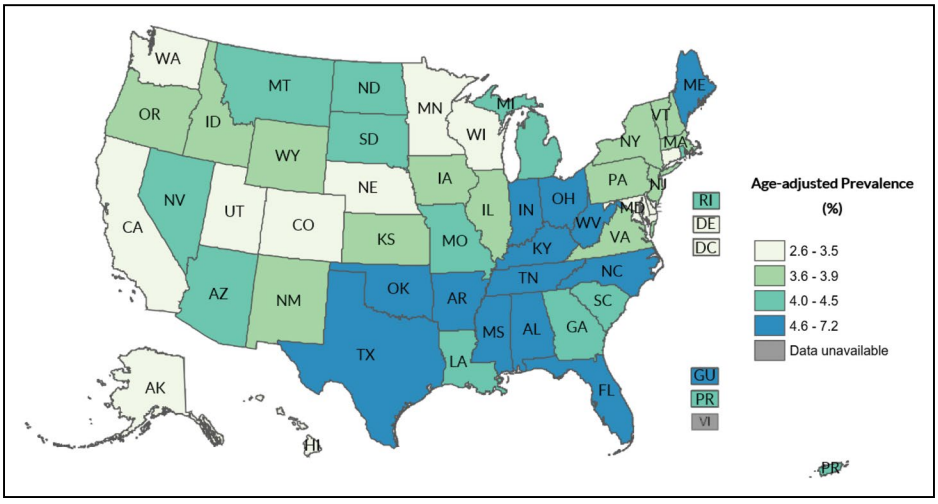

Chart 20-3. "Ever told you had a heart attack (myocardial infarction)?" Age-adjusted US prevalence by state (BRFSS prevalence and trends data, 2018).
Original figure has been modified to remove white space between map and legend.
BRFSS indicates Behavioral Risk Factor Surveillance System.
Source: BRFSS prevalence and trends data, 2018.[3]

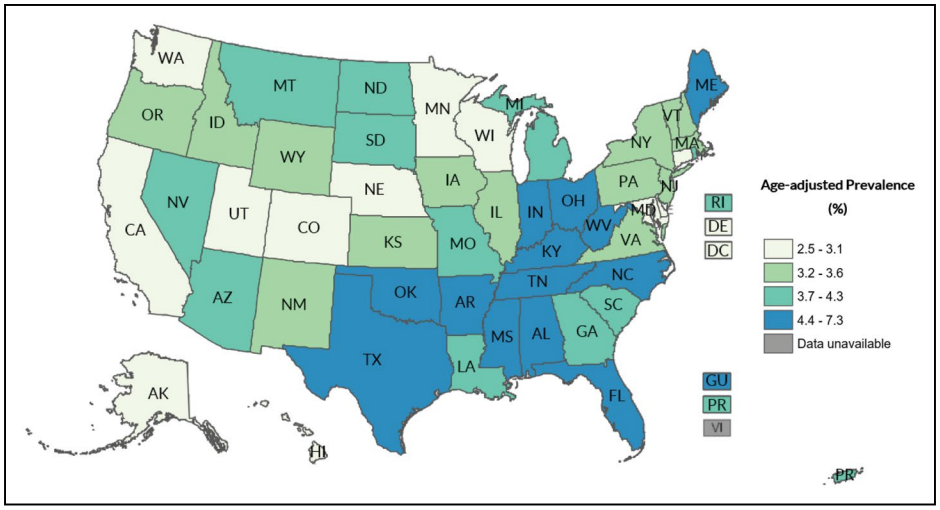

Chart 20-4. "Ever told you had angina or coronary heart disease?" Age-adjusted US prevalence by state (BRFSS prevalence and trends data, 2018).
Original figure has been modified to remove white space between map and legend.
BRFSS indicates Behavioral Risk Factor Surveillance System.
Source: BRFSS prevalence and trends data, 2018.[3]

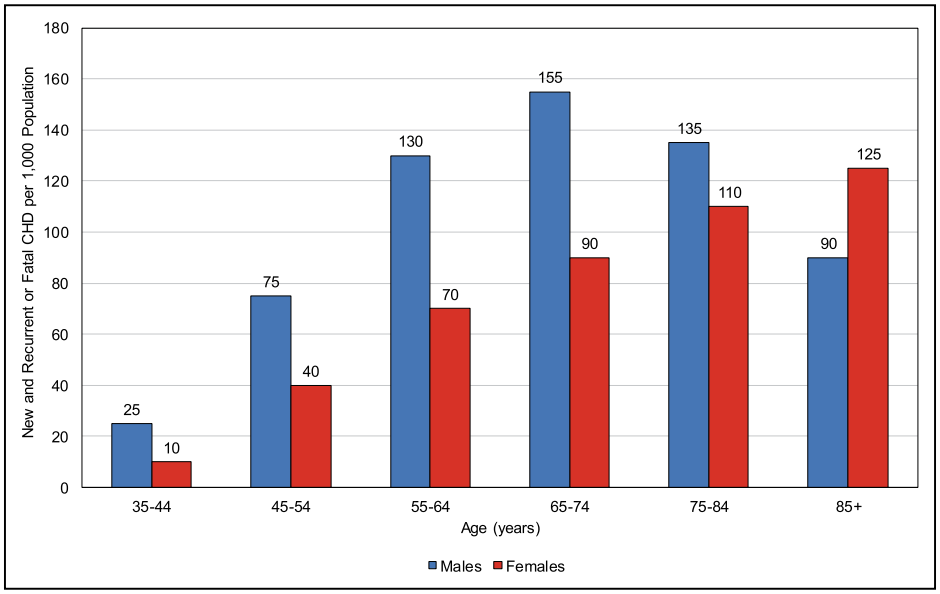

Chart 20-5. Annual number of US adults per 1000 having diagnosed heart attack or fatal CHD by age and sex (ARIC Surveillance, 2005–2014 and CHS).
These data include myocardial infarction (MI) and fatal CHD but not silent MI.
ARIC indicates Atherosclerosis Risk in Communities; CHD, coronary heart disease; and CHS, Cardiovascular Health Study.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using ARIC, 2005 to 2014[4] and CHS.[126]

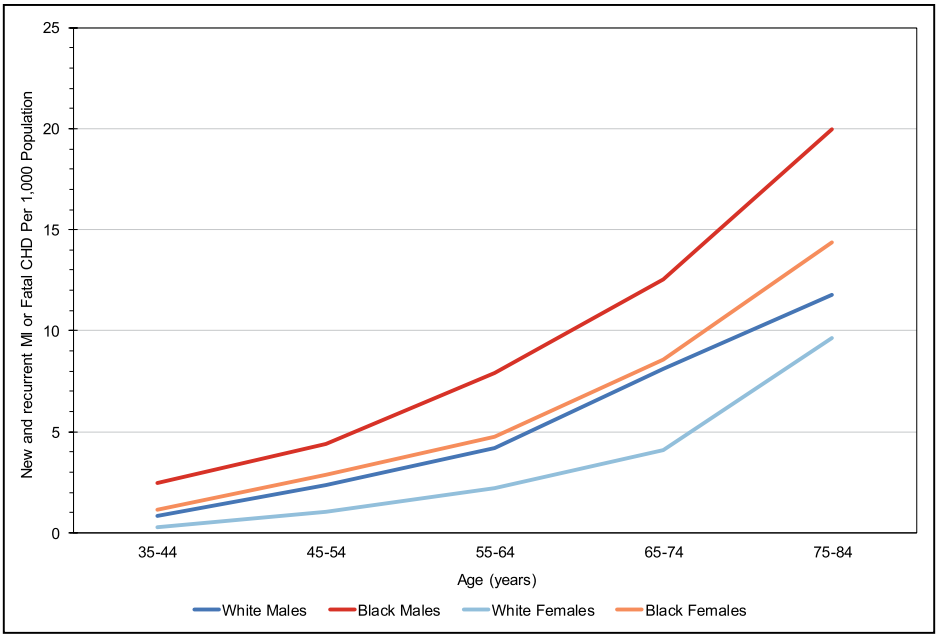

Chart 20-6. Incidence of heart attack or fatal CHD by age, sex, and race, United States (ARIC Surveillance, 2005–2014).
ARIC indicates Atherosclerosis Risk in Communities; CHD, coronary heart disease; and MI, myocardial infarction.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using ARIC, 2005 to 2014.[4]

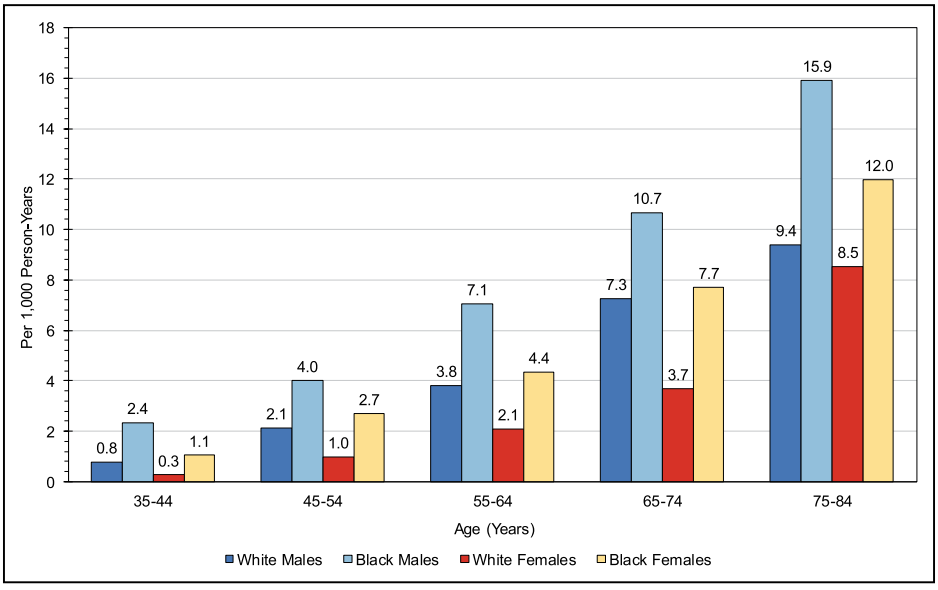

Chart 20-7. Incidence of myocardial infarction by age, sex, and race, United States (ARIC Surveillance, 2005–2014).
ARIC indicates Atherosclerosis Risk in Communities.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using ARIC, 2005 to 2014.[4]

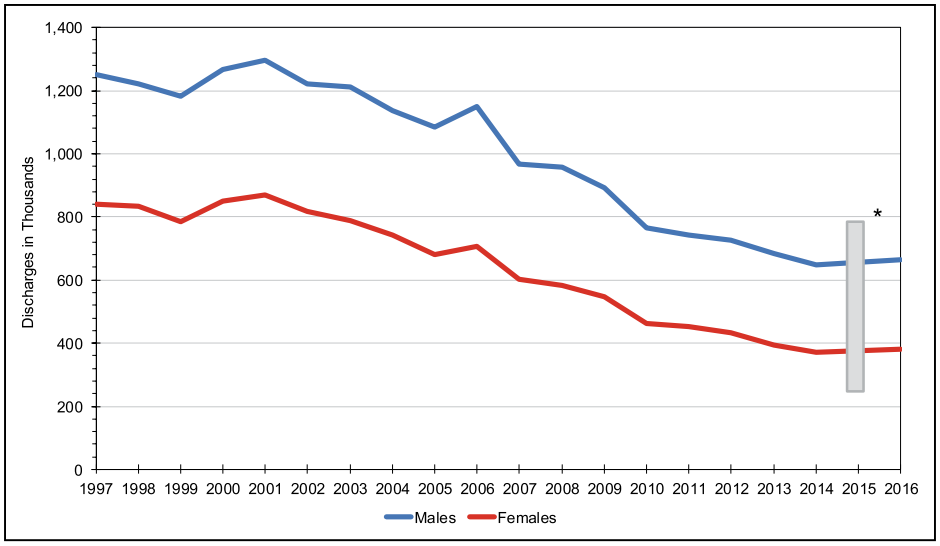

Chart 20-8. Hospital discharges for coronary heart disease by sex, United States (HCUP, 1997–2016).
Hospital discharges include people discharged alive, dead, and status unknown.
HCUP indicates Healthcare Cost and Utilization Project.
*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using HCUP.[57]

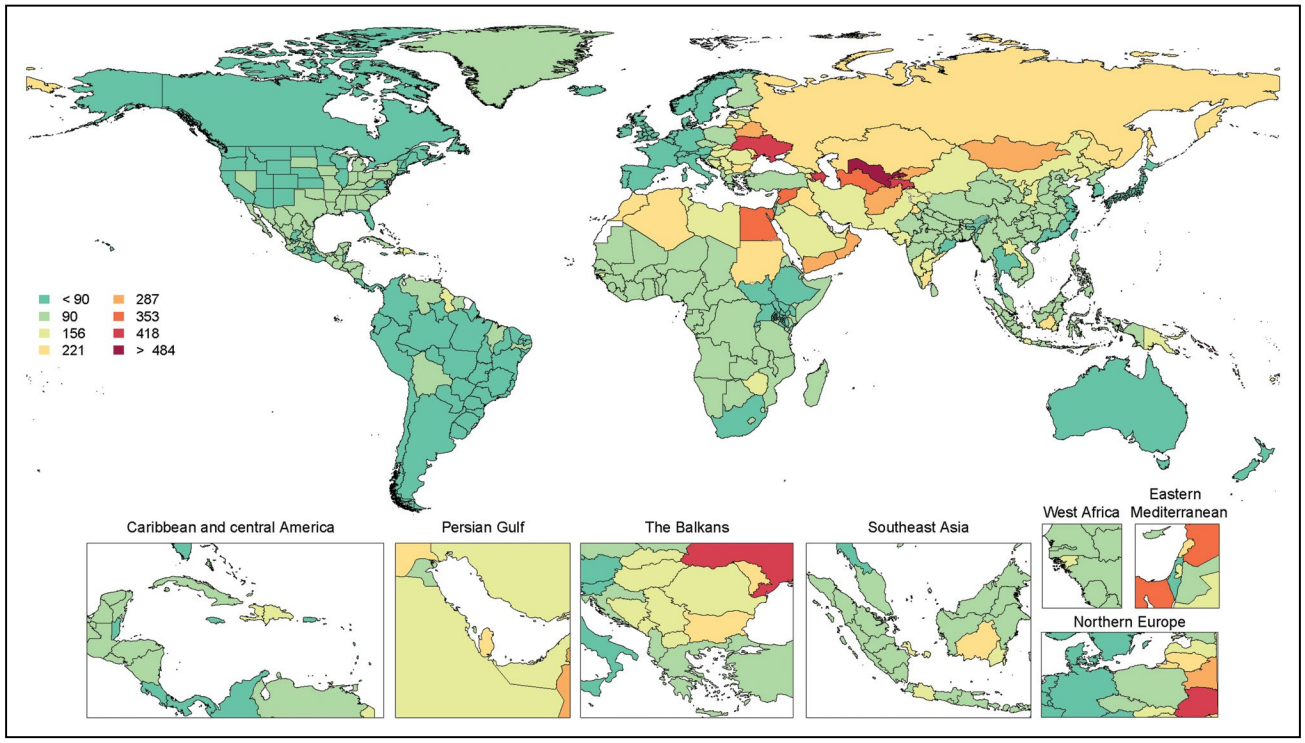

Chart 20-9. Age-standardized global mortality rates of ischemic heart disease per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[116] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[127]

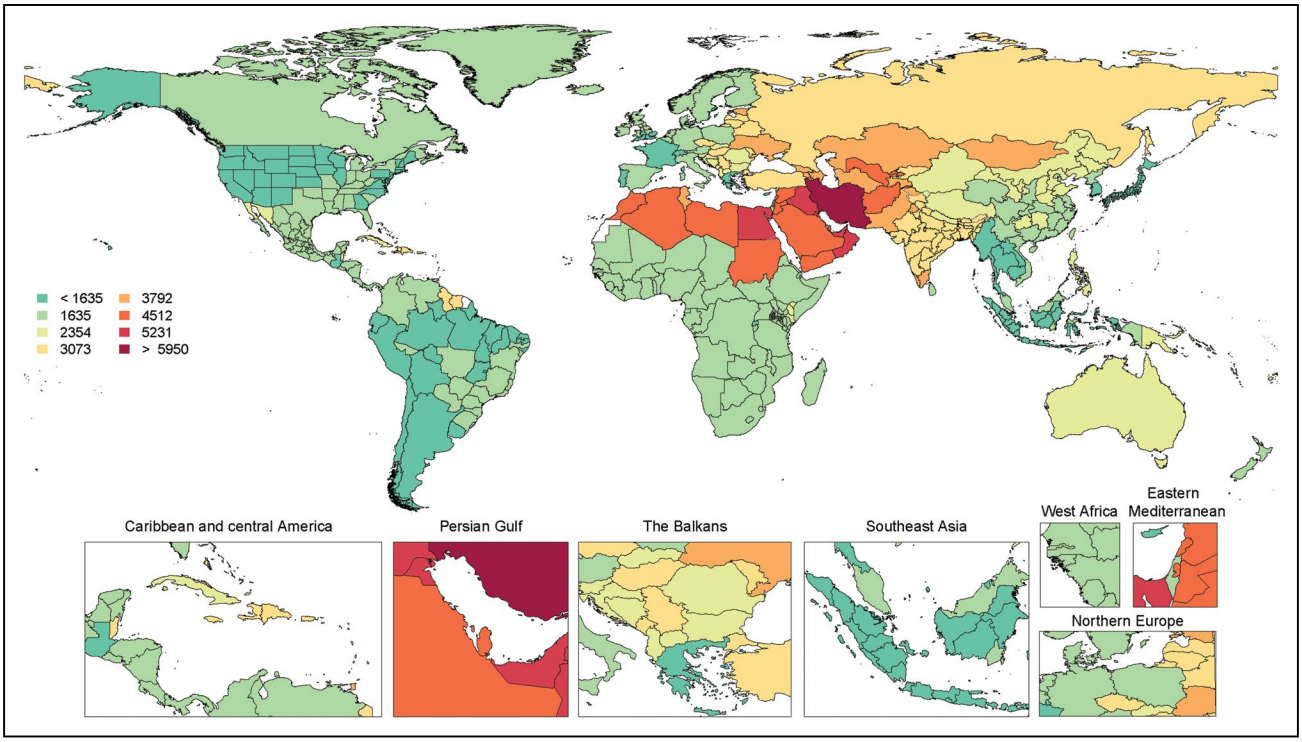

Chart 20-10. Age-standardized global prevalence rates of ischemic heart disease per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[116] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[127]

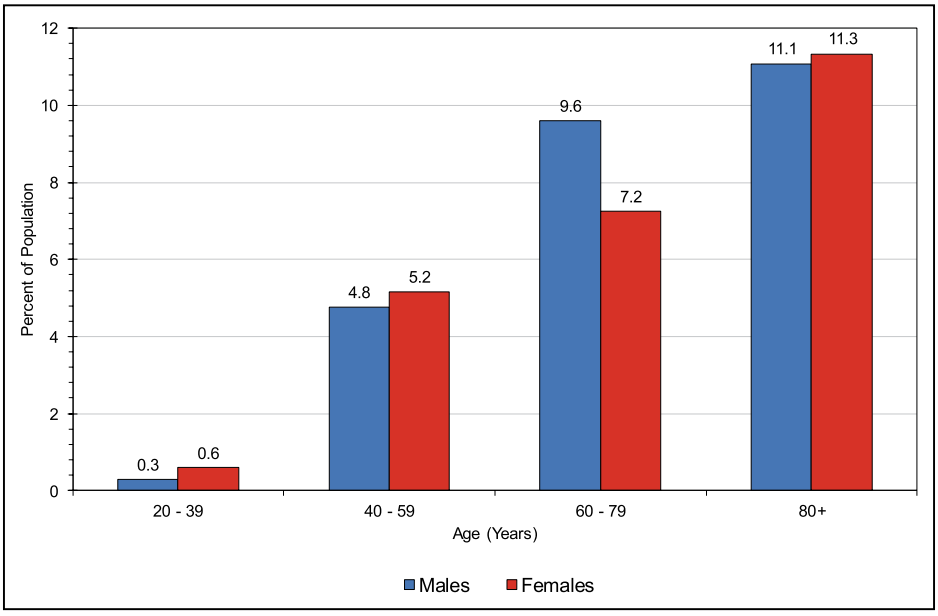

Chart 20-11. Prevalence of angina pectoris by age and sex, United States (NHANES, 2015–2018).
Angina pectoris includes people who either answered "yes" to the question of ever having angina or angina pectoris or were diagnosed with Rose angina. NHANES indicates National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2015 to 2018.[1]

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21. CARDIOMYOPATHY AND HEART FAILURE

See Tables 21-1 and 21-2 and Charts 21-1 through 21-5

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Cardiomyopathy

ICD-9 425; ICD-10 I42.

2017: Mortality—21 223. Any-mention mortality—42 853.

Cardiomyopathy diagnoses account for a substantial number of inpatient and outpatient encounters annually. According to 2016 HCUP data[1] for inpatient hospitalizations, cardiomyopathy was the principal diagnosis for 19 000 (11 000 for males; 8000 for females), and it was included among all-listed diagnoses for 994 000.

Abbreviations Used in Chapter 21

ACE	angiotensin-converting enzyme
ACR	albumin-to-creatinine ratio
AF	atrial fibrillation
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities study
BIOSTAT-CHF	Biology Study to Tailored Treatment in Chronic Heart Failure
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
CAD	coronary artery disease
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research
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
ED	emergency department

(*Continued*)

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Abbreviations Used in Chapter 21 Continued

EF	ejection fraction
ESRD	end-stage renal disease
FHS	Framingham Heart Study
GBD	Global Burden of Disease Study
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
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
IHD	ischemic heart disease
IL	interleukin
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
JHS	Jackson Heart Study
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
MRI	magnetic resonance imaging
NAMCS	National Ambulatory Medical Care Survey
NCDR	National Cardiovascular Data Registry
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
NVSS	National Vital Statistics System
OR	odds ratio
PA	physical activity
PAR	population attributable risk
PHS	Physicians' Health Study
PINNACLE	Practice Innovation and Clinical Excellence
PPCM	peripartum cardiomyopathy
PVC	premature ventricular contraction
QALY	quality-adjusted life-year
ROADMAP	Randomized Olmesartan and Diabetes Microalbuminuria Prevention
RV	right ventricular
SBP	systolic blood pressure
SCD	sudden cardiac death
SES	socioeconomic status
TNF	tumor necrosis factor
Txpl	transplantation
UI	uncertainty interval

Hypertrophic Cardiomyopathy

- The prevalence of unexplained LVH has been estimated at 0.2% and up to 1.4% in the community.[2]
- Of people with unexplained LVH, ≈20% to 30% are likely to have a sarcomere mutation suggestive of 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).[3]
- The Sarcomeric Human Cardiomyopathy Registry studied 4591 patients with HCM, contributing >24 000 person-years of follow-up, and observed ≈3- to 4-fold higher mortality risk in patients with HCM compared with individuals of a similar age in the US general population. Risk for adverse events (ie, any ventricular arrhythmia, HF, AF, stroke, or death) was highest in patients diagnosed before 40 years of age versus after 60 years of age (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 to decades after the initial diagnosis.[4]

Dilated Cardiomyopathy

- Commonly recognized causes of chronic DCM are mutations in a diverse group of genes inherited in an autosomal dominant fashion with age-dependent penetrance and variable clinical expression (see Family History and Genetics for more details).[5] Other causes of DCM of variable chronicity and reversibility include cardiomyopathies developing after an identifiable exposure such as tachyarrhythmia, stress, neurohormonal disorder, alcoholism, chemotherapy, infection, autoimmunity, or pregnancy (see Peripartum Cardiomyopathy).[6,7] The annual incidence of chronic idiopathic DCM has been reported to be between 5 and 8 cases per 100 000, although these estimates might be low because of underrecognition, especially in light of prevalent asymptomatic LV dysfunction observed in community-based studies (see LV Function).[8,9]

Peripartum Cardiomyopathy

- PPCM is a global problem, with the highest incidence (1 in 102 births) seen in Nigeria and lowest incidence (1 in 15 533 births) seen in Japan.[10] Accordingly, worldwide and in the United States, women with Black ancestry appear to have highest risk, especially women with Nigerian and Haitian background.[11]
- In the United States, according to NIS data, 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 diabetes.[12] Stratified by race/ethnicity, incidence of PPCM was lowest in Hispanic women and highest in Black women. Stratified by region, incidence was lowest in the West (6.5 [95% CI, 6.3–6.7] per 10 000 live births) and highest in the South (13.1 [95% CI, 12.9–13.1] per 10 000 live births).[12]
- Global mortality from PPCM is 9% and is lower in developed (4%) than developing (14%) countries; overall mortality rates are highest for countries with women of African descent.[13] Nonfatal major outcomes include HF, cardiac transplantation, implantation of an LVAD, and cardiovascular events, in addition to persistent severe cardiomyopathy at 12 months.[13]
- In most cases of PPCM (50%–80%), LVEF recovers to at least near-normal (≥50%) function and often within 6 months; however, a proportion remain affected by overtly impaired cardiac function.[14–17] Black women tend to have worse LV dysfunction at presentation and at up to 12 months postpartum.[14,16,17]

Youth

- Since 1996, the Pediatric Cardiomyopathy Registry has collected data on children with cardiomyopathy in New England and central Southwestern states.[18]
  - Overall incidence of cardiomyopathy is 1.13 cases per 100 000 in children <18 years of age.
  - The incidence is 8.34 (95% CI, 7.21–9.61) per 100 000 for children <1 year of age.
  - Annual incidence (cases per 100 000) is higher in Black (1.47) than in White (1.06) children, in boys (1.32) than in girls (0.92), and in New England (1.44) than in the central Southwest (0.98).
- The annual incidence of HCM in children is ≈4.7 per 1 million (95% CI, 4.1–5.3), with higher incidence in New England than in the central Southwest region and in boys than in girls.[19] Approximately 9% progress to HF and 12% to SCD.[20] See Chapter 17 (Disorders of Heart Rhythm) for statistics on sudden death. Data from the NIS indicate that hospitalization rates increase with age and are higher in Black individuals than White individuals.[21]
- The annual incidence of DCM in children is ≈0.57 per 100 000 (95% CI, 0.52–0.63), with a higher incidence in boys than girls (0.66 versus 0.47) and in Black children than White children (0.98 versus 0.46). Commonly recognized causes include myocarditis (46%) and neuromuscular disease (26%).[22] The 5-year incidence rate of SCD is 3% at the time of DCM diagnosis.[23]
- For all cardiomyopathies seen in children, 5-year transplantation-free survival of DCM, HCM, restrictive cardiomyopathy, and LV noncompaction is 50%, 90%, 30%, and 60%, respectively.[24]

- Data from the Childhood Cancer Survivor Study cohort of 14358 survivors of childhood or adolescent cancers showed a 5.9-fold (95% CI, 3.4–9.6) increased risk for HF,[25] usually preceded by asymptomatic cardiomyopathy persisting up to 30 years after the cancer diagnosis, especially in patients treated with chest radiation or anthracycline chemotherapy diagnosis.

Global Burden of Cardiomyopathy (See Table 21-1 and Charts 21-1 through 21-2)

- The GBD 2019 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate burden for diseases and injuries across 204 countries and territories.[26]
  - — Between 1990 and 2019, deaths attributable to cardiomyopathy and myocarditis increased, although the age-adjusted death rate decreased (Table 21-1).
  - — The highest age-standardized death rates in 2019 attributable to cardiomyopathy and myocarditis were in Eastern Europe (Chart 21-1).
  - — Age-standardized prevalence of cardiomyopathy and myocarditis in 2019 was highest in sub-Saharan Africa and parts of North America (Chart 21-2).

Heart Failure

ICD-9 428; *ICD-10* I50.

2018: Mortality—83616. Any-mention mortality—366464.

2016: Hospital discharges—809000.

Prevalence (See Table 21-2 and Chart 21-3)

- On the basis of data from NHANES 2015 to 2018, ≈6.0 million Americans ≥20 years of age had HF (Table 21-2), which is increased from ≈5.7 million according to NHANES 2009 to 2012 (NHLBI unpublished tabulation using NHANES[27]). The breakdown of HF prevalence by age and sex is shown in Chart 21-3.
- Prevalence of HF is projected to increase by 46% from 2012 to 2030, affecting >8 million people ≥18 years of age. The total percentage of the population with HF is projected to rise from 2.4% in 2012 to 3.0% in 2030.[28]

Incidence (See Table 21-2)

- According to ARIC Community Surveillance data, the incidence of HF in people ≥55 years of age was ≈1000000 in 2014, with slightly more new-onset cases seen in females than in males (Table 21-2).
- The Chicago Heart Association Detection Project in Industry, ARIC, and CHS cohorts indicate that HF incidence ranges from 6.0 to 7.9 per 1000 person-years after 45 years of age and ≈21 per 1000 population after 65 years of age.[29]
- In the Southern Community Cohort Study, estimated age-standardized HF incidence rates are 34.8, 37.3, 34.9, and 35.6 per 1000 person-years in White females, White males, Black males, and Black females, respectively.[30]
- Data from Olmsted County, Minnesota, indicate that the age- and sex-adjusted incidence of HF declined substantially, from 315.8 per 100000 in 2000 to 219.3 per 100000 in 2010, with a greater rate reduction for HFrEF (–45% [95% CI, –33% to –55%) than for HFpEF (–27.9% [95% CI, –12.9% to –40.3%]).[31]
- In the NCDR PINNACLE, 1 in 6 patients with HFrEF developed worsening HF within 18 months of diagnosis, and vulnerable patients were more likely to be Black, to be >80 years of age, and to have greater comorbidity burden; the 30-day readmission rate was 56% and 2-year mortality rate was 22.5%.[32]
- In MESA, Black individuals had the highest risk of developing HF, followed by Hispanic, White, and Chinese American individuals; higher risk reflected differential prevalence of hypertension, diabetes, and low SES.[33] Black individuals also had the highest proportion of incident HF not preceded by MI (75%).[33]

Secular Trends

- Some data suggest that improvements in survival in individuals with HF could be leveling off over time. Data from the Rochester Epidemiology Project in Olmsted County, Minnesota, showed improved survival after HF diagnosis between 1979 and 2000[34]; however, 5-year mortality did not decline from 2000 to 2010 and remained high at ≈50% (52.6% overall; 24.4% for those 60 years of age and 54.4% for those 80 years of age). Mortality was more frequently attributed to noncardiovascular causes (54.3%), and the risk of noncardiovascular death was greater in HFpEF than in HFrEF.[31]
- Data collected between 1985 and 2014 from 12857 person-observations in the FHS showed that the frequency of HFrEF (EF <40%) decreased over time, whereas HF with midrange EF (40% to <50%) remained stable, and HFpEF (EF ≥50%) increased over time. These findings appeared attributable to risk factor trends, especially a decrease in prevalent CHD among people with HF.[35]

Lifetime Risk

- Because most forms of HF present in older age, lifetime risk for HF in the community is high given aging of the population. Data from the NHLBI-sponsored Chicago Heart Association Detection Project in Industry, ARIC, and CHS cohorts have indicated[29]:
  - — From 45 through 95 years of age, overall lifetime risks for HF range from 20% to 45%.

— Lifetime risks 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 attributable to competing risks.
— Lifetime risk of HF was higher with higher BP and BMI at all ages, with a 1.6-fold higher risk for BP >160/90 mm Hg compared with <120/90 mm Hg and a doubling of risk for BMI ≥30 kg/m^2 compared with BMI <25 kg/m^2.

Risk Factors

- Traditional factors account for a large proportion of HF risk. Data from Olmsted County, Minnesota, indicate that CHD, hypertension, diabetes, obesity, and smoking account for 52% of incident HF with PARs as follows[36]: CHD, 20% (23% in males versus 16% in females); cigarette smoking, 14%; hypertension, 20% (28% in females versus 13% in males); obesity, 12%; and diabetes, 12%.
- Data from NHANES show that one-third of US adults have at least 1 HF risk factor.[37]
- Racial disparities in risks for HF persist, as shown in the Health ABC Study[38]: Black people versus White people have 68% versus 49% of the proportion of HF risk when considering elevated SBP, fasting glucose level, LVH, CHD, and smoking. For both races, the highest PARs were for CHD (24% for White individuals, 30% for Black individuals) and uncontrolled BP (21% for White individuals, 30% for Black individuals).[38] Hispanic people carry multiple HF risk factors and health care disparities, which suggests elevated HF risk in this population as well.[39,40]
- Risk factors differ by HF subtype: Patients with HFpEF versus those with HFrEF are older, are more likely female, and have more prevalent hypertension, obesity, and anemia.[41]
- Dietary and lifestyle factors also affect HF risk: Among 20 900 male physicians in the PHS, lower HF risk was associated with normal weight, not smoking, regular PA, moderate alcohol intake, consumption of breakfast cereals, and consumption of fruits and vegetables.[42]
- In the ARIC study, greater alignment with the AHA's Life's Simple 7 guidelines (better profiles in smoking, BMI, PA, diet, cholesterol, BP, and glucose) was associated with lower lifetime risk of HF, as well as more ideal echocardiographic parameters of cardiac structure and function.[43]
- In the Southern Community Cohort Study, the associations between the AHA's Life's Simple 7 and risk for incident HF varied by race and sex.[44]
- Multiple nontraditional risk markers for HF have been identified:
— In the FHS, higher levels of circulating BNP, urinary ACR, serum γ-glutamyl transferase, hematocrit, resistin, adiponectin, inflammatory markers (IL-6 and TNF-α), serum albumin, and cigarette smoking were identified as HF risk markers.[45–52]
— In the CHS, baseline and changes in cardiac high-sensitivity troponin were related to higher HF incidence.[53] Conversely, circulating individual and total omega-3 fatty acid concentrations were related to lower HF incidence.[54]
— In the ARIC study, white blood cell count, CRP, albuminuria, HbA_{1c}, cardiac troponin, PVCs, and socioeconomic position were identified as HF risk factors.[55–60]
— In MESA, N-terminal pro-BNP and MRI-determined LV mass index predicted incident symptomatic HF.[61]
— In the FHS, measures of major multiorgan 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.[62]

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 that of diastolic dysfunction was 36%; both were associated with increased HF incidence.[62]
— In Olmsted County, Minnesota, diastolic dysfunction was seen to progress with advancing age and was associated with an increased risk of incident clinical HF during 6 years of follow-up after adjustment for age, hypertension, diabetes, and CAD.[63]
— In race/ethnicity analyses, presence of asymptomatic LV systolic dysfunction in MESA was higher in Black people than in White, Chinese, and Hispanic people (1.7% overall and 2.7% in Black people); over 9 years of follow-up, asymptomatic LV dysfunction was associated with incident HF (HR, 8.69 [95% CI, 4.89–15.45]), as well as CVD and all-cause death.[8]
— Among African American participants in the JHS, the combination of higher LV mass and high-sensitivity cardiac troponin-I was associated with much higher risk of HF compared with no LVH and no sign of myocardial injury (HR, 5.35 [95% CI, 3.66–7.83]), with greater magnitudes of risk seen in males compared with females.[64]
— In the Echocardiographic Study of Latinos, almost half (49.7%) of middle-aged or older

Hispanic individuals had some form of cardiac dysfunction (systolic, diastolic, or both); paradoxically, <1 in 20 Hispanic/Latino individuals had symptomatic or clinically recognized HF.[65]

- LV function is variably abnormal in the setting of clinical HF.
  - Among 110 621 patients hospitalized with HF between 2005 to 2010 in the GWTG-HF database, EF was reduced (<40%) in half, intermediate (≥40% and <50%) in 14%, and preserved (≥50%) in 36%.[41]

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.[66]
- Familial DCM accounts for up to 50% of cases of DCM, with a prevalence of 1 in 2500, but is likely underestimated.[67] Familial DCM often displays an age-dependent penetrance.[68] Up to 40% of cases have an identifiable genetic cause.[67]
- 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.[69] Variants in *MYH7* (β-myosin heavy chain) were some of the earliest to be associated with familial HCM,[70,71] with >30 other genes implicated since, each accounting for <5% of cases, as reviewed elsewhere.[68,72,73] 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,[74] as well as to DCM, with incomplete penetrance in the general population.[74] 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.[75]
- Several GWASs have been conducted to identify common variations associated with cardiomyopathy and HF in the general population, albeit with modest results,[68,71] highlighting a small number of putative loci, including *HSPB7*[76-78] and *CACNB4*.[79] In a GWAS of >47 000 cases and >930 000 controls, 11 HF loci were identified, all of which have known relationships to other CVD traits.[80] In a sample of >1 million individuals, >100 AF loci were identified.[81] 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 patients with HF.[82] A large meta-analysis of >73 000 subjects identified 52 loci associated with myocardial mass.[83] 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 *MYBPC3* (cardiac myosin-binding protein C) being the most common, with each having 40 HCM cases attributed to it.[84] A mutation is identifiable in 50% to 75% of cases of familial HCM.
- Clinical genetic testing is recommended for patients with DCM with significant conduction system disease or a family history of SCD, as well as for 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.[85]
- Genetic testing is also recommended in family members of patients with DCM, HCM, restrictive cardiomyopathy, and LV noncompaction.[85]

Mortality (See Table 21-2)

- Survival after HF onset has improved, but such improvements are not even across demographics. Among Medicare beneficiaries, the 1-year HF mortality declined slightly from 1998 to 2008 but remained high at 29.6%, with uneven rates across states.[86] In the 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, with Black individuals having a greater 5-year case fatality rate than White individuals.[87]
- In the Southern Community Cohort Study, all-cause mortality after a diagnosis code for HF varied by sex, with HRs of 1.63 (95% CI, 1.27–2.08), 1.38 (95% CI, 1.11–1.72), and 0.90 (95% CI, 0.73–1.12) for White males, Black males, and Black females compared with White females.[30]
- Mortality declines have been attributed primarily to evidence-based approaches to treat HF risk factors and the implementation of treatment with ACE inhibitors, β-blockers, coronary revascularization, implantable cardioverter-defibrillators, and cardiac resynchronization therapies.[88] 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 guidelines.[89]
- 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 (unpublished NHLBI tabulation).[90]
- Hospitalizations of children with advanced HF in congenital HD have increased, but overall hospital mortality has improved.[91]
- In 2018, HF was the underlying cause in 83 616 deaths (38 487 males and 45 129 females; Table 21-2). Table 21-2 shows the numbers of these deaths coded for HF as the underlying cause.
- The number of underlying causes of deaths attributable to HF was 47.1% higher in 2018 (83 616) than it was in 2008 (56 830; unpublished NHLBI tabulation using NVSS[90]).
- In 2018, the overall any-mention age-adjusted death rate for HF was 91.4 per 100 000, with variation across racial/ethnic groups. In males, the rates were 113.5 for NH White males, 120.9 for NH Black males, 49.6 for NH Asian or Pacific Islander males, 98.1 for NH American Indian or Alaska Native males, and 71.5 for Hispanic males. In females, the respective rates were 81.9 for NH White females, 87.3 for NH Black females, 35.8 for NH Asian or Pacific Islander females, 72.8 for NH American Indian or Alaska Native females, and 49.5 for Hispanic females (unpublished NHLBI tabulation using CDC WONDER[92]).
- Residents of rural communities in the West (OR, 1.47), Midwest (OR, 1.30), and South (OR, 1.21) have higher mortality risk during HF hospitalizations compared with residents of large metropolitan areas.[93]

Health Care Use: Hospital Discharges/Ambulatory Care Visits (See Table 21-2 and Chart 21-4)

- Data from the 2005 to 2014 ARIC Community Surveillance study indicate that HF hospitalization rates are increasing over time, apparently driven by HFpEF. Events included 50% HFrEF and 39% HFpEF, with the remaining attributable to intermediate or recovered EF. HFrEF was more common in Black males and White males, and HFpEF was most common in White females. Age-adjusted rates of HF hospitalization were highest in Black individuals (38 per 1000 Black males, 31 per 1000 Black females).[94]
- In the BIOSTAT-CHF Study, inpatients with symptomatic HF have higher rates of death or HF hospitalization than outpatients with symptomatic HF (33.4 versus. 18.5 per 100 person-years).[95]
- Hospital discharges for HF (including discharged alive, dead, and status unknown) are shown for the United States (1997–2016) by sex in Chart 21-4. Discharges for HF decreased from 2006 to 2016, with principal diagnosis discharges of 1 020 000 and 809 000, respectively (Table 21-2).
- In 2016, there were 1 932 000 physician office visits with a primary diagnosis of HF (NAMCS,[96] unpublished NHLBI tabulation). In 2016, there were 414 000 ED visits for HF (NHAMCS,[97] unpublished NHLBI tabulation).
- Data from the ARIC Community Surveillance study have shown[98]:
  - The average incidence of hospitalized HF for those ≥55 years of age was 11.6 per 1000 people per year; recurrent HF hospitalization incidence 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 HFrEF and 47% had HFpEF. Black males had the highest proportion of hospitalized HFrEF (70%); White females had the highest proportion of hospitalized HFpEF (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.
- Among 1077 patients with HF in Olmsted County, Minnesota, hospitalizations were common after HF diagnosis, with 83% of patients hospitalized at least once and 43% hospitalized at least 4 times. More than one-half of all hospitalizations were related to noncardiovascular causes.[99]
- Among Medicare beneficiaries, the overall HF hospitalization rate declined substantially from 1998 to 2008 but at a lower rate for Black males,[86] and the temporal trend findings were uneven across states.
- In the GWTG-HF Registry, only 1/10th of eligible patients with HF received cardiac rehabilitation referral at discharge after hospitalization for HF.[100]
- Among Medicare Part D coverage beneficiaries, HF medication adherence (ACE inhibitors/angiotensin receptor blockers, 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.[101]
- Rates of HF rehospitalization or cardiovascular death were greatest for those previously hospitalized for HF regardless of subtype, including both HFpEF and HFrEF.[102]

- Hispanic patients hospitalized with HF were significantly younger than NH White patients but with higher prevalence of diabetes, hypertension, and overweight/obesity. Hispanic patients with HFpEF (but not HFrEF) also had an adjusted 45% lower in-hospital mortality risk.[103] Data from the Health and Retirement Study from 1998 to 2014 show racial/ethnic differences in hospitalization trajectories over 24 months after HF diagnosis.[104] 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 White individuals, Black individuals had significantly more hospitalizations throughout the follow-up period.
- Data from Olmsted County, Minnesota, indicate among those with HF, hospitalizations were particularly common among males and did not differ by HFrEF versus HFpEF, 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.[31]

Cost

The overall cost of HF continues to rise. See Chapter 27 (Economic Cost of Cardiovascular Disease) for further statistics.

- In 2012, total cost for HF was estimated to be $30.7 billion (2010 dollars), of which more than two-thirds was attributable to direct medical costs.[28] 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.[28]
- Implantable cardioverter-defibrillators could be cost-effective in the guideline-recommended groups of individuals with HFrEF; however, the benefit might not be as great in those with high overall mortality risk (eg, ≥75 years of age, New York Heart Association functional class III, LVEF ≤20%, BNP ≥700 pg/mL, SBP ≤120 mm Hg, AF, diabetes, chronic lung disease, and CKD).[105,106]
- 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 health care costs.[107]

Open Heart Transplantation and Mechanical Circulatory Support Device Placement in the United States (See Chart 21-5)

- According to United Network for Organ Sharing data from 1988 to 2019, a total of 75 904 heart transplantations were performed, with the annual number of transplantations approximately doubling over this period from 1676 to 3552.[108] Of the 3552 recipients in 2019:
  - The primary diagnosis was cardiomyopathy (57.7%), CAD (23.5%), congenital HD (10.8%), and retransplantation (3.0%).
  - A ventricular assist device was present in 35.1% at the time of transplantation.
  - See Chapter 26, Medical Procedures, for additional heart transplantation data.
- From September 1987 to December 2012, 40 253 people were waiting for heart transplantations, with a median survival of 2.3 years; 26 943 received transplantations, with median survival of 9.5 years. Life-years saved were 465 296; life-years saved per patient were 5.0.[109]
- SCD after heart transplantation is estimated to occur at a rate of 1.3%/y (95% CI, 1.08%/y–1.52%/y) according to a meta-analysis of 47 901 patients. Risk factors included cardiac allograft vasculopathy, lower LVEF, rejection, infection, cancer, and non-White race.[110]
- In the NIS data, outcomes after HF admission are similar in patients with history of heart transplantation compared with those without prior transplantations.[111]
- INTERMACS reported 25 145 mechanical circulatory support device implantations from June 2006 to December 2017, of which >20 000 were primary left mechanical circulatory support devices, including total artificial hearts (339), pulsatile-flow LVADs (923), and continuous-flow LVADs (19 206), including axial and centrifugal pumps. This includes both isolated LVAD and combined LVADs and RV assist devices. As of 2017, 51% of the LVADs were centrifugal and 49% were axial-flow devices.[112]
- In the ROADMAP study, among 195 patients with advanced ambulatory non–inotrope-dependent HF, only those with higher severity of HF (defined as INTERMACS profile 4) benefited from LVAD implantation compared with optimal medical management, despite increased complications. In individuals with INTERMACS profiles 5 through 7, no benefit of LVADs was noted.[113]
- After continuous-flow LVAD placement, 1- and 5-year survival rates were 83% and 46%, respectively. Among patients requiring biventricular assist devices, 1- and 5-year survival rates were 58% and 28%, respectively.[112]
- The proportion of LVADs implanted as destination therapy increased from 2% in 2008 to 49% in 2017 for continuous-flow LVADs, with an overall decline in those in whom the LVAD was implanted as a bridge to decision or transplantation over this time period (Chart 21-5).[112] However, a substantial

difference in indications exists across device type, with 73% of axial-flow pump–type LVADs being used as destination therapy in 2017 versus only 27% of centrifugal-flow LVADs.

- The 1-year survival of individuals with an LVAD implanted as a bridge to transplantation was 88%; for those with a bridge-to-decision implantation, survival was 85%; and for those with an LVAD as destination therapy, survival was 80%.[112]
- From 2006 to April 2017, 450 individuals in INTERMACS underwent a total artificial heart implantation. Among those, 266 underwent transplantation and 162 died on support. The 1- and 2-year survival rates were 53.2% and 33.9%, with most deaths occurring because of multiorgan failure. Accounting for competing risks, at 12 months, 53% of the patients had undergone transplantation, 34% had died, and 13% were alive with the device.[114]
- On the basis of NIS data from 2009 to 2014, outcomes after ventricular assist device implantation did not differ across US geographic areas despite differences in cost and length of stay.[115]
- Among Medicare beneficiaries, in-hospital mortality with LVAD implantation decreased from 29.7% in 2006 to 10.1% in 2011. Average hospital length of stay markedly decreased from the pulsatile LVAD (before 2008) to the continuous-flow LVAD (2008–2011) eras.[116] The mean cost of LVAD-related hospitalization increased from $194 380 in 2005 to $234 808 in 2011.
- In a comparable cost-effectiveness analysis in the French health care system, LVAD implantations were associated with improved survival at a high cost, exceeding €100 000 per QALY.[117]
- 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).[118]
- In a Markov model analysis, LVADs in patients with non–inotrope-dependent HF improved quality of life, at a substantial increase in costs, mostly attributable to frequent readmissions and cost of follow-up care. The gain in quality of life was from 2.67 to 4.41 QALYs. However, the incremental cost-effectiveness ratio was $209 400 per QALY gained and $597 400 per life-year gained. Moreover, those results were sensitive to readmission rates and outpatient care costs.[119]
- 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. In a retrospective study with continuous-flow LVAD, 44% of patients were readmitted within 30 days of discharge, with a median cost of $7546. Common causes of readmission were gastrointestinal bleeding, infection, and stroke, with device malfunction and arrhythmias being the costliest.[120]
- In a study that used the United Network for Organ Sharing registry between 2006 and 2015 and addressed insurance status, among those with bridge-to-transplantation LVADs, Medicaid insurance was associated with worse survival of patients on the heart transplantation waiting list compared with patients with private insurance, although access to transplantation was not different.[121]
- Among Medicare beneficiaries undergoing LVAD implantation, the outcomes vary widely according to the presence of ESRD. During a median follow-up of 762 days, 81.9% of individuals with ESRD died, whereas only 36% of those without ESRD died. Even after adjustment for confounding, the OR for mortality was 36.3 (95% CI, 15.6–84.5) for the presence of ESRD.[122]

LVAD and Open Heart Transplantation Disparities

- Data from the International Society for Heart and Lung Transplantation Transplant Registry indicate that of all open heart transplant recipients, those previously with versus without LVAD had worse early (but not late) survival and more early complications; however, outcomes were not substantially affected by high- versus low-risk donor status.[123]
- According to INTERMACS data from 2017 to 2019, for patients receiving contemporary centrifugal LVADs, the risk of death appeared to be higher in males (HR, 1.63; P=0.01).[124]
- In a study of 111 patients with ventricular assist devices, SES was not associated with adverse prognosis or complications after implantation.[125]
- In the United Network for Organ Sharing database of 18 085 patients who had open heart transplantation performed at 102 centers, Black patients 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).[126] Compared with White and Hispanic patients, a higher proportion of Black patients were treated at centers with higher-than-expected mortality, which persisted after adjustment for insurance type and education level.

Global Burden of HF

- In 2019, age-standardized HF prevalence was lowest in South Asia (406.15 in males and 374.85 in

females per 100 000).[26] HF contributed to age-standardized disability-years lived in males to the greatest degree in high-income North America, eastern Sub-Saharan Africa, East Asia, and Southeast Asia.

- HF risk factors vary substantially across geographies, with hypertension being highly associated across all regions and most commonly in Latin America, the Caribbean, Eastern Europe, and sub-Saharan Africa, with a minimal association of IHD with HF in sub-Saharan Africa.[127] IHD prevalence in HF is highest in Europe and North America and rare in sub-Saharan Africa, whereas hypertension prevalence in HF is highest in Eastern Europe and sub-Saharan Africa; valvular and rheumatic HD prevalence in patients with HF is highest in East Asia and Asia-Pacific countries.[127] 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 on the global burden of HF.[128] HF is common throughout sub-Saharan Africa. According to a meta-analysis, the most common pathogenesis is hypertensive HD in 39.2%, followed by cardiomyopathies in 21.4% and rheumatic HD in 14.1%, whereas IHD was reported in only 7.2% of cases, amid substantial variability by region.[129]
- 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 trends toward an ischemic cause for HF have been observed in Asia, including China and Japan.[130]
- Age-standardized HF prevalence in 2019 was highest (>800 per 100 000) in high-income North America, East Asia, Oceania, and eastern sub-Saharan Africa. In particular, HF prevalence in 2019 was highest in high-income North America (993.84 [95% CI, 866.22–1140.37] per 100 000 in females; 1344.62 [95% CI, 1159.53–1556.54] per 100 000 in males) and East Asia (1001.01 [95% CI, 819.06–1245.62] per 100 000 in females; 991.23 [95% CI, 808.02–1228.71] per 100 000 in males), followed by Oceania and eastern Sub-Saharan Africa.[26]

Table 21-1. Global Prevalence and Mortality of Cardiomyopathy and Myocarditis, 2019

	Both sexes combined		Males		Females	
	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)
Total number (millions)	0.3 (0.3 to 0.4)	4.1 (3.2 to 5.2)	0.2 (0.2 to 0.2)	2.3 (1.8 to 2.9)	0.1 (0.1 to 0.2)	1.8 (1.4 to 2.3)
Percent change in total number 1990 to 2019	42.8 (28.5 to 53.5)	75.4 (65.0 to 86.3)	55.6 (26.9 to 70.7)	79.1 (68.8 to 90.4)	27.9 (14.7 to 44.5)	70.7 (59.7 to 82.9)
Percent change in total number 2010 to 2019	3.3 (–2.3 to 10.5)	19.7 (16.4 to 22.7)	1.9 (–5.4 to 12.1)	20.0 (16.3 to 23.4)	5.4 (–1.0 to 14.1)	19.4 (15.4 to 23.4)
Rate per 100 000, age standardized	4.4 (3.7 to 4.8)	51.5 (40.1 to 65.8)	5.6 (4.5 to 6.3)	65.0 (51.0 to 81.7)	3.3 (2.7 to 3.6)	40.2 (30.9 to 52.3)
Percent change in rate, age standardized 1990 to 2019	–35.9 (–40.4 to –31.7)	–20.8 (–24.6 to –16.6)	–29.3 (–37.0 to –21.1)	–19.9 (–23.7 to –15.7)	–43.6 (–49.2 to –35.4)	–23.0 (–27.5 to –18.4)
Percent change in rate, age standardized 2010 to 2019	–18.8 (–23.0 to –13.4)	–9.1 (–11.4 to –6.7)	–18.0 (–23.4 to –10.5)	–9.0 (–11.4 to –6.7)	–19.4 (–24.3 to –12.4)	–9.4 (–12.1 to –6.4)

UI indicates uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[26] Printed with permission. Copyright © 2020, University of Washington.

Table 21-2. HF in the United States

Population group	Prevalence, 2015–2018, age ≥20 y	Incidence, 2014, age ≥55 y	Mortality, 2018, all ages*	Hospital discharges, 2016, all ages	Cost, 2012†
Both sexes	6 000 000 (2.1%) [95% CI, 1.8%–2.4%]	1 000 000	83 616	809 000	$30.7 billion
Males	3 400 000 (2.5%)	495 000	38 487 (46.0%)‡	415 000	…
Females	2 600 000 (1.7%)	505 000	45 129 (54.0%)‡	394 000	…
NH White males	2.4%	430 000§	31 246	…	…
NH White females	1.4%	425 000§	37 112	…	…
NH Black males	3.6%	65 000§	4354	…	…
NH Black females	3.3%	80 000§	4961	…	…
Hispanic males	2.4%	…	1950	…	…
Hispanic females	1.7%	…	2035	…	…
NH Asian males	1.9%	…	718‖	…	…
NH Asian females	0.7%	…	793‖	…	…
NH American Indian or Alaska Native	…	…	300	…	…

HF includes people who answered "yes" to the question of ever having congestive heart failure. Confidence intervals have been added for overall prevalence estimates in key chapters. Confidence intervals have not been included in this table for all subcategories of prevalence for ease of reading.

Ellipses (…) indicate data not available; HF, heart failure; 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.[28]

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

§Estimates for White people include other non-Black races.

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

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey 2015 to 2018.[27] 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: Unpublished NHLBI tabulation using Atherosclerosis Risk in Communities study Community Surveillance, 2005 to 2014.[131] Mortality: Unpublished NHLBI tabulation using National Vital Statistics System, 2018.[90] Mortality for NH Asian people includes Pacific Islander people. Hospital discharges: Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2016 (data include those inpatients discharged alive, dead, or status unknown).[1]

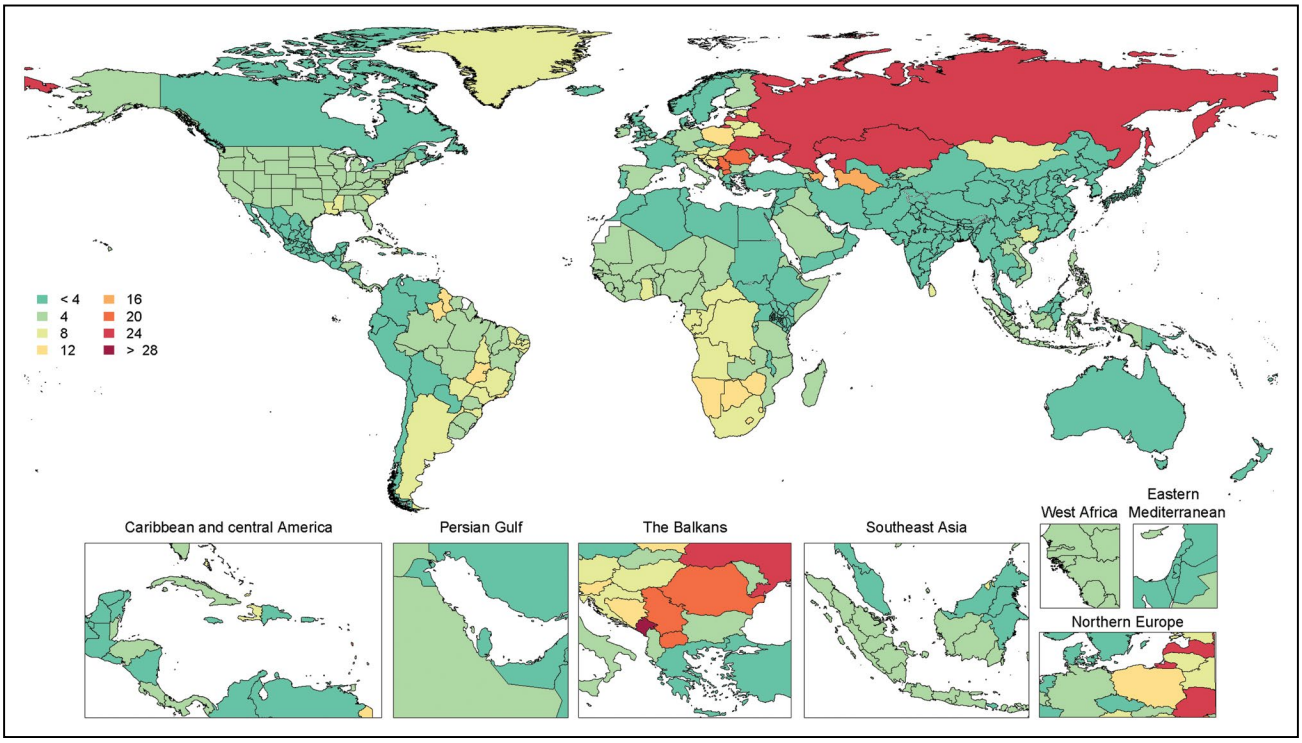

Chart 21-1. Age-standardized global mortality rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[26] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease website.[132]

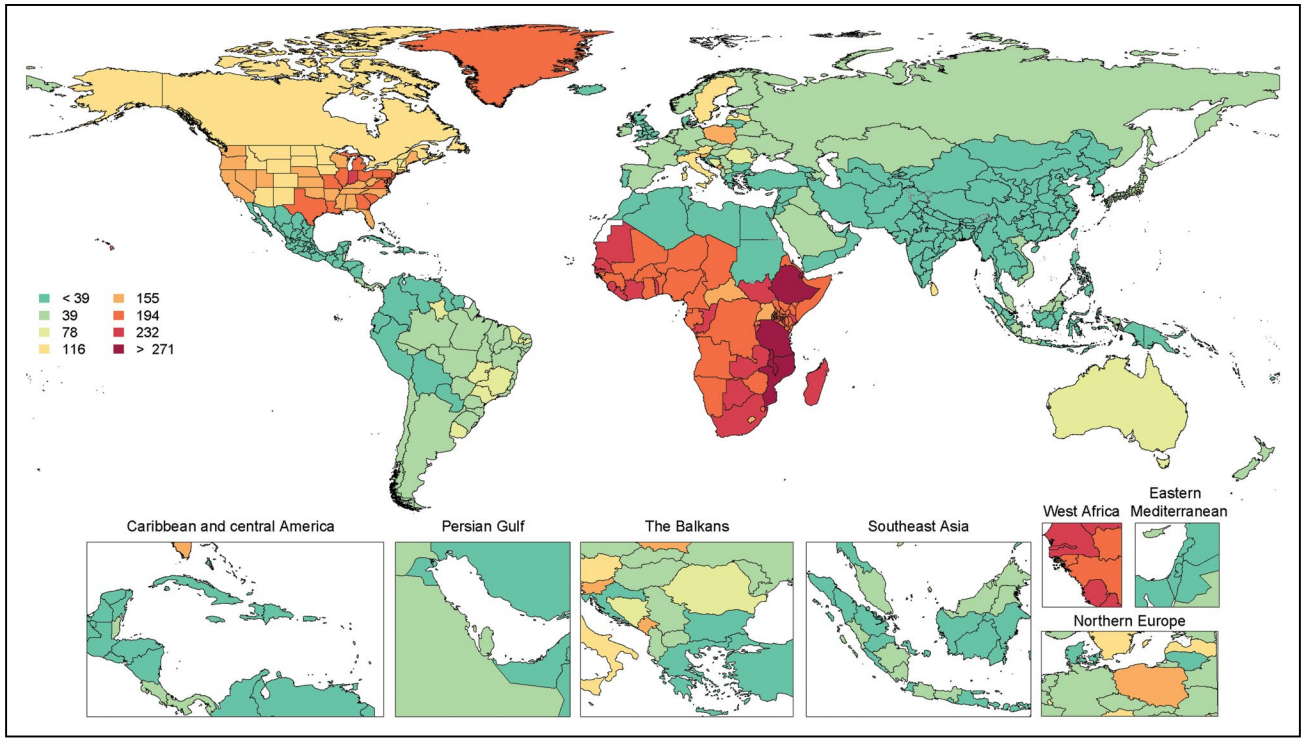

Chart 21-2. Age-standardized global prevalence rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[26] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease website.[132]

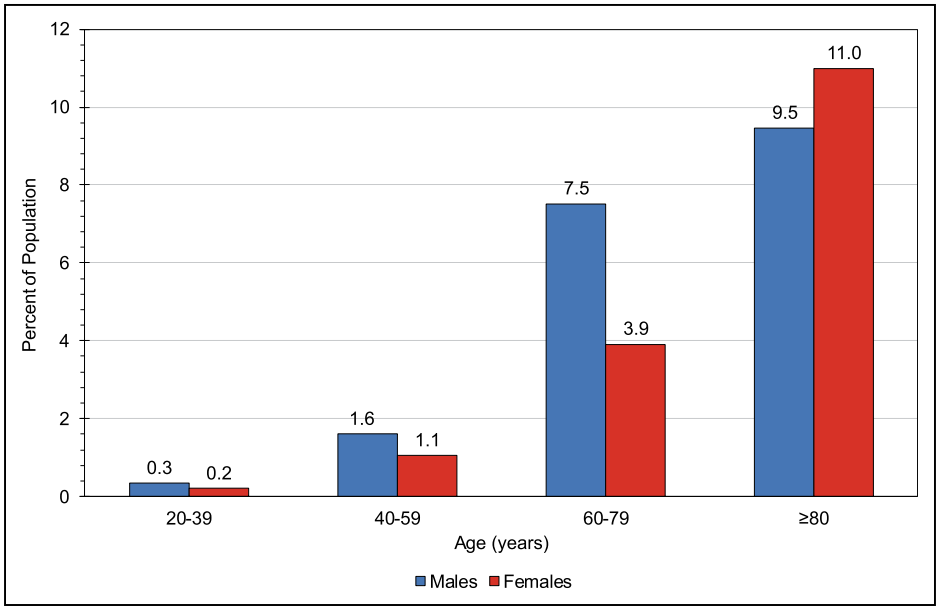

Chart 21-3. Prevalence of heart failure among US adults ≥20 years of age by sex and age (NHANES, 2015–2018).
NHANES indicates National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2015 to 2018.[27]

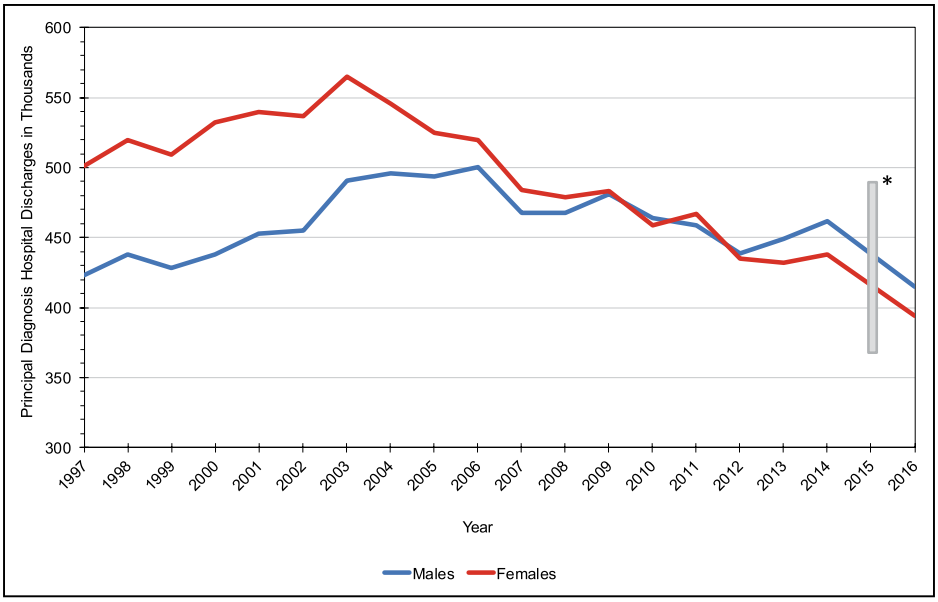

Chart 21-4. Hospital discharges for heart failure by sex, United States, 1997 to 2016.
Hospital discharges include people discharged alive, dead, and status unknown.
*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project, 1997 to 2016.[1]

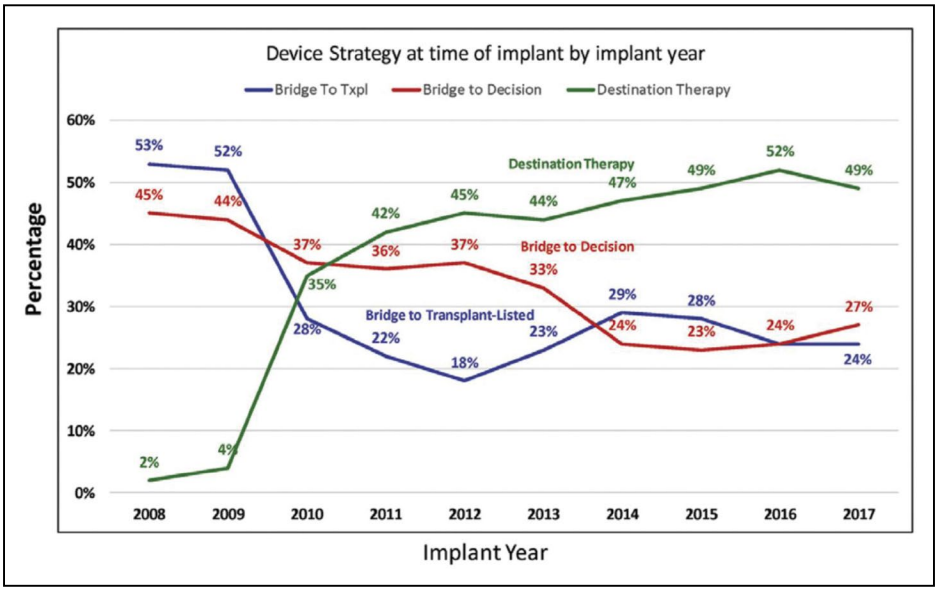

Chart 21-5. Device strategy at the time of implantation by year, United States, 2008 to 2017.
Implantations are continuous-flow left ventricular assist devices, April 2008 to December 2017 (N=18359).
Txpl indicates transplantation.
Source: Reprinted from Kormos et al[112] with permission from The Society of Thoracic Surgeons. Copyright © 2019, The Society of Thoracic Surgeons. Published by Elsevier Inc. on behalf of the International Society for Heart and Lung Transplantation.

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22. VALVULAR DISEASES

See Tables 22-1 through 22-4 and Charts 22-1 through 22-6

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Mortality and any-mention mortality in this section are for 2018 and based on unpublished NHLBI tabulations using the NVSS and CDC WONDER.[1,2] Mortality is the number of deaths in 2018 for the given underlying cause based on *ICD-10*. Prevalence data are for 2016 and 2017. Hospital discharge data are from HCUP[3] (2016); data included are for inpatients discharged alive, dead, or status unknown. Hospital discharge data for 2016 are based on *ICD-10* codes.

Abbreviations Used in Chapter 22

ACC	American College of Cardiology
AF	atrial fibrillation
AGES	Age, Gene/Environment Susceptibility
AHA	American Heart Association
aHR	adjusted hazard ratio
aOR	adjusted odds ratio
APAC	Asia-Pacific
BMI	body mass index
CABG	coronary artery bypass graft
CALA	Caribbean and Latin America
CANHEART	Cardiovascular Health in Ambulatory Care Research Team
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research
CI	confidence interval
COAPT	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation
DALY	disability-adjusted life-year
DCM	dilated cardiomyopathy
EF	ejection fraction
EVEREST	Endovascular Valve Edge-to-Edge Repair
EVEREST II HRS	Endovascular Valve Edge-to-Edge Repair High-Risk Study
FDA	US Food and Drug Administration
FHS	Framingham Heart Study

(*Continued*)

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Abbreviations Used in Chapter 22 Continued

GBD	Global Burden of Disease Study
GRS	genetic risk score
GWAS	genome-wide association study
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HF	heart failure
HIV	human immunodeficiency virus
HR	hazard ratio
ICER	incremental cost-effectiveness 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
iSAVR	isolated surgical aortic valve replacement
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
LV	left ventricular
LVEF	left ventricular ejection fraction
MIDA	Mitral Regurgitation International Database
MITRA-FR	Percutaneous Repair With the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation
MR	mitral regurgitation
NH	non-Hispanic
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NOTION	Nordic Aortic Valve Intervention
NVSS	National Vital Statistics System
OR	odds ratio
PAR	population attributable risk
PARTNER	Placement of Aortic Transcatheter Valve
QALY	quality-adjusted life-year
RCT	randomized controlled trial
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
TAVI	transcatheter aortic valve implantation
TAVR	transcatheter aortic valve replacement
TIA	transient ischemic attack
TOF	tetralogy of Fallot
TV	transvascular
TVT	Transcatheter Valve Therapy
UI	uncertainty interval

Valvular HD

ICD-9 424; *ICD-10* I34 to I38.

2018: Mortality—24 337. Any-mention mortality—52 995.

2016: Hospital discharges—120 000.

Prevalence

- Previously undiagnosed, predominantly mild valvular HD was found in 51% of 2500 individuals ≥65 years of age from a primary care population screened with transthoracic echocardiography. The prevalence of undiagnosed moderate or severe valvular HD was 6.4%.[4] In a population-based study of 1818 Hispanic/Latino people (mean age, 55 years; 57% female), the prevalence of any valvular HD was 3.1%. The prevalence of regurgitant or stenotic valvular HD of moderate or greater severity was 2.6%.[5]

Incidence

- In a report using a 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 ≥65 years of age). 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.[6]

Aortic Valve Disorders

ICD-9 424.1; *ICD-10* I35.

2018: Mortality—16 322. Any-mention mortality 35 105.

2016: Hospital discharges—91 000.

Prevalence

- Prevalence of aortic stenosis by echocardiography was 4.3% among individuals ≥70 years of age in the Icelandic AGES-Reykjavik cohort.[7]
- 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%).[8]

Incidence

- Nationally representative data from Sweden demonstrate an 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.[9]
- 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.[10]
- In the Canadian CANHEART aortic stenosis study, absolute incidence of severe aortic stenosis among individuals >65 years of age was 144 per 100 000 person-years (169 and 127 per 100 000 person-years in males and females, respectively).[11]

Lifetime Risk and Cumulative Incidence

- The number of elderly patients with calcific aortic stenosis is projected to more than double by 2050 in both the United States and Europe according to 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 who are ≥70 years of age by 2040 and a tripling by 2060.[7]

Risk Factors

- In the Canadian CANHEART study, among 1.12 million individuals >65 years of age followed up for a median of 13 years, 20 995 subjects developed severe aortic stenosis. Hypertension (aHR, 1.71 [95% CI, 1.66–1.76]), diabetes (HR, 1.49 [95% CI, 1.44–1.54]), and dyslipidemia (HR, 1.17 [95% CI, 1.14–1.21]) were the strongest predictors of development of severe aortic stenosis (all $P<0.001$).[11]
- In the Copenhagen General Population Study, among 108 275 individuals, the risk of aortic stenosis was particularly high if BMI was >40 kg/m^2 (HR, 4.6 [95% CI, 2.3–9.3]).[12]
- 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]; $P<0.005$).[13]

Genetics and Family History

- 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.[14] However, heritability of aortic dilatation in first-degree relatives of probands with bicuspid aortic valve did not reach statistical significance ($P=0.06$) in a separate study.[15] Bicuspid aortic valve has been linked to mutations of *NOTCH1, GATA5*, and more recently *GATA4*.[16–18]
- 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) for being diagnosed with aortic stenosis. These

findings indicate an overall familial aggregation of this disease beyond bicuspid aortic valve alone.[19]

- A GWAS in 6942 individuals identified an SNP located in an intron of the Lp(a) gene that was significantly associated with the presence of aortic calcification (OR per allele, 2.05), circulating Lp(a) levels, and the development of aortic stenosis.[20]
- A GWAS meta-analysis of 5115 cases and 354 072 controls identified *IL6*, *ALPL*, and *NAV1* as susceptibility genes for calcific aortic valve stenosis,[21] adding to knowledge from previous GWASs and transcriptome studies of aortic valve stenosis that have established several loci, including *LPA*, *PALMD*, and *TEX41*.[20,22–24]
- Multiple SNPs that encode for LDL-C have been combined to form a GRS that has been associated with prevalent aortic valve calcification (OR, 1.38 [95% CI, 1.09–1.74] per GRS increment) and incident aortic valve stenosis (HR, 2.78 [95% CI, 1.22–6.37] per GRS increment) by use of a mendelian randomization design.[25]

Awareness, Treatment, and Control (See Chart 22-1)

- After the US FDA approved TAVR for patients with severe aortic stenosis at high surgical risk in 2011, implantation numbers increased steeply. From 2011 through 2014, the STS/ACC TVT Registry recorded 26 414 TAVR procedures performed at 348 centers in 48 US states.[26] Sixty-eight percent of patients were ≥80 years of age; 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 report from the same registry.[27]
- Despite the increase in TAVR procedures, the percentage of Black patients undergoing TAVR was 3.8% compared with 93% among White patients in the STS/ACC TVT Registry.[26,28]
- 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.[27]
- In Germany, >15 000 TAVR procedures were performed in 2016, a number 3 times higher than in 2011 according to data from the German Institute for Quality Assurance and Transparency in Healthcare. Over the same period (2011–2016), the number of SAVR procedures remained relatively stable at ≈10 000 per year, a lower number than for TAVR (Chart 22-1). In the same European registry, mortality decreased continuously, with overall in-hospital mortality being similar for TAVR and SAVR (2.6% versus 2.9%; $P=0.19$, respectively) in 2016 despite the higher risk profile in patients undergoing TAVR (Chart 22-1).
- On the basis of a retrospective study of 8210 patients using the NIS (2012–2014), females with severe aortic stenosis undergoing TAVR experienced similar mortality (4.7% versus 3.9%; $P=0.15$) as males; however, females had higher rates of stroke (3% versus 2%; $P=0.04$), hemorrhage requiring transfusion (28% versus 20%; $P<0.0001$), and pericardial complications (1.3% versus 0.5%; $P=0.0009$).[29]
- Two RCTs (PARTNER 1A and US CoreValve High Risk) using balloon-expandable and self-expanding devices, respectively, have shown that TAVR is able to compete with SAVR in terms of mortality in high-risk patients at 1 and 5 years. In the US CoreValve High Risk trial, death resulting from any cause at 1 year was significantly lower in the TAVR than in the SAVR group (14.2% versus 19.1%), with an absolute reduction in risk of 4.9 percentage points (upper boundary of the 95% CI, –0.4; $P<0.001$ for noninferiority; $P=0.04$ for superiority).[30] In the PARTNER 1A trial, risk of death at 5 years was 67.8% in the TAVR group compared with 62.4% in the SAVR group (HR, 1.04 [95% CI, 0.86–1.24]; $P=0.76$).[31]
- 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 (using a self-expanding device) 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 using a balloon-expandable device, the Kaplan-Meier event rates of the same end point were 19.3% in the TAVR group and 21.1% in the SAVR group (HR in the TAVR group, 0.89 [95% CI, 0.73–1.09]; $P=0.25$) at the 2-year follow-up. At 5 years, the incidence of death resulting from any cause or disabling stroke in the PARTNER 2 trial was 47.9% and 43.4% in the TAVR (transfemoral access) and SAVR group, respectively (HR, 1.09 [95% CI, 0.95–1.25]; $P=0.21$).[32] Overall, these findings demonstrate that TAVR is a noninferior alternative to SAVR in patients with severe aortic stenosis at intermediate surgical risk.[33,34]
- In 1000 patients with severe aortic stenosis at low surgical risk randomized in the PARTNER 3 trial[35] to either balloon-expandable TAVR or SAVR, the

Kaplan-Meier estimate of the rate of the primary composite end point (death, stroke, or rehospitalization) was significantly lower in the TAVR group than in the SAVR group (8.5% versus 15.1%; absolute difference, −6.6 percentage points [95% CI, −10.8 to −2.5]; *P*<0.001 for noninferiority; HR, 0.54 [95% CI, 0.37–0.79]; *P*=0.001 for superiority). Similar results were obtained in the Evolut Low Risk trial[36] using a self-expanding valve in low-risk patients with severe aortic stenosis. Among the 1403 patients randomized to either TAVR or SAVR, the 24-month incidence of composite death or disabling stroke was 5.3% in the TAVR group and 6.7% in the SAVR group (difference, −1.4 percentage points [95% bayesian credible interval for difference, −4.9 to 2.1]; posterior probability of noninferiority >0.999). Noninferiority of TAVR versus SAVR in low-surgical-risk patients with severe aortic stenosis was confirmed at the 5-year follow-up in the European NOTION study.[37]

- Although TAVR and SAVR are comparable in terms of mortality and disabling stroke in patients with severe aortic stenosis at low and intermediate risk, a meta-analysis of RCTs and propensity score–matching observational studies demonstrated a higher proportion of aortic valve reintervention in TAVR (RR 3.16 [95% CI, 1.61–6.19]; heterogeneity *P*=0.60, I^2=0% at 2 years).[38]
- Among 96256 transfemoral TAVR procedures, adjusted 30-day mortality was higher at institutions with low procedural volume (3.19% [95% CI, 2.78%–3.67%]) than at institutions with high procedural volume (2.66% [95% CI, 2.48%–2.85%]; OR, 1.21; *P*=0.02).[39]

Mortality

- On the basis of *ICD-10* (with data coded from 1999–2009), there were 146304 deaths over 10 years 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 age- and sex-adjusted mortality rate increased over time by 1.56% (95% CI, 1.52%–1.61%; *P*<0.001) per year for nonrheumatic aortic valve disease.[40]
- In 145 asymptomatic patients with very severe aortic stenosis, the cumulative incidence of a combined outcome of 30-day operative mortality or cardiovascular death was significantly lower in patients undergoing early surgery versus watchful waiting (1% at both 4 and 8 years versus 6% at 4 years and 26% at 8 years; *P*=0.003).[41]
- In the community, morbidity related to bicuspid aortic valve is higher in males than in females, with a total combined risk of aortic regurgitation, surgery, and IE of 52±4% in males versus 35±6% in females (*P*=0.01).[42] Nevertheless, females have 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).[42] The risk of death is independently associated with aortic regurgitation (*P*≤0.04).

Complications

- In a cohort of 416 community-based participants from Olmsted County, Minnesota, with bicuspid aortic valve followed up for a mean of 16 (SD, 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 10000 patient-years. For patients ≥50 years of age 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 10000 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 10000 patient-years, for an age-adjusted RR of 86.2 (95% CI, 65.1–114) compared with the general population.[43]

Cost

- Initial length of stay was an average of 4.4 days shorter for patients at high surgical risk who were treated with TAVR than for those who underwent SAVR. 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 $11260 and $17849 per patient, respectively). However, TAVR was estimated to provide a lifetime gain of 0.32 QALYs (0.41) with 3% discounting. Lifetime ICERs were $55090 per QALY gained and $43114 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 ICER of <$50000 per QALY gained.[44]
- In a European study of patients at intermediate surgical risk with severe aortic stenosis, TAVR was associated with an increase of 0.42 years and 0.41 QALYs and lifetime cost savings of €439 compared with SAVR.[45]
- In patients undergoing TAVR at low surgical risk in the Danish health care system, the ICERs (range, 334200–904100 Danish kroner per QALY gained) were all below the country-specific willingness to pay of 1.13 million Danish kroner.[46]

Global Burden (See Table 22-1)

- The global burden of calcific aortic valve disease is shown in Table 22-1.

Mitral Valve Disorders

ICD-9 424.0; *ICD-10* I34.

2018: Mortality—2692. Any-mention mortality—6345.
2016: Hospital discharges—26 000.

Prevalence

- A systematic review by de Marchena et al[47] 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 (MR associated with mitral valve prolapse): 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
- Primary MR includes Carpentier types I, II, and IIIa, with the most common cause being mitral valve prolapse (type II MR). Secondary MR is associated with ischemic cardiomyopathy, LV dysfunction, or DCM (type IIIb MR).

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 a 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.[48–50]

Genetics and Family History

- Among 3679 Third Generation participants in the FHS (53% female; mean age, 40±9 years) with available parental data, 49 (1%) had mitral valve prolapse.[51] Parental mitral valve prolapse was associated with a higher prevalence of mitral valve prolapse in offspring (10 of 186 [5.4%]) compared with no parental mitral valve prolapse (39 of 3493 [1.1%]; aOR, 4.51 [95% CI, 2.13–9.54]; *P*<0.0001). 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 *GLIS1*, *FLNA*, *DCHS1*, *DZIP1*, *TNS1*, and *LMCD1*.[52–56]
- Familial clustering exists across different MR subtypes, including both primary (ie, related to mitral valve prolapse) and nonprimary MR. Heritability of MR in the FHS was estimated at 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).[57] In Sweden, sibling MR was associated with an HR of 3.57 (95% CI, 2.21–5.76; *P*<0.001) for the development of MR.

Awareness, Treatment, and Control (See Charts 22-2 and 22-3)

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 deemed not to be 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.[58] 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. Most of the patients undergoing transcatheter mitral valve repair (90.8%) had degenerative disease, and the procedure was successful in reducing MR to moderate levels in 93% of cases.
- In the EVEREST II trial, which included mostly patients with primary MR (73%) and compared MitraClip with surgical mitral valve repair, the respective rates of the components of the primary end point at 12 months were as follows: death, 6% in each group; surgery for mitral valve dysfunction, 20% versus 2%; and grade 3+ or 4+ MR, 21% versus 20%.[59]
- 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 22-2).
- The role of MitraClip in secondary MR has been investigated in 2 published randomized clinical trials with divergent results (Chart 22-3).[60–62] MITRA-FR included 304 patients with HF, severe secondary MR, and LVEF of 15% to 40% on optimal medical therapy and cardiac resynchronization therapy as indicated. There was no difference in the combined end point of death or rehospitalization for HF at 12 months (83 of 152 patients or 54.6% versus 78 of 152 or 51.3% for interventional and conservative management, respectively). The COAPT trial included 614 patients with HF and moderate-severe or severe secondary MR who were symptomatic (New York Heart Association functional class II–IV) despite optimal medical therapy and cardiac resynchronization therapy. With MitraClip, there was a significant reduction of the primary end point of rehospitalization because of HF at 2 years (35.8%

versus 67.9%; HR, 0.53 [95% CI, 0.40–0.70]; *P*<0.001). There was also a significant reduction of all-cause mortality at 2 years (29% versus 46.1%; HR, 0.62 [95% CI, 0.46–0.82]; *P*<0.001). The divergent results of the 2 trials may be related to differences in sample characteristics, sample size, duration of follow-up, and primary end point. Further studies are needed to solve this controversy.

- Females treated with mitral valve surgery for severe MR secondary to ischemic cardiomyopathy have a higher mortality at 2 years (27.1% versus 17.4%; absolute risk increase, 9.7%; aHR, 1.86 [95% CI, 1.05–3.29]; *P*=0.03) and a trend toward higher surgical failure (57.0% versus 43.2%; absolute risk increase, 13.8%; aOR, 1.78 [95% CI, 0.98–3.23]; *P*=0.06) compared with males.[63]
- 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: 88%, 75%, and 47% versus 92%, 74%, and 39%, respectively; *P*=0.6).[64] 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, 0.38–2.12]; *P*=0.81).[65]
- Despite the poor prognosis associated with severe MR, only a small minority of affected patients meeting criteria for surgical intervention undergo mitral surgery (29% for mitral valve prolapse–related MR and 5% for secondary MR), even in the Olmsted County community with advanced and readily accessible means of diagnosis and treatment.[66]

Mortality

- Secondary MR (or Carpentier type IIIb) is associated with 47% mortality over 5 years in patients with HF and is a predictor of long-term mortality (HR, 1.61 [95% CI, 1.22–2.12]; *P*=0.001 after adjustment for clinical variables; and HR, 1.38 [95% CI, 1.03–1.84]; *P*=0.03 after adjustment for echocardiographic parameters).[67]

Complications

- In the Olmsted County, Minnesota, 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[68]; 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).[69]
- AF is a common occurrence of severe primary regurgitation and is associated with persistence of excess risk after mitral valve repair. In MIDA, 10-year postsurgical survival in sinus rhythm and in paroxysmal and persistent AF was 82±1%, 70±4%, and 57±3%, respectively (*P*<0.0001).[70]

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 for primary MR.[71] The EVEREST II HRS provided data on treatment-specific overall survival, risk of clinical events, quality of life, and resource use. 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.
- In the COAPT trial comparing MitraClip plus optimal medical therapy with optimal medical therapy alone in symptomatic patients with HF with moderate-severe or severe secondary MR, MitraClip increased life expectancy by 1.13 years and QALYs by 0.82 years at a cost of $45 648. This translated into an ICER of $40 361 per life-year and $55 600 per QALY gained.[72]

Global Burden (See Table 22-2)

- The global burden of degenerative mitral valve disease is shown in Table 22-2.

Pulmonary Valve Disorders

ICD-9 424.3; *ICD-10* I37.

2018: Mortality—12. Any-mention mortality—62.

- Pulmonic valve stenosis is a relatively common congenital defect, occurring in ≈10% of children with congenital HD.[73] Among 44 neonates with critical pulmonic stenosis who underwent balloon pulmonary valvuloplasty from 1990 to 2017, 15 (34.1%) needed reintervention. At a median follow-up of 8.2 years (IQR, 3.4–13.1 years), moderate or severe pulmonary regurgitation was seen in 22 children (half of the sample), 3 of whom required pulmonary valve repair/replacement.[74]
- In an observational registry of 82 adults with either congenital pulmonic stenosis or subpulmonic stenosis associated with TOF, percutaneous pulmonic valve implantation with a SAPIEN valve was demonstrated to be feasible and safe.[75]

- 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.[76] Transcatheter pulmonic valve implantation of either a Melody or a SAPIEN valve is an effective and relatively safe option in patients with prosthetic pulmonic valve regurgitation, including those with a pulmonary artery conduit with regurgitant prosthetic valve.[76–78] In a study using the NIS database and including 57 transcatheter pulmonic valve implantation procedures performed in 2012, vascular complications occurred in 8 (14%), but serious complications occurred in only 3 patients (1 died, 2 required surgical intervention).[79] 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.[80]
- In a meta-analysis including 4364 patients with either pulmonic stenosis or regurgitation, transcatheter pulmonic valve replacement had lower in-hospital mortality (OR, 0.18 [95% CI, 0.03–0.98)] and long-term mortality (OR,0.43 [95% CI, 0.22–0.87]) compared with surgical pulmonic valve replacement.[81] However, postprocedural IE was higher (OR, 4.56 [95% CI, 0.07–0.42]) compared with surgical replacement. The risk of reoperation was higher in the group treated with transcatheter pulmonic valve replacement, although it was not statistically significant (OR, 2.19 [95% CI, 2.03–10.26]).

Tricuspid Valve Disorders

ICD-9 424.2; *ICD-10* I36.

2018: Mortality—57. Any-mention mortality—233.

- The frequency of tricuspid regurgitation and valvular pathology was evaluated in a study of 5223 adults (predominantly males; mean age, 67 years) who underwent echocardiography at 3 Veterans Affairs medical centers.[82] 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%).[82]
- Patients with rapid development of significant tricuspid regurgitation have worse survival than patients in whom severe tricuspid regurgitation develops more slowly (log-rank *P*=0.001). Fast development of severe tricuspid regurgitation is the most powerful predictor of all-cause mortality (HR per preceding year of development, 0.92 [95% CI, 0.90–0.94]; *P*<0.001).[83]
- 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%.[84]
- Outcomes of transcatheter tricuspid valve interventions were analyzed in 317 high-risk patients with severe tricuspid regurgitation from the international Trivalve registry. Such patients were treated either with transcatheter repair at the level of the leaflets (MitraClip, PASCAL), annulus (Cardioband, TriCinch, Trialign), or coaptation (FORMA) or with transcatheter replacement (Caval Implants). Procedural success, defined as successful device implantation with moderate or less tricuspid regurgitation, was 72.8%. Thirty-day mortality was significantly lower among patients with procedural success (1.9% versus 6.9%; *P*=0.04). Actuarial survival at 1.5 years was 82.8±4% and was significantly higher among patients who had procedural success (70.3±8% versus 90.8±4%; *P*<0.0002).[85]

Rheumatic Fever/Rheumatic HD

ICD-9 390 to 398; *ICD-10* I00 to I09.

2018: Mortality—3560. Any-mention mortality—7129.
2016: 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.[86]

Subclinical Disease

- The prevalence of subclinical or latent rheumatic HD among children is estimated by echocardiography and can be classified as definite or borderline.[87] The prevalence of combined definite and borderline disease ranges between 10 and 45 per 1000 in studies from endemic countries (eg, Nepal, Brazil, and Uganda) compared with <8 per 1000 in low-risk populations.[88–91]
- The natural history of latent rheumatic HD detected by echocardiography is not clear. Emerging data suggest that up to 20% to 30% of children with definite rheumatic HD may have progression of disease, but 30% to 50% of those with borderline

rheumatic HD may return to normal over 2 to 8 years of follow-up.[92–95]

- Few echocardiographic screening studies for rheumatic HD have been conducted in adults, for whom the criteria are not well validated. In a study from Uganda, the prevalence of rheumatic HD in adults >20 years of age was 2.34% (95% CI, 1.49%–3.49%).[96]
- Latent rheumatic HD appears to be half as common among HIV-infected youth compared with the general Ugandan population (1.5% [95% CI, 0.88%–2.54%] versus 3% [95% CI, 2.7%–3.24%]), possibly related to improved access to preventive care or nearly universal trimethoprim-sulfamethoxazole prophylaxis among HIV-infected youth.[97]

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.[98]
- 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%]).[99]

Mortality (See Table 22-3)

- In the United States in 2018, mortality attributable to rheumatic fever/rheumatic HD was 3560 for all ages (2322 females and 1238 males; Table 22-3).
- 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.[100]
- In 1950, ≈15 000 Americans (adjusted for changes in *ICD* codes) died of rheumatic fever/rheumatic HD compared with ≈3500 annually in the present era (Table 22-3). Recent declines in mortality have been slowest in the South compared with other regions.[100]

Complications

- People living with rheumatic HD experience high rates of morbid complications. In the international REMEDY cohort study, 33% had HF, 22% had AF, 7% had prior stroke, and 4% had prior endocarditis at baseline.[98] 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.[101]
- 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.[102]
- The PAR of rheumatic HD for maternal mortality may approach 10% in sub-Saharan Africa.[103]

Global Burden of Rheumatic HD (See Charts 22-4 through 22-6)

- In 2019, 40.5 million people were estimated to be living with rheumatic HD around the world, with Oceania and South Asia having the highest rate of age-standardized DALYs attributable to rheumatic HD.[104]
- 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.[86]
- The REMEDY study is a prospective registry of 3343 patients with rheumatic HD from 25 hospitals in 12 African countries, India, and Yemen. The age and sex distributions of the subjects are shown in Chart 22-4. Rheumatic HD was twice as common among females, a finding consistent with prior studies across a variety of populations.[98]
- 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.[105] 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.[101]
- The GBD 2019 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 369 diseases and injuries in 204 countries and territories.[104]
  - Age-standardized mortality attributable to rheumatic HD is highest in South Asia and Oceania (Chart 22-5).
  - Rheumatic HD prevalence is generally highest in sub-Saharan Africa (Chart 22-6).

Infective Endocarditis

ICD-9 421.0; *ICD-10* I33.0.

2018: Mortality—1607. Any-mention mortality—3530.
2016: Hospital discharges—12 000.

Prevalence and Incidence (See Table 22-4)

- In 2011, there were 47 134 cases of IE and valve replacement in the United States (Table 22-4).
- Data from the NIS (2000–2011)[106] 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.[107] These findings from referral centers were corroborated by a community-based review of adults in Olmsted County, Minnesota.[108] 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[109] 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).

Secular Trends

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 5 decades (coagulase-negative *Staphylococcus* 2% to 10%, *P<0*.001), with increases in *S aureus* IE (21% to 30%; *P<0*.05) and enterococcal IE (6.8% to 10.5%; *P<0*.001) over the 2000 to 2011 decade and a corresponding decrease in streptococcal endocarditis (32% to 17%) over the same time period.[110]

Risk Factors

- The 15-year cohort risk (through 2006) of IE after diagnosis of mitral valve prolapse (between 1989 and 1998) among Olmsted County, Minnesota, 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).[111]
- Admissions for IE related to injection drug use have risen in parallel with the opioid drug crisis. IE admissions increased from 33 073 in 2008 to 39 805 in 2014. At the same time, the prevalence of documented intravenous drug use among patients admitted for IE in the NIS rose from 4.3% in 2008 to 10% in 2014. This trend was accentuated among the young (<30 years of age) and among White individuals (compared with Black individuals and those of other races).[112]
- 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 health care–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]).[113]
- 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]).[114]
- Antibiotic prophylaxis is currently not recommended for bicuspid aortic valve and mitral valve prolapse.[107] However, in a Spanish registry of 3208 consecutive patients with IE, subjects with these conditions had a higher incidence of viridans group streptococci IE than did a high-risk group with an antibiotic prophylaxis indication and patients in a low- to moderate-risk group without an antibiotic prophylaxis indication (35.2% and 39.3% versus 12.1% and 15.0%, respectively; all *P*<0.01). Subjects with bicuspid aortic valve and mitral valve prolapse had more intracardiac complications than did those at low or moderate risk (50% and 47.2% versus 30.6%; both *P*<0.01) and were similar to patients in the high-risk group.[115]

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.[116]
- In a randomized, noninferiority multicenter trial of 400 stable cases with left-sided native IE, the combined outcome of all-cause mortality, unplanned surgery, embolic events, or relapse of bacteremia was similar in those treated with continuous intravenous antibiotic drugs compared with those switched from intravenous to oral antibiotic drugs after 10 days (24 cases or 12.1% versus 18 cases or 9%; between-group difference, 3.1 percentage points [95% CI, −3.4 to 9.6]; *P*=0.40).[117]

Mortality

- According to the GBD 2019 Study, the age-standardized death rate attributable to endocarditis in 2019 was 0.87 per 100 000.[104]
- 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 of age) with and without congenital HD, respectively.[118]

Complications

- Among 162 cases of left-sided native-valve *S aureus* IE retrospectively identified in 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).[119]

Heart Valve Procedure Costs

- In 2013, for heart valve procedures[120]:
  - 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.[120]

Table 22-1. Global Prevalence and Mortality of Nonrheumatic Calcific Aortic Valve Disease, 2019

	Both sexes		Male		Female	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions)	0.13 (0.11 to 0.14)	9.40 (8.08 to 10.89)	0.05 (0.05 to 0.06)	5.03 (4.28 to 5.86)	0.07 (0.06 to 0.08)	4.38 (3.77 to 5.08)
Percent change in total number 1990 to 2019	137.96 (113.37 to 159.29)	442.65 (414.00 to 477.61)	120.97 (100.95 to 144.41)	462.02 (434.06 to 493.98)	152.44 (124.63 to 178.36)	421.99 (391.76 to 460.89)
Percent change in total number 2010 to 2019	31.02 (26.52 to 35.98)	75.75 (69.57 to 81.38)	33.43 (27.53 to 40.85)	83.48 (77.19 to 90.06)	29.28 (24.42 to 34.63)	67.64 (60.71 to 73.66)
Rate per 100 000, age-standardized	1.76 (1.45 to 1.97)	116.34 (100.39 to 134.50)	1.85 (1.58 to 2.01)	133.38 (113.79 to 154.58)	1.66 (1.32 to 1.92)	99.86 (86.10 to 115.88)
Percent change in rate, age standardized 1990 to 2019	0.37 (−8.85 to 7.99)	155.47 (141.66 to 171.70)	−0.74 (−9.20 to 9.14)	160.54 (146.70 to 176.16)	2.05 (−6.84 to 10.75)	147.89 (134.10 to 165.70)
Percent change in rate, age standardized 2010 to 2019	−5.98 (−8.96 to −2.52)	34.81 (30.15 to 39.07)	−3.04 (−7.15 to 2.83)	40.76 (35.86 to 45.73)	−7.54 (−10.83 to −3.87)	29.01 (23.82 to 33.61)

UI indicates uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[104] Printed with permission. Copyright © 2020, University of Washington.

Table 22-2. Global Prevalence and Mortality of Nonrheumatic Degenerative Mitral Valve Disease, 2019

	Both Sexes		Male		Female	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions)	0.03 (0.03 to 0.04)	24.23 (23.08 to 25.42)	0.01 (0.01 to 0.02)	9.38 (8.89 to 9.90)	0.02 (0.02 to 0.03)	14.85 (14.16 to 15.55)
Percent change in total number 1990 to 2019	53.44 (39.74 to 85.27)	70.41 (68.85 to 72.00)	66.84 (46.20 to 95.98)	78.77 (76.39 to 81.06)	46.46 (31.30 to 83.03)	65.52 (63.45 to 67.41)
Percent change in total number 2010 to 2019	23.11 (17.04 to 29.18)	23.72 (22.62 to 24.73)	27.39 (19.20 to 35.98)	24.56 (23.25 to 25.92)	20.70 (13.87 to 27.66)	23.20 (22.03 to 24.21)
Rate per 100 000, age standardized	0.45 (0.37 to 0.58)	296.06 (282.38 to 310.48)	0.39 (0.29 to 0.46)	242.69 (230.41 to 255.54)	0.49 (0.39 to 0.67)	341.30 (325.42 to 357.33)
Percent change in rate, age standardized 1990 to 2019	−32.10 (−37.73 to −14.85)	−16.99 (−17.69 to −16.29)	−25.21 (−33.20 o −10.42)	−13.23 (−14.34 to −12.20)	−34.91 (−40.99 to−17.07)	−18.72 (−19.69 to−17.79)
Percent change in rate, age standardized 2010 to 2019	−7.76 (−11.71 to−3.90)	−2.84 (−3.75 to−2.09)	−3.58 (−8.93 to 2.02)	−1.92 (−3.01 to−0.87)	−9.25 (−13.83 to−4.46)	−3.36 (−4.35 to−2.58)

UI indicates uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[104] Printed with permission. Copyright © 2020, University of Washington.

Table 22-3. Rheumatic Fever/Rheumatic HD in the United States

Population group	Mortality, 2018: all ages*	Hospital discharges, 2016: all ages
Both sexes	3560	26 000
Males	1238 (34.8%)†	11 000
Females	2322 (65.2%)†	15 000
NH White males	988	…
NH White females	1885	…
NH Black males	109	…
NH Black females	198	…
Hispanic males	80	…
Hispanic females	148	…
NH Asian or Pacific Islander males	42‡	…
NH Asian or Pacific Islander females	77‡	…
NH American Indian or Alaska Native	28	…

Ellipses (…) indicate data not available; HD, heart disease; 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 people.

Sources: Mortality: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics System, 2018[1]; data represent underlying cause of death only. Hospital discharges: Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2016[3]; data include those inpatients discharged alive, dead, or status unknown.

Table 22-4. Incidence of IE and Valve Replacement, United States, 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.

Source: Adapted from Pant et al[106] with permission from The American College of Cardiology Foundation. Copyright © 2015, The American College of Cardiology Foundation.

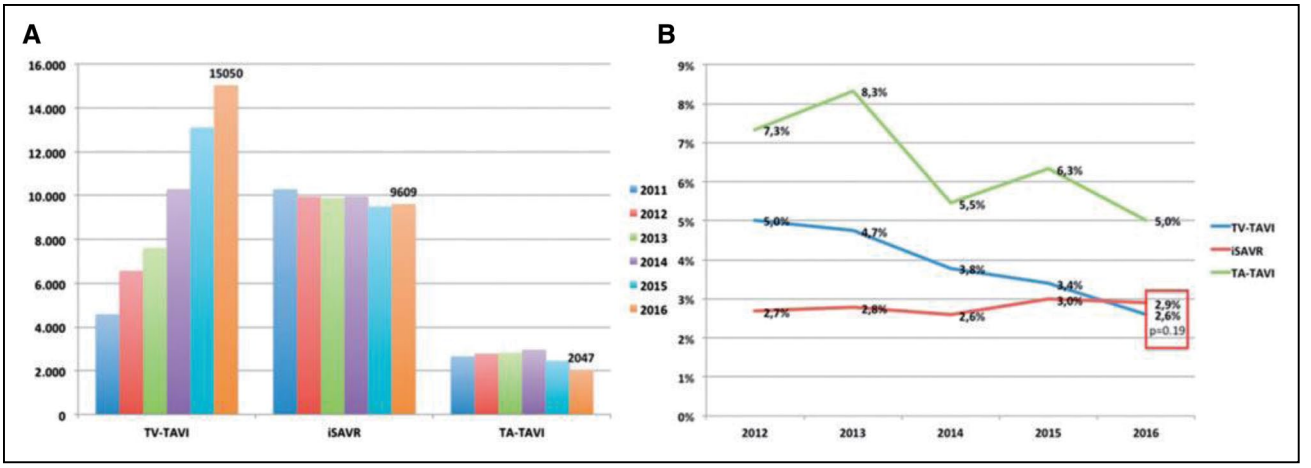

Chart 22-1. Number of TAVI and surgical aortic valve replacement (SAVR) procedures performed and in-hospital mortality according to type of procedure, Germany, 2011 to 2016.

A, Number of TAVI and SAVR procedures. **B**, In-hospital mortality.

iSAVR indicates isolated SAVR; TA, transapical; TAVI, transcatheter aortic valve implantation; and TV, transvascular.

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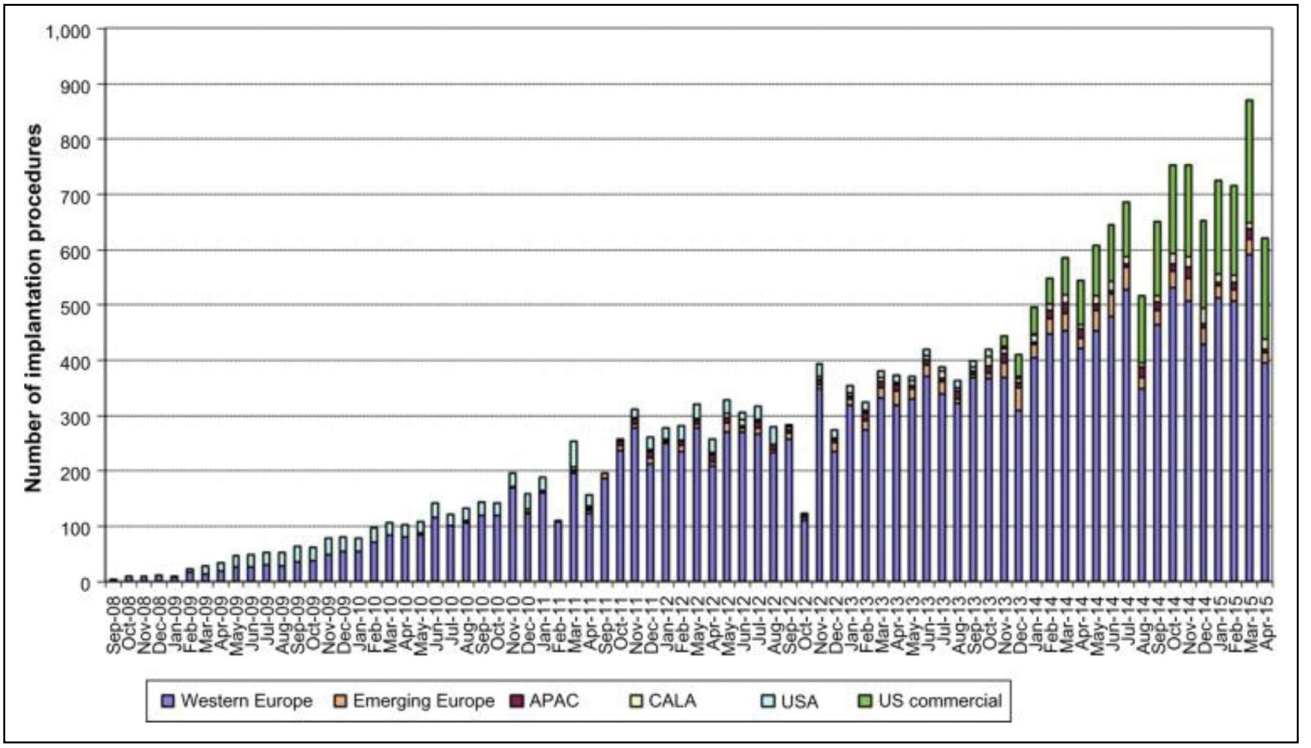

Chart 22-2. Worldwide experience with the MitraClip procedure from September 2008 until April 2015.

APAC indicates Asia-Pacific; and CALA, Caribbean and Latin America.

Source: Figure courtesy of Abbott Laboratories.

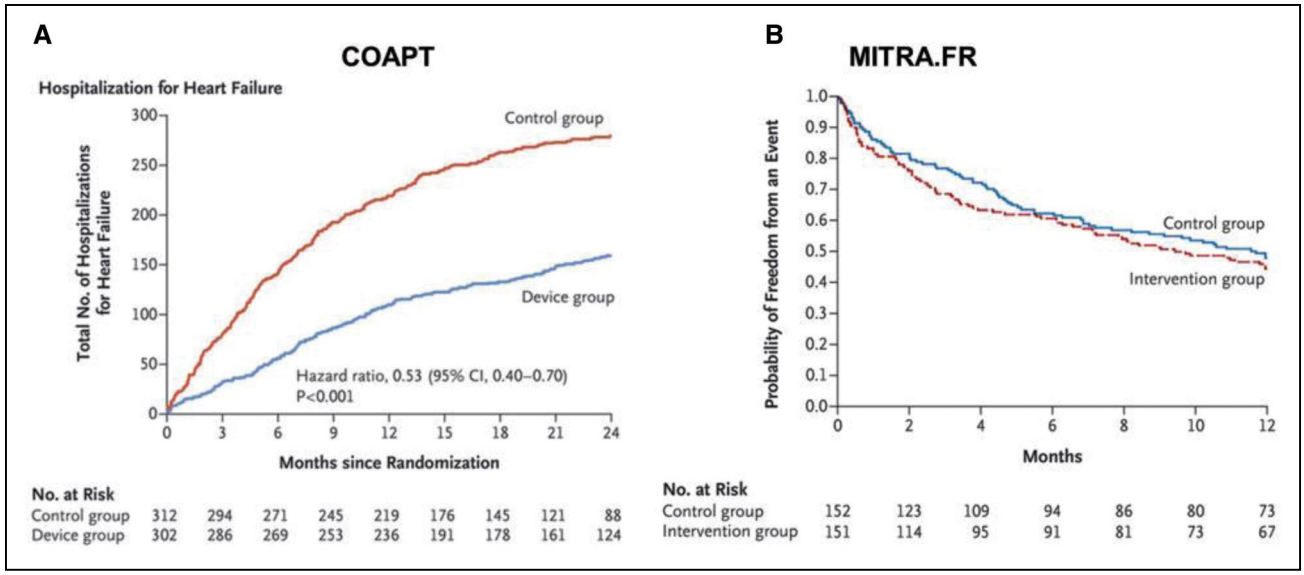

Chart 22-3. Comparison of primary outcomes after MitraClip implantation for secondary mitral regurgitation in the COAPT and MITRA-FR trials.
A, COAPT trial. **B**, MITRA-FR trial.
COAPT indicates Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; and MITRA-FR, Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation.
Source: **A**, Reprinted from Stone et al[61] with permission from the Massachusetts Medical Society. Copyright © 2018, Massachusetts Medical Society. **B**, Reprinted from Obadia et al[62] with permission from the Massachusetts Medical Society. Copyright © 2018, Massachusetts Medical Society.

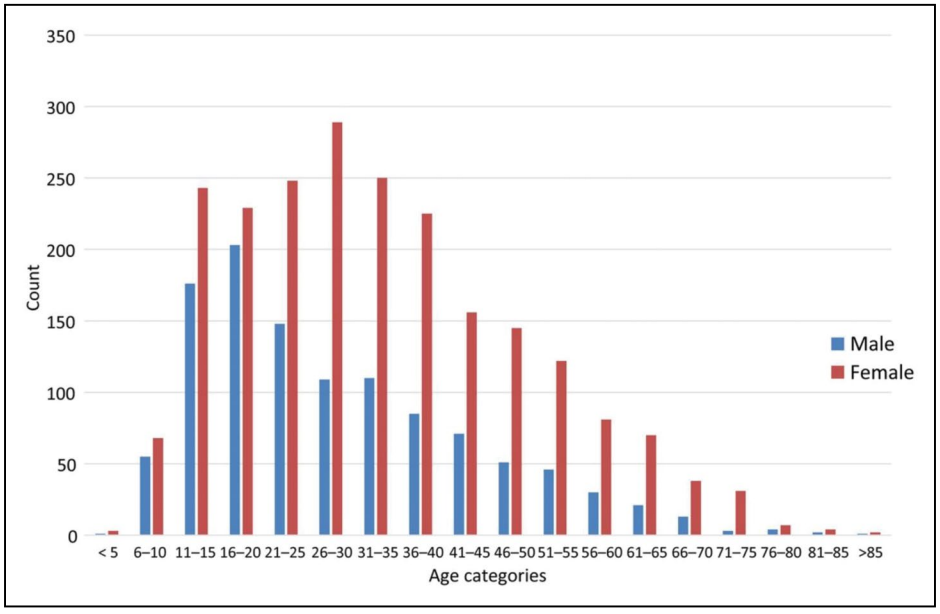

Chart 22-4. Age and sex distribution of 3343 subjects with rheumatic heart disease participating in the REMEDY study, 2010 to 2012.
REMEDY indicates Global Rheumatic Heart Disease Registry.
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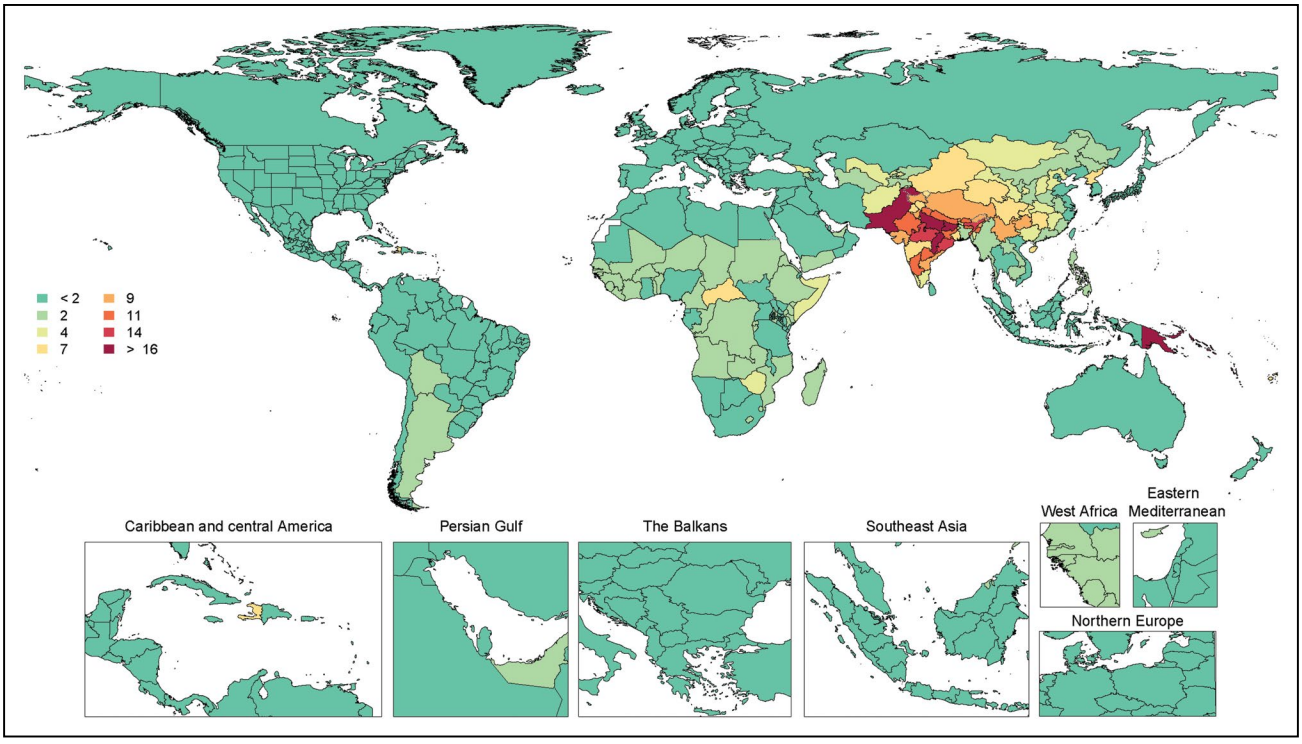

Chart 22-5. Age-standardized global mortality rates of rheumatic heart disease per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[104] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease website.[122]

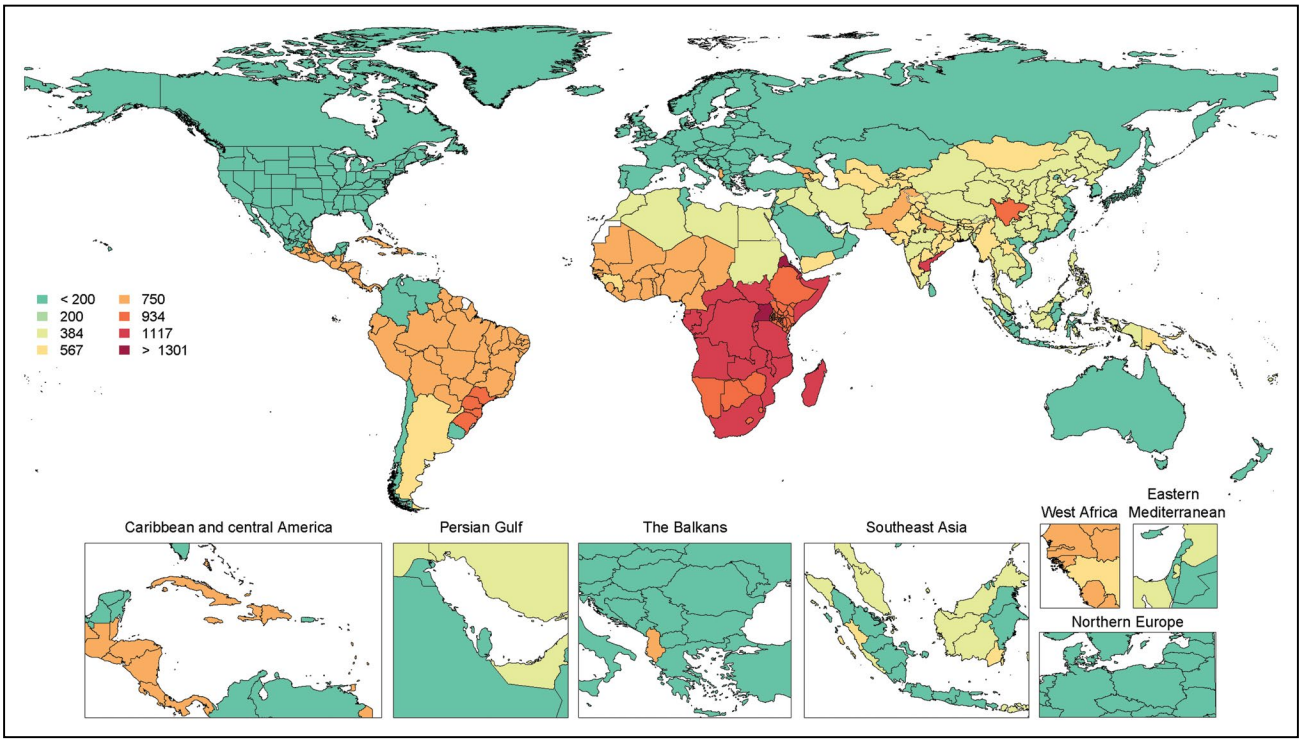

Chart 22-6. Age-standardized global prevalence rates of rheumatic heart disease per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[104] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease website.[122]

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23. VENOUS THROMBOEMBOLISM (DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM), CHRONIC VENOUS INSUFFICIENCY, PULMONARY HYPERTENSION

See Charts 23-1 and 23-2

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In this chapter, 2018 mortality data come from unpublished NHLBI tabulations using the NVSS[1] and CDC WONDER.[2] Hospital discharge data, from 2016, come from unpublished NHLBI tabulations using the HCUP.[3]

Abbreviations Used in Chapter 23

AF	atrial fibrillation
ARIC	Atherosclerosis Risk in Communities study
ASPIRE	Assessing the Spectrum of Pulmonary hypertension Identified at a Referral Center Registry
BMI	body mass index
BNP	B-type natriuretic peptide
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research
CI	confidence interval
CKD	chronic kidney disease
CT	computed tomography
CTEPH	chronic thromboembolic pulmonary hypertension
CVI	chronic venous insufficiency
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
ED	emergency department
FDA	US Food and Drug Administration
FHS	Framingham Heart Study
FVL	factor V Leiden
GRS	genetic risk score
GWAS	genome-wide association study
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*

(*Continued*)

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Abbreviations Used in Chapter 23 Continued

NAMCS	National Ambulatory Medical Care Survey
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NVSS	National Vital Statistics System
OR	odds ratio
PAH	pulmonary arterial hypertension
PE	pulmonary embolism
PH	pulmonary hypertension
PTS	postthrombotic syndrome
RCT	randomized controlled trial
REVEAL	Registry to Evaluate Early and Long-term PAH Disease Management
RV	right ventricular
USD	US dollars
VTE	venous thromboembolism
WHO	World Health Organization

Pulmonary Embolism

ICD-9 415.1; *ICD-10* I26.

2018: Mortality—8809. Any-mention mortality—36 494.

2016: Hospital discharges—185 000 (principal diagnosis), 367 000 (all-listed diagnoses).

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.

2018: Mortality—3230. Any-mention mortality—17 160.

2016: Hospital discharges—102 000 (principal diagnosis), 602 000 (all-listed diagnoses).

Venous Thromboembolism

Incidence

(See Charts 23-1 and 23-2)

- VTE includes both PE and DVT. In 2016, there were an estimated ≈370 000 cases of PE (HCUP NIS Chart 23-1), ≈857 000 cases of DVT (HCUP NIS Chart 23-2), and ≈1 220 000 total VTE cases in the United States (US population was 323 million in 2016); these estimates used the all-listed diagnoses hospitalization data and assumed that 30% of DVTs were treated in an outpatient setting.
- In 2016, there were 1 001 000 physician office visits and 211 000 ED visits with a principal diagnosis of DVT (unpublished NHLBI tabulation using NAMCS[4] and NHAMCS[5]).
- Incidence rates for PE and DVT increase exponentially with advancing age for both males and females.[6,7]
- VTE incidence varies by race/ethnicity.[8–10] Black people are at greatest risk, followed by White, Hispanic, and Asian people.

- Educational attainment has been inversely associated with VTE risk.[11]

Lifetime Risk

- The remaining lifetime risk of VTE at 45 years of age was 8.1% (95% CI, 7.1%–8.7%) overall, 11.5% in Black individuals, 10.9% in those with obesity, 17.1% in individuals with the FVL genetic mutation, and 18.2% in people with sickle cell trait or disease, according to data derived from nearly 20 000 participants of 2 US cohorts who were 45 to 99 years of age.[12]

Secular Trends

- The HCUP NIS (Chart 23-1) shows increasing numbers of hospitalized cases for PE from 1996 to 2016. Focusing on all-listed diagnoses (Chart 23-2), the number of hospitalized DVT cases also increased from 2005 to 2016.
- Interpretation of the HCUP NIS, as well as 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,[13] increase in the 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[14] and a smaller portion of PE cases,[15,16] misdiagnosis of VTE events, and failure to ascertain fatal PEs because of low autopsy rates).
- According to 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.[17] Trends in DVT incidence were not reported.

Risk Factors

- Approximately one-half to two-thirds of VTEs are considered provoked because they occur subsequent to strong triggering factors or persistent risk factors such as immobilization, trauma, surgery, cancer, or hospitalization in the preceding 3 months. The remainder are classified as unprovoked.[6,11,18,19]
- Hospitalized patients are at particularly high risk of VTE; a 2019 publication demonstrated that asymptomatic DVT was associated with 3-fold greater risk of death among acutely ill hospitalized patients.[20] Two randomized trials were published in the *New England Journal of Medicine* in 2019 addressing VTE prevention in critically ill patients. The trials showed that (1) among critically ill patients who were receiving pharmacological thromboprophylaxis, adjunctive intermittent pneumatic compression did not result in a significantly lower incidence of proximal lower-limb DVT than pharmacological thromboprophylaxis alone[21] and (2) early prophylactic placement of a vena cava filter after major trauma did not result in lower incidence of symptomatic PE or death at 90 days after filter placement.[22]
- Independent VTE risk factors, beyond the provoking factors noted above, include increasing age, obesity, family history or personal history of thrombosis, indwelling central venous catheter or transvenous pacemaker, prior superficial vein thrombosis, infection, autoimmune disease, inherited or acquired thrombophilia, kidney disease, AF, neurological disease with leg paresis, sickle cell anemia and sickle cell trait, and long-distance travel.[23–28]
- Presence of HF was associated with a 3-fold greater VTE risk in a 2019 publication from the ARIC study. The association was present for both HFpEF and HFrEF.[29]
- Use of testosterone therapy was also associated with doubling of VTE risk in males with and without evidence of hypogonadism.[30] These 2019 findings applied a case-crossover design to a large administrative database.
- Traditional atherosclerotic risk factors, including hypertension, hyperlipidemia, and diabetes, are generally not associated with VTE risk, according to large-scale individual-level meta-analyses.[31,32] In one of the meta-analyses, cigarette smoking was associated with provoked but not with unprovoked VTE events.[31]
- Among females, VTE risk is elevated among those using estrogen-based contraceptives, hormone therapy, or infertility treatment.[33]
- Risk is also elevated in pregnant females and females in the postpartum period compared with females of a similar age who are not in an obstetric period. VTE complicates ≈1.2 of every 1000 pregnancies.[34] In the postpartum period, VTE risk is highest during the first week after delivery (≈0.9 per 1000).[35] It drops to ≈0.25 per 1000 in the second week and continues to drop through the 12th week. Disparities are present; pregnancy-associated VTE is more common in Black than White females.[36] Furthermore, among females who are pregnant or postpartum, certain obstetric procedures and complications such as cesarean delivery, preeclampsia, hemorrhage, and postpartum infection conferred an increased risk for VTE (ORs ranging from 1.3–6.4 in an analysis of administrative data).[35]

Family History and Genetics

- VTE is highly heritable.[37,38]
- FVL is the most common inherited thrombophilia in populations of European descent but is rare in African and Asian populations.[39] In ARIC, ≈5% of White and <1% of Black people are heterozygous carriers of FVL, and lifetime risk of VTE was 17.1% in individuals with the FVL genetic mutation.[12] Pooling data from 36 epidemiological studies showed that risk of VTE was increased 4-fold in people with heterozygous FVL (OR, 4.2 [95% CI, 3.4–5.3]) and

11-fold in those with homozygous FVL (OR, 11.4 [95% CI, 6.8–19.3]) compared with noncarriers.[40]
- Antithrombin deficiency is a rare mutation that is associated with greatly increased risk of incident VTE (OR, ≈14).[41] A bayesian meta-analysis found that for childbearing females with this mutation, VTE risk was 7% in the antepartum period and 11% postpartum.[42]
- 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.[43] GWASs have identified additional common genetic variants associated with VTE risk, including variants in *F5*, *F2*, *F11*, *FGG*, and *ZFPM2*.[44] These common variants individually increase the risk of VTE to a small extent, but a GRS composed of a combination of common variants yielded an OR for VTE risk of 7.5.[45]
- Exome-wide analysis of rare variants in >24 000 individuals of European ancestry and 1858 individuals of African ancestry confirmed previously implicated loci but did not uncover novel rare variants associated with VTE. Similarly, targeted sequencing efforts did not uncover novel rare variants for DVT. However, GWAS meta-analyses of >1 million individuals established >30 VTE loci.[46,47]

Treatment

- In the latter half of the past decade, substantial progress has been made in the management of patients with suspected VTE. This includes patient-tailored diagnostic and therapeutic strategies resulting from the confluence and refined use of biomarkers (eg, age-adjusted D-dimer threshold), risk prediction algorithms (PE Rule-Out Criteria), and the introduction of DOACs.[48]
- 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).[49] When oral anticoagulation is contraindicated or ineffective, inferior vena cava filters can be used. However, in general, they should be avoided.[48] Thrombolysis is generally reserved for patients with massive PE or those with DVT that is threatening to result in limb loss.[48]
- Current treatment guidelines consider anticoagulation with either warfarin or DOAC drugs (ie, apixaban, rivaroxaban, dabigatran, edoxaban) as the standard of care.[49]

Mortality

- PE is an important contributor to maternal mortality, being responsible for ≈9% of pregnancy-associated deaths.[50]
- Among Medicare beneficiaries with DVT, the 30-day mortality rate was 5.1% and the 1-year mortality rate was 19.6% in 2010.[51] These rates were similar to those in 1999 (5.0% and 21.5%, respectively).
- Among Medicare beneficiaries with PE, the 30-day mortality rate was 9.1% and the 6-month mortality rate was 19.6% in 2010.[52] These rates showed only slight improvements from rates in 1999 (12.3% and 23.0%, respectively).
- The 1-year VTE survival varies greatly by underlying cause. In an analysis using administrative data for first-time VTE in Quebec, Canada, the 1-year survival rate for VTE was 77% overall, but when stratified by VTE-provoking status, it was 47% for cancer-associated VTE, 84% for provoked VTE, and 93% for unprovoked VTE.[53]
- Asymptomatic DVTs diagnosed with compression ultrasound were associated with a 3-fold increased risk of short-term all-cause mortality in patients with acute medical illness relative to those with no evidence of DVT.[54]

Complications

- 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.[11,23,55]
- Independent predictors of recurrence within 180 days include active cancer and inadequate anticoagulation.[56]
- 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 DOACs, instead of warfarin, for VTE primary treatment could further reduce bleeding risk.[57]
- PTS/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.[58]
- CTEPH affects ≈4% of patients with PE within 2 years of their initial PE event.[59]

Costs

- A literature review estimated incremental direct medical costs (2014 USD) 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 billion to $10 billion.[60]

Chronic Venous Insufficiency

ICD-10 I87.2.

2018: Mortality—53. Any-mention mortality—616.

Prevalence

- Varicose veins are a common manifestation of CVI. In the San Diego Population Study (mean age, 59 years), visible disease was common; 6.2% had trophic changes (eg, hyperpigmentation, edema, ulcers), 23.3% had varicose veins, and 51.9% had spider veins.[61]
- PTS is a common complication of DVT that develops in 20% to 50% of cases after proximal DVT and is severe in 5% to 10% of cases.[62] Approximately 4% of patients with DVT experience venous stasis ulcers.[58]

Incidence

- The FHS reported an annual incidence of varicose veins of 2.6% in females and 1.9% in males.[63]

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.[64] Risk factors for more severe CVI include smoking in males and leg injury in females. Inflammation, endothelial dysfunction, and blood coagulation disorders are thought to predispose to CVI.[65,66]
- PTS, a subset of CVI, has specific risk factors that can be identified at the time of or after DVT: recurrent ipsilateral DVT, obesity, CKD, 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.[62,67]
- Using data from 762 patients with DVT, Rabinovich et al[68] developed a clinical prediction model for PTS. High-risk predictors were index DVT in the iliac vein, BMI of ≥35 kg/m^2, and moderate to severe Villalta (PTS severity) score at DVT diagnosis.
- In a meta-analysis of patients with DVT who underwent ultrasonography at least 6 weeks after their DVT, 2 ultrasound parameters were predictive of PTS: residual vein thrombosis (pooled OR, 2.17 [95% CI,1.79–2.63]) and venous reflux at the popliteal level (pooled OR, 1.34 [95% CI, 1.03–1.75]).[69]

Family History and Genetics

- 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 have been implicated,[70] the genetic factors predisposing to varicose veins have not been definitively identified.[71] GWASs in >400 000 individuals established 12 candidate loci for varicose veins in individuals with European ancestry.[72]

Treatment

- A number of treatment options are available for patients with severe varicose veins. In a 2019 RCT of patients with severe varicose veins, quality of life 5 years after treatment was better after laser ablation or surgery than after foam sclerotherapy.[73]
- For patients with DVT, use of compression stockings for 24 months is standard therapy for the prevention of PTS. In a 2018 RCT, a total of 865 patients were randomized to either standard duration or individualized therapy length.[74] Individualized therapy was noninferior to standard duration of therapy of 24 months. Individualization of therapy duration may potentially enhance patients' well-being. Furthermore, in a comparison of initial compression with either compression hosiery or multilayer bandaging, multilayer bandaging was slightly more effective than hosiery but had substantially higher costs without a gain in health-related quality of life.[75]
- In 300 patients treated for advanced CVI with radiofrequency ablation procedures, Black patients presented with higher-severity CVI and had less improvement with ablation.[76]

Pulmonary Hypertension

ICD-10 I27.0, I27.2.

2018: Mortality—7953. Any-mention mortality—25 709.

Incidence

- In the United States 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 ≥85 years of age.[77]
- PH incidence is somewhat higher in females than males,[77,78] although females are at 3-fold greater risk for PAH.[79]
- The WHO classifies PH into 5 groups (described below) according to underlying pathogenesis. Limited information is available on the prevalence of PH subtypes in nonreferral settings. In a study by Wijeratne et al[80] conducted in Ontario, Canada, among adults with PH, 26.8% had group 1 (PAH), 79.6% had group 2, 42.6% had group 3, and 14.4% had group 4. Groups 2 through 4 were not mutually exclusive, and group 5 was not reported.
- 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.[81]
- 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.[81]
- The prevalence and incidence of WHO group 3 PH (attributable to lung disease or hypoxia) are

difficult to estimate but likely would track with lung disease prevalence.[81]

- The prevalence of WHO group 4 PH (CTEPH and other pulmonary obstructions) ranges from 1.0% to 8.8% among those with PE.[81] CTEPH incidence, however, may be underestimated according to general population data; in a 2017 modeling study, only 7% to 29% of CTEPH cases were diagnosed.[82]
- 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%.[81,83]

Secular Trends

- In the United States, between 2001 and 2010, hospitalization rates for PH increased significantly, and among those ≥85 years of age, hospitalization rates nearly doubled.[77]

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 cohort of 23 329 patients with first VTE (mean follow-up, 3.5 years) 283 patients were diagnosed with CTEPH. Cumulative incidence was 1.3% and 3.3% at 2 and 10 years after PE and 0.3% and 1.3% after DVT, respectively. Risk factors for CTEPH included >70 years of age, female sex, chronic obstructive pulmonary disease, HF, and AF.[84]
- In a study of 772 consecutive patients with PE 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, diabetes, 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%).[85] 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.[86]

Family History and Genetics

- A 2018 study reported clustering of CTEPH in families, providing novel evidence that heritable genetic factors influence an individual's risk of developing CTEPH.[87]
- A Japanese family study identified *BMPR2* (bone morphogenetic protein receptor type 2) as a risk factor for PAH.[88] GWASs in >11 000 individuals have identified additional risk loci for PAH, including *SOX17* and *HLA-DPA1/DPB1*.[89]

Treatment

- Clinical guidelines[90] and consensus statements[91] guide PH management. The FDA has approved several medications for group 1 PH (PAH); most of these do not have approval for treatment in other PH groups (II–V). The PAH drugs act via vasodilation, platelet aggregation inhibition, or antiproliferative effects on vascular smooth muscle cells.

Mortality

- Five-year survival of patients with PH is ≈60% but varies by WHO group.[92,93] In a 2019 study of US veterans with PH, 5-year survival was 66.1% for group 1 (PAH), 42.4% for group 2 (left-sided HD), 52.3% for group 3 (lung disease), 72.7% for group 4 (CTEPH), 67.8% for group 5 (miscellaneous), and 34.9% for PH with multiple causes.[94]
- Five-year survival was 61.2% to 65.4% in the US-based REVEAL registry of patients with group 1 PH. In this registry, lower 5-year survival was strongly associated with worse functional class at presentation,[95] shorter 6-minute walk distance,[92] and high (>340 pg/mL) versus low (≤340 pg/mL) baseline BNP.
- For patients with groups 2 through 4 PH, 2019 findings from the ASPIRE Registry demonstrated that greater incremental shuttle walking test distance was associated with better survival.[96]
- In sickle cell disease–related PH, the 5-year survival rate in 1 study was 63% with and 83% without PH.[97]
- An international prospective registry that included 679 patients with CTEPH estimated that the 3-year survival was 89% with and 70% without pulmonary thromboendarterectomy.[98]

Costs

- Health care costs associated with PH are substantial. In an analysis of administrative data, the per-patient per-month total all-cause health care costs for patients with PH who were commercially insured were $9503 for those on monotherapy and $16 240 for those on combination therapy. Among patients with PH with Medicare Advantage and Part D, the monthly costs for patients on monotherapy and combination therapy were $6271 and $14 340, respectively.[99]

Global Burden

- Of patients with PH, 80% 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 at onset, <40 years).[81]
- In high-income countries, rates of CTEPH are believed to be lower in Japan than in the United States and Europe.[82]

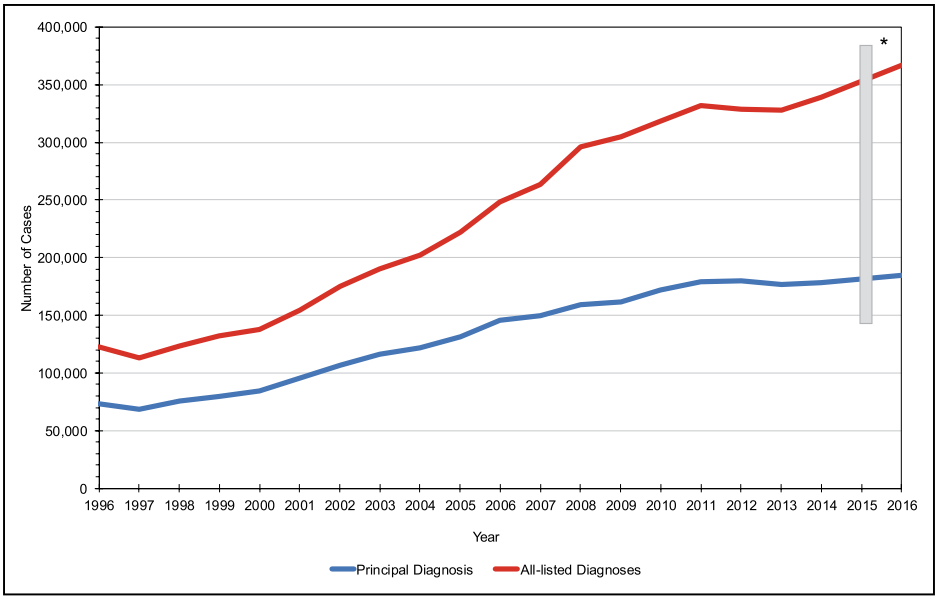

Chart 23-1. Trends in hospitalized pulmonary embolism, United States, 1996 to 2016.
*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.[3]

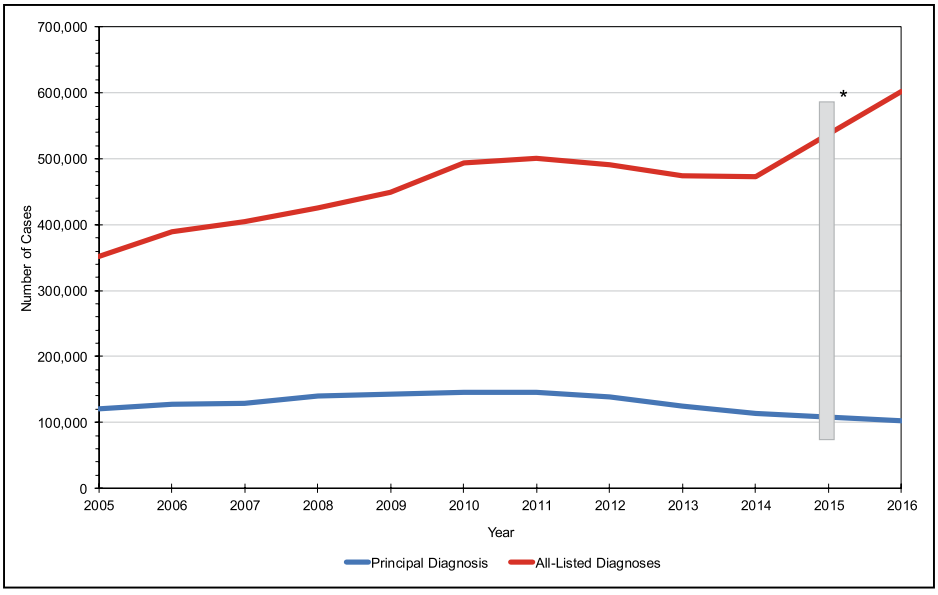

Chart 23-2. Trends in hospitalized deep vein thrombosis, United States, 2005 to 2016.
*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.[3]

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24. 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 24-1 through 24-3 and Charts 24-1 through 24-9

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Peripheral Artery Disease

Prevalence (Charts 24-1 and 24-2)

- Estimates for the prevalence of PAD in the United States among individuals ≥40 years of age range from 5.8% to 10.7% and are derived from data ascertained before 2010.[1–3]
- Population-based estimates indicate that ≈6.5 million (5.8%) individuals ≥40 years of age have PAD, defined as an ABI <0.9, on the basis of the most contemporary pooled data from 7 US cohorts obtained between the 1970s and 2000s and extrapolated with the 2000 US census.[1]

Abbreviations Used in Chapter 24

AAA	abdominal aortic aneurysm
ABI	ankle-brachial index
ACC	American College of Cardiology
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities study
AUC	area under curve
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass graft
CAD	coronary heart disease
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CMS	Centers for Medicare & Medicaid Services
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies

(*Continued*)

Abbreviations Used in Chapter 24 Continued

CORAL	Cardiovascular Outcomes in Renal Atherosclerotic Lesions
CT	computed tomography
CVD	cardiovascular disease
ED	emergency department
eGFR	estimated glomerular filtration rate
FH	familial hypercholesterolemia
FOURIER	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk
FPG	fasting plasma glucose
GBD	Global Burden of Disease Study
GRS	genetic risk score
GWAS	genome-wide association study
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HCUP	Healthcare Cost and Utilization Project
HDL	high-density lipoprotein
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
KD	Kawasaki disease
MetS	metabolic syndrome
MI	myocardial infarction
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
NIS	Nationwide Inpatient Sample
NVSS	National Vital Statistics System
OR	odds ratio
OVER	Open Versus Endovascular Repair
PA	physical activity
PAD	peripheral artery disease
PCSK9	proprotein convertase subtilisin/kexin type 9
REACH	Reduction of Atherothrombosis for Continued Health
RR	relative risk
SAVR	surgical aortic valve replacement
SBP	systolic blood pressure
SES	socioeconomic status
SNP	single-nucleotide polymorphism
TAA	thoracic aortic aneurysm
TC	total cholesterol
TGF-β	transforming growth factor-β
TRA 2°P TIMI-50	Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–TIMI-50
UI	uncertainty interval
USD	US dollars

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Estimates of PAD prevalence by age, sex, and race/ethnicity are shown in Charts 24-1 and 24-2.
  - PAD prevalence increases with age, approximately doubling per decade.[1,4]
  - PAD prevalence in females and males varies by age and race/ethnicity.[1]
  - PAD prevalence is greater in Black compared with NH White individuals, particularly after 50 and 60 years of age in males and females, respectively.[1,4]
- Approximately 8.5 million (7.2%) adults ≥40 years of age have PAD when individuals with ABI >0.9 (after revascularization or false-negative ABI) are included in the aforementioned analysis.[1]
- The overall prevalence of PAD, defined as an ABI <0.9, was 8.6% among adult participants in the NHANES 1999 to 2004.[3]
- The prevalence of PAD among individuals >40 years of age between 2003 and 2008 was estimated at 10.7% when defined as present with the use of *ICD* codes extracted from nationwide claims data from large employers' health plans and from Medicare and Medicaid programs. From these data sources, the prevalence of critical limb ischemia, the most severe form of PAD, was 1.3%.[2]
- PAD prevalence is higher among older individuals and those with atherosclerotic risk factors. For example, PAD was identified in 29% of 6979 patients seen in US primary care clinics in 1999 who were either ≥70 years of age or 50 to 69 years of age with diabetes or history of smoking cigarettes.[5] In a similar study of 6880 individuals ≥65 years of age seen in general practitioner clinics in Germany in 2001, the prevalence of PAD was 16.8% and 19.8% in women and men, respectively.[6] In 2 studies of Danish men 65 to 74 years of age conducted between 2011 and 2017, PAD was present in ≈11% of individuals.[7,8]

Incidence

- Among individuals >40 years of age, the annual incidence of PAD and critical limb ischemia was 2.69% and 0.35%, respectively, when defined with *ICD* codes extracted from nationwide claims data from large employers' health plans and from Medicare and Medicaid programs between 2003 and 2008.[2]

Lifetime Risk and Cumulative Incidence

- The lifetime risk (80-year horizon) of PAD was estimated at ≈19%, 22%, and 30% in White, Hispanic, and Black individuals, respectively, with the use of pooled data from 6 US community-based cohorts.[3]

Secular Trends

See Table 24-1

- Between 2000 and 2010, the prevalence of PAD, defined as an ABI ≤0.9, increased in both high- and low- to middle-income countries 13.1% and 28.7%, respectively.[9]
- Between 2000 and 2014, in the United Kingdom, the incidence of symptomatic PAD declined from 38.6 to 17.3 per 10 000 person-years, with a corresponding decline in prevalence from 3.4 to 2.4%.[10]
- From 2006 to 2016, principal discharge diagnosis for PAD decreased from 156 000 and 111 000 (HCUP,[11] unpublished NHLBI tabulation; Table 24-1).
- Between 2003 and 2011, admission rates for critical limb ischemia remained constant in the NIS.[12]
- Between 2006 and 2011, the annual rate of peripheral vascular intervention increased slightly from 401.4 to 419.6 per 100 000 individuals among Medicare beneficiaries.[13]
- Between 2003 and 2011, endovascular treatment for critical limb ischemia increased from 5.1% to 11.0%.[12]
- Between 2000 and 2008, the overall rate of lower-extremity amputation decreased significantly, from 7258 to 5790 per 100 000 Medicare beneficiaries with PAD.[14]
- Between 2009 and 2015, a 50% increase in the rate of nontraumatic lower-extremity amputation was observed in adults with diabetes according to NIS data.[15]

Risk Factors

- PAD risk factors largely parallel those for atherosclerosis in other vascular beds, for example, CAD, and include smoking, diabetes, hypertension, and dyslipidemia.[3,4,9,16]
  - Current or former smoking is among the strongest PAD risk factors with ORs ranging from 1.3 to 5.4 and relatively greater risk among current smokers.[3,4,9]
    - Heavy smoking appears to be a stronger risk factor for PAD compared with CAD, with age- and sex-adjusted ORs of 3.94 and 1.66, respectively.[17]
  - Diabetes is associated with increased risk for PAD with ORs ranging from 1.38 to 1.84.[3,9]
  - Hypertension, defined as BP ≥140/90 mm Hg, is associated with ≈50% increased odds of PAD (OR, 1.47 [95% CI, 1.37–1.57]).[9]
    - Each 20–mm Hg increase in SBP was associated with an OR of 1.27 (95% CI, 1.22–1.32) for PAD.[3]
  - Dyslipidemia, defined as TC >200 mg/dL, is associated with an OR of 1.16 (95% CI, 1.08–1.25).[9]
    - Each 39-mg/dL increase in TC was associated with an OR of 1.14 (95% CI, 1.09–1.19) for PAD.[3]
  - Smoking, type 2 diabetes, hypertension, and hypercholesterolemia accounted for 75% (95% CI, 64%–87%) of risk associated with

the development of clinical PAD in the Health Professionals Follow-Up Study of males.[18]
  - MetS was associated with increased risk for incident PAD on the basis of data from the CHS.[19]
- Other possible PAD risk factors include sedentary lifestyle, inflammation, hypertension in pregnancy, and CKD.[16,19–21]
- Mediterranean diet compared with counseling for a low-fat diet was associated with lower risk of incident PAD according to a secondary analysis of a randomized feeding trial conducted in Spain between 2003 and 2010.[22]

Social Determinants of Health
See Chart 24-3

- Lower income and lower education are associated with greater incidence and prevalence of PAD according to ARIC and NHANES (1999–2004) data, respectively.[23,24]
- Lower SES is associated with greater risk for amputation (HR, 1.12 [95% CI, 1.06–1.17]).[25]
- The rate of lower-extremity amputation varies geographically within the United States (Chart 24-3).[14]

Risk Prediction

- Models for predicting the probability of an ABI <0.9 have been developed from NHANES data.[3,26] Included variables were age, sex, race, pulse pressure, TC and HDL (or the ratio), and smoking status, with a C statistic of 0.76 (95% CI, 0.72–0.79).[26] Another model with NHANES data additionally included diabetes and history of CAD or stroke, which yielded a similar C statistic of 0.75.[3,27]
- A lifetime risk prediction model for PAD using the variables described above, including diabetes and history of CAD or stroke, has been developed.[3]

Borderline Risk Factors/Subclinical/Unrecognized Disease

- Intermittent claudication, the classic PAD symptom, is present in a minority (8.7% to 32%) of individuals with PAD.[5,28]
  - More commonly (≈50%), individuals report a range of symptoms differing from classic claudication (ie, nonlimiting exertional leg pain or limiting exertional pain but without calf symptoms or resolution within 10 minutes of rest).[5,28]
  - Approximately 20% to 34% of individuals with ABI <0.9 are asymptomatic, that is, have no leg pain.[5,28]
- Screening for PAD with ABI in individuals without a history or physical features suggestive of PAD is reasonable in those with the PAD risk factors listed below[29]:
  - >65 years of age
  - 50 to 64 years of age and at least 1 atherosclerotic risk factor (ever smoker, diabetes, hypertension, dyslipidemia, family history of PAD)
  - <50 years of age, diabetes, and 1 additional atherosclerotic risk factor
  - Any age with known atherosclerosis in another vascular bed (coronary, carotid, subclavian, renal, mesenteric, or AAA)
- Screening for PAD (with ABI), AAA (with abdominal ultrasound), and hypertension followed by optimal care resulted in lower risk (HR, 0.93 [95% CI, 0.88–0.98]) of 5-year mortality compared with no screening in a randomized trial of 50 156 Danish males 65 to 74 years of age.[30]

Genetics/Family History

- Atherosclerotic PAD is heritable, independently of the heritable risk factors described above.
  - Family history of PAD was independently associated with a 1.83-fold greater odds of PAD in the San Diego Population Study.[31]
  - Monozygotic twins compared with dizygotic twins had a greater risk for PAD with an OR of 17.7 and 5.7, respectively, in the Swedish Twin Registry, with heritable factors accounting for 58% of phenotypic variance between twins.[32] The NHLBI Twin Study found that 48% of the variability in ABI with similar environmental risk factors could be attributed to additive genetic effects.[33]
  - Causes of PAD include monogenic (mendelian) diseases such as familial lipoprotein disorders like chylomicronemia and FH, hyperhomocysteinemia, and pseudoxanthoma elasticum.[34]
  - GWASs have identified genetic loci associated with atherosclerotic PAD, including the CHD-associated chromosome 9p21 genetic locus associated with PAD, AAA, and intracranial aneurysm.[35]
    - Other PAD-associated genetic loci include SNPs on chromosome 9 near *CDKN2B*, *DAB21P* (DAB2 interaction protein), and *CYBA* (cytochrome B-245 α-chain) genes.[36]
    - A large-scale GWAS in >31 000 PAD cases and >211 000 controls from the Million Veterans Program and the UK Biobank identified 18 new PAD loci. Eleven of the loci were associated with disease in 3 vascular beds, including *LDLR, LPA*, and *LPL*, whereas 4 of the variants were specific for PAD (including variants in *TCF7L2* and *F5*).[37]
    - Given this overlap between genetic risk factors between different vascular beds, a GRS composed of genetic variants associated with CAD has been shown to be associated with PAD in the UK Biobank (OR 1.28 [95% CI, 1.23–1.32]).[38] In another study, targeted sequencing of 41 genome regions associated

with CHD performed in 1749 PAD cases and 1855 controls found overlap of several genes between CHD and PAD.[39]
- GWASs have also identified genetic variants associated with inflammatory forms of PAD such as KD.[40]

Prevention (Primary)

- Approaches to primary prevention of PAD extrapolate from recommendations for prevention of atherosclerotic disease with a focus on optimization of healthy lifestyle behaviors (healthy diet, PA, and never smoking), avoidance of the development of modifiable risk factors, and control of the modifiable risk factors if present.

Awareness, Treatment, and Control

Awareness

- Awareness of PAD, its risk factors, and complications is relatively low.
  - In a US-based survey of 2501 adults ≥50 years of age in 2006, 25% of individuals expressed familiarity with PAD compared with 67.1% for CAD and 73.9% for stroke.[41]
    - Of those familiar with PAD, ≈50% were aware of smoking, diabetes, hypertension, and dyslipidemia as PAD risk factors.[41]
    - Approximately 25% to 28% knew PAD is associated with increased risk of MI and stroke, with 14% awareness of amputation or death as a PAD-related complication.[41]
    - Income and education levels were positively associated with all knowledge domain levels.[41]
  - Physicians may underappreciate PAD.
    - A US-based cross-sectional study conducted at 350 primary care clinics in 1999 examined awareness of PAD in individuals ≥70 years of age or those 50 to 69 years of age with a history of diabetes or smoking, as well as their physicians. Although 83% of patients recognized their prior PAD diagnosis, only 49% of their primary care physicians were aware of the diagnosis.[5]
    - Patients with PAD alone receive optimal medical therapy less frequently than patients with CAD or concomitant CAD and PAD (eg, statin use, 59% versus 72%; antiplatelet use, 66% versus 84%, respectively) according to data from the US Department of Veterans Affairs ascertained between 2013 and 2014.[42]
    - Among 2120 patients without a known diagnosis of PAD who underwent coronary angiography, ABI <0.9 was found in 12.8% in a prospective study performed in 2014 in Jordan.[43]

Treatment

- Treatment of patients with lower-extremity PAD is summarized in the 2016 AHA/ACC guideline.[29] Management of PAD is directed toward reduction in symptoms, improvement in quality of life, and limb preservation through addressing modifiable risk factors, including PA, smoking cessation, dyslipidemia, BP and glycemic control, and mechanical revascularization approaches.
  - Optimal exercise programs for patients with PAD are summarized in a 2019 AHA scientific statement.[44] Supervised exercise therapy (up to 36 sessions over 12 weeks) for patients with intermittent claudication PAD is covered by CMS.[45]
  - In a 2017 Cochrane review with meta-analysis, aerobic exercise compared with usual care was associated with the following[46]:
    - Increased pain-free walk distance (mean difference, 82 m [95% CI, 72–92])
    - Increased maximum walk distance (mean difference, 120 m [95% CI, 51–190])
  - In a randomized trial of optimal medical care, supervised exercise training, and iliac artery stent placement, supervised exercise resulted in superior treadmill walking time at 6 months compared with stenting (mean increase from baseline, 5.8±4.6 minutes versus 3.7±4.9 minutes; P=0.04). Results in the exercise group and stent group were superior to results in the group with optimal medical care alone (1.2±2.6 minutes).[47]
  - Smoking cessation, compared with continued smoking, is associated with lower risks of death (HR, 0.33 [95% CI, 0.13–0.80]), MI (11% versus 53% at 10-year follow-up; P=0.043), and amputation (HR, 0.40 [95% CI, 0.19–0.83]) among patients with PAD in observational studies.[48,49]
  - Lipid-lowering therapy is recommended for the treatment of PAD.[29]
    - In a subanalysis of the Heart Protection Study (enrollment 1994–1997), compared with placebo, simvastatin treatment was associated with 22% lower risk (95% CI, 15%–29%) for first major vascular event among patients with PAD and 16% lower risk (95% CI, 5% to 25%) of first peripheral vascular event in all subjects.[50]
    - More contemporary (2003–2014), albeit retrospective, studies of patients with PAD also support statins for risk reduction of adverse leg outcomes and mortality.[51–53]
    - In a subanalysis of the FOURIER trial (enrollment 2013–2015), compared with placebo, the PCSK9 inhibitor evolocumab reduced the risk of major adverse limb events, including acute limb ischemia, major amputation, and urgent revascularization (HR, 0.58

[95% CI, 0.38–0.88]), in patients with and without existing PAD.[54]

— The antithrombotic medications rivaroxaban and vorapaxar may reduce the risk of adverse limb outcomes (eg, revascularization or amputation) among patients with PAD.[55,56]
  - In a subanalysis of the COMPASS trial (enrollment 2013–2016), among the 6391 subjects with PAD at baseline, compared with aspirin alone, the combination of rivaroxaban 2.5 mg twice daily plus aspirin 81 mg daily was associated with lower risk of major adverse limb events (2.6% versus 1.5%; HR, 0.57 [95% CI, 0.37–0.88]; *P*=0.01).[55]
  - In an exploratory analysis of the TRA 2°P TIMI-50 trial (enrollment 2007–2009), among the 5845 subjects with PAD at baseline, 16% underwent ≥1 peripheral revascularization procedures during the follow-up period, with a significantly lower rate with vorapaxar (15.4%) compared with placebo (19.3%; HR, 0.82 [95% CI, 0.72–0.93]).[56]

— Among patients with PAD and hypertension, treatment to BP goals is recommended.[29]

— Glycemic control may be associated with better limb outcomes among patients with PAD according to observational studies.[57–59] In a study of 149 patients with diabetes, 1-year patency after infrapopliteal percutaneous intervention was greater among patients with below- compared with above-median FPG (HR, 1.8 [95% CI, 1.2–2.8]).[58] Among 197 Japanese patients with diabetes who underwent percutaneous transluminal angioplasty for critical limb ischemia, an HbA_{1c} ≥ 6.8% was associated with 2.91 times greater risk for major amputation (95% CI, 1.61–5.26) over a mean follow-up of 1.7 years.[59]

— Cilostazol is recommended to reduce claudication symptoms in patients with PAD.[60]

— Revascularization for patients with claudication or critical or acute limb ischemia may be associated with improvement in quality of life and limb preservation.[29] A meta-analysis of 10 studies found that revascularization was associated with improved quality of life on the basis of a 6.1-point improvement (95% CI, 3.0–9.2) in the Short Form-36 physical functioning domain.[61]

Mortality (Chart 24-4)

- In 2018, PAD was the underlying cause in 12 264 deaths. The number of any-mention deaths attributable to PAD was 56 684 (unpublished NHLBI tabulation using NVSS[62] and CDC WONDER).[63]
- In 2018, the overall any-mention age-adjusted death rate for PAD was 14.1 per 100 000 (unpublished NHLBI tabulation using CDC WONDER).[63]
  — Any mention-mortality rates were 12.0 for NH White females, 14.1 for NH Black females, 5.5 for NH Asian or Pacific Islander females, 14.0 for NH American Indian or Alaska Native females, and 8.9 for Hispanic females.
  — Any mention-death rates were 17.2 for NH White males, 22.5 for NH Black males, 7.7 for NH Asian or Pacific Islander males, 14.4 for NH American Indian or Alaska Native males, and 13.9 for Hispanic males.
- A meta-analysis of 16 cohorts including a total of 48 294 individuals (48% female) demonstrated a continuous association between ABI and mortality. Increased all-cause and cardiovascular mortality risk began at an ABI ≤1.1, whereas individuals with an ABI between 1.11 and 1.40 had the lowest risk (Chart 24-4).[64]
  — ABI ≤0.9 was associated with approximately triple the risk of all-cause death compared with ABI of 1.11 to 1.40 in both males (RR, 3.33 [95% CI, 2.74–4.06]) and females (RR, 2.71 [95% CI, 2.03–3.62]).[64]
- In-hospital mortality was higher in females than males, regardless of disease severity or types of procedure, even after adjustment for age and comorbidities (*P*<0.01 for all comparisons)[65]:
  — 0.5% versus 0.2% after percutaneous revascularization for intermittent claudication;
  — 1.0% versus 0.7% after surgical revascularization for intermittent claudication;
  — 2.3% versus 1.6% after percutaneous revascularization for critical limb ischemia; and
  — 2.7% versus 2.2% after surgical revascularization for critical limb ischemia.

Complications

- Tissue (limb) loss
  — Risk factors for amputation were evaluated in 2 730 742 Medicare beneficiaries ≥65 years of age with PAD using data from 2000 to 2008.[14]
    - Black race and diabetes each accounted for ≈30% of the multivariable-adjusted logistic model for predicting lower-extremity amputation and had an OR of 2.9 and 2.4, respectively. CKD, dementia, older age, HF, cerebrovascular disease, and male sex were the next strongest factors associated with increased risk of amputation. CAD, cancer, hypertension, and Asian race were associated with significantly lower risk of amputation. Smoking status was not included in the models.

  — Patients with microvascular disease, defined as retinopathy, neuropathy, and nephropathy, were at increased risk for amputation (HR, 3.7 [95% CI, 3.0–4.6]), independently of traditional risk factors and prevalent PAD, in

125 674 patients in the Veterans Aging Cohort Study (enrollment 2003–2014).[66]
  - Mortality by 1 year after major lower-extremity amputation was estimated at 48.3% among 186 338 older Medicare patients with PAD.[67]
  - Statin therapy in patients with PAD was associated with significantly lower risk of amputation and lower mortality rate on the basis of data obtained from 155 647 Veterans Affairs patients between 2003 and 2014.[53]
- Quality of life
  - Regardless of leg symptoms, individuals with PAD report impaired function and quality of life and experience a decline in lower-extremity function over time.[68,69]
    - Individuals with low-normal ABI (0.91–0.99) also may have reduced physical function compared with those with normal ABI.[70]
  - Among patients with PAD, lower PA levels are associated with worse all-cause and cardiovascular mortality rate and faster rates of functional decline.[71,72] In addition, shorter 6-minute walk test distance and slower walking speed are associated with higher rates of all-cause mortality, cardiovascular mortality, and mobility loss.[73,74]
- Individuals with PAD are more likely to have atherosclerosis in other vascular beds (eg, coronary, carotid, and renal arteries and abdominal aorta).[75–78]
  - Pooled data from 11 studies in 6 countries found higher age-, sex-, risk factor–, and CVD-adjusted risk in people with PAD (defined by ABI <0.9) versus those without (RR, 1.45 [95% CI, 1.08–1.93] for CAD and 1.35 [95% CI, 1.10–1.65] for stroke).[79]

Health Care Use: Hospital Discharges and Ambulatory Care Visits

- In 2016, primary diagnosis of PAD accounted for 1 600 000 physician office visits and 11 000 ED visits (NAMCS[80]/NHAMCS,[81] unpublished NHLBI tabulation).

Cost

- Among patients with PAD in the REACH registry (enrollment 2003–2004), average health care costs over 2 years for vascular-related hospitalizations ranged from $7000 to $11 693 in 2004 USD.[82]
- Among 25 695 patients with PAD between 2009 and 2016 in the Optum Integrated Database, the health care costs incurred over 1 year were substantially higher in those who had a major adverse cardiovascular (mean difference, $44 659) or limb (mean difference, $34 216) event compared with patients without these events.[83]
- In 72 199 Medicare beneficiaries admitted to the hospital in 2011 with critical limb ischemia, average annual health care cost ranged from $49 200 to $55 700.[84]
- In a cohort of 22 203 patients with PAD in Minnesota, total health care costs were approximately $18 000 (2011 USD) greater among tobacco users (9.0%) compared with nonusers over 1 year.[85]

Global Burden (Table 24-2 and Charts 24-5 and 24-6)

Prevalence

  - In 2010, an estimated 202 million people worldwide had PAD according to a systematic review of 34 studies.[9]
  - Approximately 6.6% of the Chinese population >35 years of age, or 45 million individuals, have PAD according to a population-based survey in China conducted between 2012 and 2015.[86]
  - PAD estimates in sub-Saharan Africa range from 3.1% to 24% in adults ≥50 years of age.[87]
  - In the GBD Study 2019 of 204 countries, PAD was estimated to affect 113.44 million individuals (UI, 99.16–128.42; Table 24-2).[88] PAD prevalence was highest in high-income North America, Western Europe, and Eastern Europe (Chart 24-5).

Mortality

- In the GBD Study 2019 the age-standardized mortality attributable to PAD was 1.01 per 100 000 individuals (UI, 0.56–1.74; Table 24-2).[88]
  - PAD mortality was highest in Eastern Europe (Chart 24-6).

Aortic Diseases

ICD-9 440, 441, 444, and 447; *ICD-10* I70, I71, I74, I77, and I79.

Aortic Aneurysm and Acute Aortic Syndromes ICD-9 441; ICD-10 I71.

Prevalence

- Estimating the prevalence of TAA is challenging because of the relatively few studies in which screening has been performed in the general population.
  - The prevalence of TAA >5 cm incidentally identified by community-based screening chest CT was estimated to be between 0.16% and 0.34% from studies performed between 1995 and 2003 in Japan and Germany.[89,90]
- AAA is more common in males than females, and its prevalence increases with age.[91–94]
  - AAA is ≈4 times more common in males than females on the basis of data from an ultrasound-based screening study of 125 722 veterans 50 to 79 years of age conducted between 1992 and 1997.[95]
    - In males, the prevalence of AAAs 2.9 to 4.9 cm in diameter ranged from 1.3% to 12.5% in individuals 45 to 54 and 75 to 84 years of

age, respectively. In females, the prevalence of AAAs 2.9 to 4.9 cm in diameter ranged from 0% in the youngest to 5.2% in the oldest age groups.[96]

- Approximately 1% of males between 55 and 64 years of age have an AAA ≥4.0 cm, and every decade thereafter, the prevalence increases by 2% to 4%.[97,98]

Incidence

- Thoracic aortic disease (aneurysm and dissection) incidence rates range between 3 and 16 per 100 000 per year in adults according to data from Sweden and the United Kingdom obtained between 1987 and 2012.[99,100]
- In 2010, the estimated annual incidence rate of AAA per 100 000 individuals was 0.83 (95% CI, 0.61–1.11) to 164.57 (95% CI, 152.20–178.78) in individuals 40 to 44 and 75 to 79 years of age, respectively, according to a meta-analysis of 26 studies.[101]

Lifetime Risk and Cumulative Incidence

- Between 1995 and 2015, the cumulative incidence of hospitalizations for aortic aneurysm and aortic dissection was ≈0.74% and 0.09%, respectively, on the basis of *ICD* codes from Swedish National Health Register databases.[102]

Secular Trends

- Between 1995 and 2015, the incidence of aortic dissection, intramural hematoma, or penetrating aortic ulcer remained stable at 10.2 and 5.7 per 100 000 person-years in males and females, respectively, according to data from the Rochester Epidemiology Project.[103]
- Between 1988 and 2013, the prevalence of AAA declined over time in a meta-analysis of data largely from European studies.[104]
- Between 1999 and 2016, deaths attributable to ruptured TAA and AAA declined significantly from 5.5 to 1.8 and 26.3 to 7.9 per million, respectively, according to US NVSS data.[105]

Risk Factors

- TAAs in younger individuals are typically caused by familial disease or genetic syndromes, the prototype examples being bicuspid aortic valve disease and Marfan syndrome. In older individuals, that is, those ≥65 years of age, smoking, hypertension, and dyslipidemia contributing to atherosclerosis are the main drivers of TAA. Inflammatory conditions such as giant cell arteritis, lupus, or infectious aortitis also may cause TAA.[106]
  - TAA is more common in males than females.
- Risk factors for AAA were assessed in a retrospective analysis of 3.1 million patients between 2003 and 2008.[107]
  - Most atherosclerotic risk factors also are associated with increased risk for AAA.[97]
  - Of these, smoking is the most important modifiable AAA risk factor.[108]
  - Giant cell arteritis is associated with a 2-fold higher risk for developing an AAA (sub-HR, 1.92 [95% CI, 1.52–2.41]) even after adjustment for competing risks according to data from the United Kingdom.[109]
- Diabetes may be associated with lower risk of aortic aneurysmal disease.[110,111] A 2014 systematic review of 17 community-based observational studies demonstrated a consistent, inverse association between diabetes and prevalent AAA (OR, 0.80 [95% CI, 0.70–0.90]).[110]

Social Determinants of Health

- Few data exist on social determinants of health for thoracic aortic disease.
- In a retrospective study of 60 784 patients who underwent thoracic aortic repair procedures between 2005 and 2008, Black, Hispanic, and Native American individuals, as well as those with lower income, were more likely to undergo thoracic endovascular aortic repair than open surgical repair.[112]
- Screening for AAA occurs less frequently in low socioeconomic areas despite a higher burden of AAA risk factors and prevalence of AAA.[113]
- Lower SES appears to be associated with worse outcomes after AAA repair on the basis of multistate US administrative claims data for 92 028 patients between 2007 and 2014.[114]
- Geographic variation in the approach to AAA appears to be present. In a comparison of AAA management between the United Kingdom and United States, 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.[115]

Borderline Risk Factors/Subclinical/Unrecognized Disease

See Chart 24-7

- Screening for TAA has not been established.
- TAAs are typically slowly expanding, increasing in size at rates of 0.1 and 0.3 cm/y in the ascending and descending aorta, respectively.[116,117] Familial and genetic causes of TAA may display faster rates of expansion.[118] Expansion rate accelerates as the size increases.[119]
- One-time screening for AAA in males 65 to 75 years of age who currently smoke or have a history of smoking is recommended because it is associated with lower AAA-related but not all-cause mortality (Chart 24-7).[120–122]
- A meta-analysis of 15 475 individuals from 18 studies on small AAAs (3.0–5.4 cm) demonstrated

a mean aneurysm growth rate of 0.22 cm/y, which did not vary significantly by age and sex.[123]
  - Growth rates were higher in smokers versus former or never smokers (by 0.35 mm/y) and lower in people with diabetes than in those without diabetes (by 0.51 mm/y).[123]
- Aneurysms in 1 location are associated with aneurysms in another, for example, cerebral berry aneurysms in thoracic aortic disease or TAA in AAA.[124–126] Approximately 25% of patients with TAA have concomitant AAA.

Genetics/Family History

- Examples of thoracic aortic diseases caused by identified genetic variation include Marfan syndrome (caused primarily by mutations in the *FBN1* [fibrillin-1] gene), Loeys-Dietz syndrome (TGF-β pathway–related genes, including *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, and *TGFB3*), vascular Ehlers-Danlos syndrome (*COL3A1*), arterial tortuosity syndrome (*SLC2A10*), and familial TAA syndrome (*ACTA2, TGBR2*, and mutations in several other genes).
  - Individuals with mutations in the aforementioned genes are at significantly increased risk for vascular aneurysms. If these disorders are suspected from clinical findings or family history, then referral to a specialty clinic for genetic testing may inform diagnosis, treatment, and cascade screening.
- Genetic variants associated with nonfamilial forms of TAA/dissection include common polymorphisms in *FBN1* (rare mutations cause Marfan syndrome), *LRP1* (LDL receptor protein–related 1), and *ULK4* (unc-51–like kinase 4).[127,128]
- AAA is heritable as evidenced by family history of AAA as a risk marker, particularly in male siblings of male patients (RR, 17.9 [95% CI, 12.9–22.9]).[129]
- Genetic variants associated with AAA include a locus on chromosome 3p12.3 and SNPs in *DAB2IP*, *LDLR*, *LRP1*, *MMP3*, *TGFBR2*, and *SORT1*.[130,131]
- Genetic variants associated with intracranial aneurysms have been found in several genes, including *RBBP8*, *STRAD13/KL*, *SOX17*, *CDKN2A/B*, and *ANGPTL6*.[132,133]
- Despite co-occurrence of aneurysms across vascular beds, a meta-analysis did not identify shared genetic variants for intracranial, thoracic, and aortic aneurysms.[134]
- Genetic associations with nonatherosclerotic arterial diseases such as fibromuscular dysplasia and spontaneous coronary artery dissection have been challenging because of the lower prevalence of disease, but studies of these diseases are ongoing. A noncoding SNP in *PHACTR1* (phosphatase and actin regulator 1) has been associated with fibromuscular dysplasia[135] and with spontaneous coronary artery dissection,[136] and rare variants in the *TSR1* gene have been associated with spontaneous coronary artery dissection.[137] In a case series of patients with spontaneous coronary artery dissection, clinical genetic testing with connective tissue disease panels showed that 8.2% of patients harbored a pathogenic variant, with the most common being for vascular Ehlers-Danlos syndrome, suggesting that genetic testing may be useful in these patients.[138]

Awareness, Treatment, and Control

- Aortic aneurysmal disease is typically asymptomatic until complications occur.
  - Screening for TAA is not established.
  - Screening for AAA is recommended in males 65 to 75 years of age who currently smoke or have a history of smoking. Awareness of this recommendation, however, appears to be low, with 1.4% of eligible individuals screened on the basis of 2015 estimates using CMS data.[139]
- Treatment of TAA and AAA is aimed at slowing progression and preventing complications, namely rupture and dissection.
  - Elective AAA repair is typically not recommended among asymptomatic individuals until diameter exceeds 5.5 cm or if annual expansion rate is ≥ 0.5 cm/y because open or endovascular repair of small AAAs (4.0–5.5 cm) did not demonstrate a benefit compared with routine ultrasound surveillance according to results from 4 trials including a total of 3314 participants.[140,141] Lower diameter thresholds apply to certain individuals, for example, 4.5 cm, if SAVR or CABG is the primary surgical indication. Thresholds for TAA repair are typically lower among patients with genetic syndromes, for example, Marfan and Loeys-Dietz syndromes.[141]
  - Surgical approaches to TAA are mixed between open and endovascular repair.
    - In a sample of 12573 and 2732 Medicare patients from 1998 to 2007, for intact TAA, perioperative mortality was similar between open and endovascular repair (7.1% versus 6.1%; *P=0*.56). In contrast, for ruptured TAA, perioperative mortality was greater for open compared with endovascular repair (45% versus 28%; *P*<0.001), although 5-year survival rates were higher (70% versus 56%; *P*<0.001).[142]
    - Racial disparities in perioperative 30-day mortality after TAA repair appear to be present with open (Black patients, 18% versus White patients, 10%; *P*<0.001) compared with endovascular (8% versus 9%; *P*=0.54) approaches on the basis of Medicare data from 1999 to 2007.[142]
    - Timing of presentation with TAA rupture is associated with mortality, with higher risk

for weekend (OR, 2.55 [95% CI, 1.77–3.68]) compared with weekday repair on the basis of NIS data from 2009.[143]

— Statin therapy may be associated with slower rate of AAA growth (0.82 mm/y [95% CI, 0.33–1.32]), rupture (OR, 0.63 [95% CI, 0.51–0.78]), and lower 30-day mortality after elective AAA repair (OR, 0.55 [95% CI, 0.36–0.83]) according to a meta-analysis of retrospective and observational studies spanning a total of 80 428 patients.[144]

— After elective AAA repair, survival within the first 1 to 3 years appears to be greater with endovascular compared with open repair, although longer-term survival at 8 to 9 years appears to be similar between the 2 approaches. Among Medicare patients, open versus endovascular 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.[145] After 8 years of follow-up, however, survival was similar between the 2 groups. The rate of eventual aneurysm rupture was higher with endovascular (5.4%) compared with open (1.4%) repair.[146] Similarly, in the OVER Veterans Affairs Cooperative trial of 881 patients, compared with open repair, endovascular repair was associated with lower mortality at 2 years (HR, 0.63 [95% CI, 0.40–0.98]) and 3 years (HR, 0.72 [95% CI, 0.51–1.00]) but no survival difference in up to 9 years (mean, 5 years) of follow-up (HR, 0.97 [95% CI, 0.77–1.22]).[147]

  - Perioperative mortality of endovascular AAA repair was not associated with surgeon case volume, but outcomes were better in hospitals with higher case 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 associated with case volume for both surgeon (6.4% in ≤3 cases versus 3.8% in 14–62 cases; $P<0.01$) and hospital (6.3% in ≤5 cases versus 3.8% in 14–62 cases; $P<0.01$).[148]
  - Of all AAA repairs, endovascular AAA repair increased from 5% to 74% between 2000 and 2010 despite stable overall number of AAAs (≈45 000 per year) according to NIS data. Furthermore, associated health care costs rose during this time period despite reductions in in-hospital mortality and length of stay.[149]

Mortality

2018: Mortality—9923. Any-mention mortality—17 141.

- TAA
  — In 2013, type A thoracic aortic dissections were surgically treated in 90% of presenting cases with in-hospital mortality of 22% and surgical mortality 18% on the basis of data from the IRAD. Type B thoracic aortic dissections were more likely to be treated with endovascular therapies, but mortality rates remained similar between 1996 and 2013.[150]
  - Mesenteric malperfusion with type A acute dissections was present in ≈3.7% of patients in IRAD and associated with greater mortality than among patients without malperfusion (63.2% versus 23.8%; $P<0.001$).[151]
  - Among patients with acute type B aortic dissection in IRAD, heterogeneous in-hospital outcomes exist. In-hospital mortality was higher (20.0%) among patients with complications (eg, mesenteric ischemia, renal failure, limb ischemia, or refractory pain) compared with patients without complications (6.1%). Among patients with complications, in-hospital mortality was higher with open surgical (28.6%) compared with endovascular (10.1%) repair ($P=0.006$).[152]
- AAA
  — 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% of patients (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.[153]
  — In ruptured AAAs, implementation of an endovascular-first protocol was associated with decreased perioperative adverse outcomes and improved long-term prognosis in a retrospective analysis of 88 consecutive patients seen at an academic medical center.[154]

Complications
(See Chart 24-8)

Dissection and rupture are the predominant complications of aortic aneurysmal disease, and their risks are proportional to aortic diameter and expansion rate, as well as familial or genetic causes.

TAA:

- At a diameter of 4.0 to 4.9 and >6.0 cm, the annual rate of TAA dissection or rupture is estimated at ≈2% and ≈7%, respectively.[155]
- Most TAA dissections in absolute numbers, however, occur at relatively smaller diameters. In IRAD, 59.1% and 40.9% of dissections occurred at diameters <5.5 and <5.0 cm, respectively.[156]
- Annual age- and sex-adjusted incidences per 100 000 people were estimated at 3.5 (95% CI,

2.2–4.9) for TAA rupture and 3.5 (95% CI, 2.4–4.6) for acute aortic dissection according to data from Olmsted County, Minnesota.[157]

AAA:

- The risk of AAA rupture is also proportionately related to diameter (Chart 24-8).[158] For incidentally identified AAA, the 5-year risk of rupture ranges from 1% to 7% and 25% to 40% for sizes 4.0 to 5.0 and >5.0 cm, respectively.[159,160]
- 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]; $P<0.001$).[123]

Health Care Use: Hospital Discharges and Ambulatory Care Visits

- In 2016, hospital discharges with aortic aneurysm as principal diagnoses totaled 68 000, of which 49 000 occurred in males and 19 000 in females (HCUP,[11] unpublished NHLBI tabulation).

Global Burden (See Table 24-3 and Chart 24-9)

- Global mortality attributable to aortic aneurysm by sex according to the GBD Study 2019 of 204 countries is shown in Table 24-3. The highest age-standardized mortality rates attributable to aortic aneurysm are reported in tropical Latin America, high-income Asia Pacific, and Eastern Europe (Chart 24-9).

Atherosclerotic Renal Artery Stenosis ICD-9 440.1; ICD-10 I70.1.

Prevalence

- The prevalence of renal artery disease by renal duplex ultrasonography was 6.8% in the North Carolina subcohort of the CHS between 1997 and 1998.[161] Among those with renal artery stenoses, 88% were unilateral and 12% were bilateral.
- The prevalence of renal artery stenosis by angiography ranged from 5.4% to 11.7% among patients undergoing coronary angiography on the basis of data ascertained from 2007 to 2008 in Italy (n=1298) and 2000 to 2002 in Argentina (n=843), respectively.[162,163]

Incidence

- The incidence rate of renal artery stenosis was estimated at 3.09 per 1000 patient-years on the basis of Medicare claims data between 1992 and 2004.[164]

Lifetime Risk and Cumulative Incidence

- The lifetime risk and cumulative incidence of renal artery stenosis have not been established.

Secular Trends

- The risk for a claim for renal artery stenosis was higher in 2004 (HR, 3.35 [95% CI, 3.17–3.55]) compared with 1992 according to Medicare claims data, even with adjustment for demographics and comorbidities.[164]

Risk Factors

- Traditional atherosclerotic risk factors such as advanced age, diabetes, smoking, and hypertension are associated with higher prevalence of atherosclerotic renal artery stenosis.[165]
- Atherosclerosis in another vascular bed is significantly associated with the presence of renal artery stenosis.[163,164,166]

Risk Prediction

- On the basis of data from a retrospective single-center study of 4177 patients in Iran who underwent renal angiography between 2002 and 2016, a predictive model for the presence of renal artery stenosis defined by ≥70% stenosis (prevalence, 14.1%) that included age, sex, history of hypertension, BMI, and eGFR had an AUC of 0.70 (95% CI, 0.67–0.72).[167]

Borderline Risk Factors/Subclinical/Unrecognized Disease

- Resistant hypertension, CKD, early-onset hypertension in the absence of family history of hypertension, acute rise in creatinine after initiation of renin-angiotensin-aldosterone blockade, asymmetrical kidney size, and recurrent flash pulmonary edema may be caused by renal artery stenosis.[165,168]

Prevention

- Although clinical trials have not specifically tested approaches for primary prevention of renal artery stenosis, optimization of traditional atherosclerotic risk factors may be of benefit.

Awareness, Treatment, and Control

- Optimal medical therapy is the first-line treatment in the management of renal artery stenosis. In CORAL, a randomized clinical trial of 943 patients with renal artery stenosis and either hypertension requiring ≥2 medications or CKD recruited between 2005 to 2010, renal artery stenting plus optimal medical therapy was not superior to optimal medical therapy alone for the reduction of the composite of major adverse cardiovascular or renal events over a median follow-up of 43 months (HR, 0.94 [95% CI, 0.76–1.17]).[169]

Mortality

- 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.[170]

Complications

- The main complications of renal artery stenosis are resistant hypertension, decline in renal function, and recurrent episodes of flash pulmonary edema.[168]

Table 24-1. PAD in the United States

Population group	Mortality, 2018, all ages*	Hospital discharges, 2016, all ages
Both sexes	12 264	111 000
Males	5566 (45.4%)†	66 000
Females	6698 (54.6%)†	45 000
NH White males	4288	…
NH White females	5327	…
NH Black males	762	…
NH Black females	795	…
Hispanic males	360	…
Hispanic females	388	…
NH Asian or Pacific Islander males	108‡	…
NH Asian or Pacific Islander females	138‡	…
NH American Indian/Alaska Native	62	…

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

*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 PAD that is for males vs females.

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

Sources: Mortality: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics System, 2017.[62] Hospital discharges: Unpublished NHLBI tabulation using Hospital Cost and Utilization Project, 2017.[11]

Table 24-2. Global Mortality From and Prevalence of PAD, by Sex, 2019

	Both sexes combined		Males		Females	
	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)
Total number (millions)	0.07 (0.04 to 0.13)	113.44 (99.16 to 128.42)	0.04 (0.02 to 0.08)	37.35 (32.51 to 42.65)	0.04 (0.02 to 0.07)	76.09 (66.59 to 86.17)
Percent change in total number 1990 to 2019	145.50 (96.50 to 176.23)	72.50 (70.18 to 74.74)	147.32 (101.91 to 189.65)	78.12 (75.45 to 80.95)	143.63 (61.91 to 179.15)	69.87 (67.46 to 72.49)
Percent change in total number 2010 to 2019	33.95 (24.78 to 42.22)	25.65 (24.76 to 26.47)	37.95 (26.19 to 48.13)	25.87 (24.70 to 27.00)	30.03 (19.25 to 39.95)	25.55 (24.62 to 26.41)
Rate per 100 000, age standardized	1.01 (0.56 to 1.74)	1401.85 (1228.48 to 1589.39)	1.23 (0.56 to 2.63)	1008.31 (881.44 to 1143.68)	0.83 (0.36 to 1.70)	1735.06 (1519.05 to 1964.03)
Percent change in rate, age standardized 1990 to 2019	–2.45 (–21.94 to 9.78)	–21.68 (–22.75 to –20.53)	–1.62 (–18.68 to 15.35)	–21.70 (–22.90 to –20.42)	–4.60 (–36.72 to 9.34)	–20.45 (–21.60 to –19.19)
Percent change in rate, age standardized 2010 to 2019	–2.86 (–9.43 to 3.62)	–3.54 (–4.15 to -3.04)	1.34 (–7.26 to 8.69)	–3.97 (–4.76 to –3.23)	–6.20 (–13.77 to 1.21)	–3.00 (–3.61 to –2.41)

PAD indicates peripheral artery disease; and UI, uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[88] Printed with permission. Copyright © 2020, University of Washington.

Table 24-3. Global Mortality From Aortic Aneurysm, by Sex, 2019

	Both sexes (95% UI)	Males (95% UI)	Females (95% UI)
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 in total number 1990 to 2019	82.1 (67.3 to 97.0)	71.6 (54.2 to 89.3)	103.1 (84.5 to 116.3)
Percent change in total number 2010 to 2019	26.9 (21.3 to 32.6)	25.1 (17.8 to 32.6)	30.1 (23.6 to 35.0)
Rate per 100 000, age standardized	2.2 (2.0 to 2.4)	3.2 (2.9 to 3.3)	1.5 (1.3 to 1.6)
Percent change in rate, age standardized 1990 to 2019	−17.9 (−24.1 to −11.7)	−24.7 (−31.6 to −17.7)	−9.5 (−17.1 to −4.0)
Percent change in rate, age standardized 2010 to 2019	−3.8 (−7.7 to 0.3)	−5.5 (−10.6 to −0.3)	−2.0 (−6.6 to 1.8)

UI indicates uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[88] Printed with permission. Copyright © 2020, University of Washington.

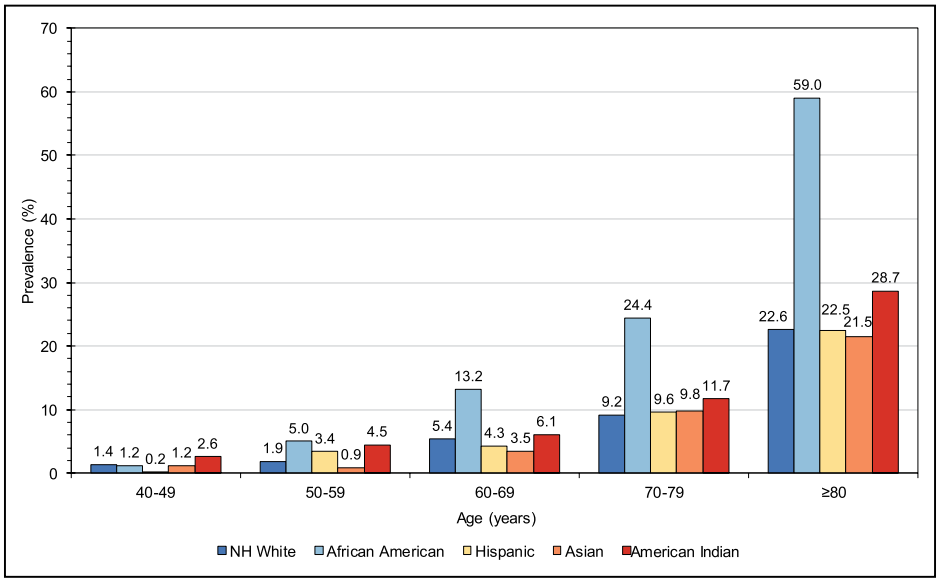

Chart 24-1. Estimates of prevalence of peripheral artery disease in males by age and ethnicity, United States, 2000.
NH indicates non-Hispanic.
Source: Data derived from Allison et al.[1]

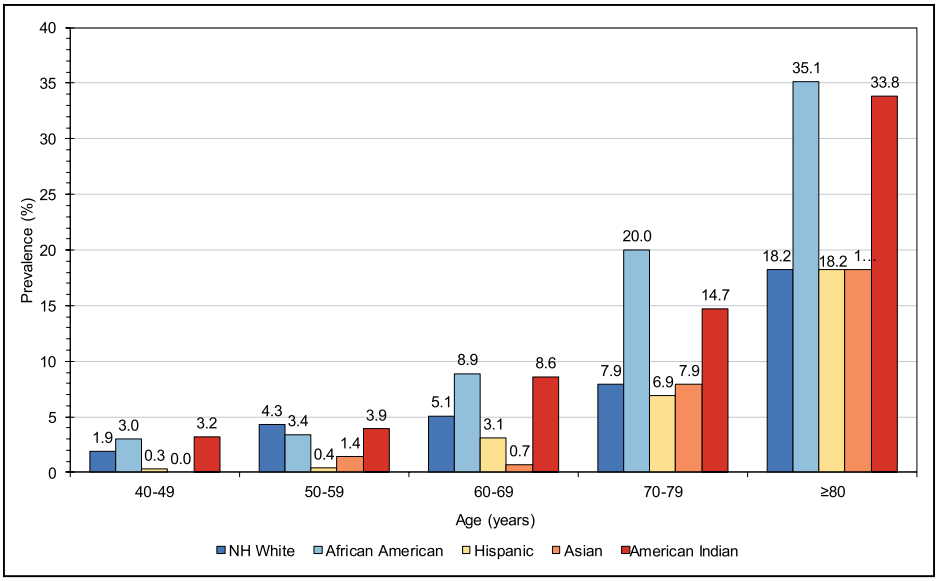

Chart 24-2. Estimates of prevalence of peripheral artery disease in females by age and ethnicity, United States, 2000.
NH indicates non-Hispanic.
Source: Data derived from Allison et al.[1]

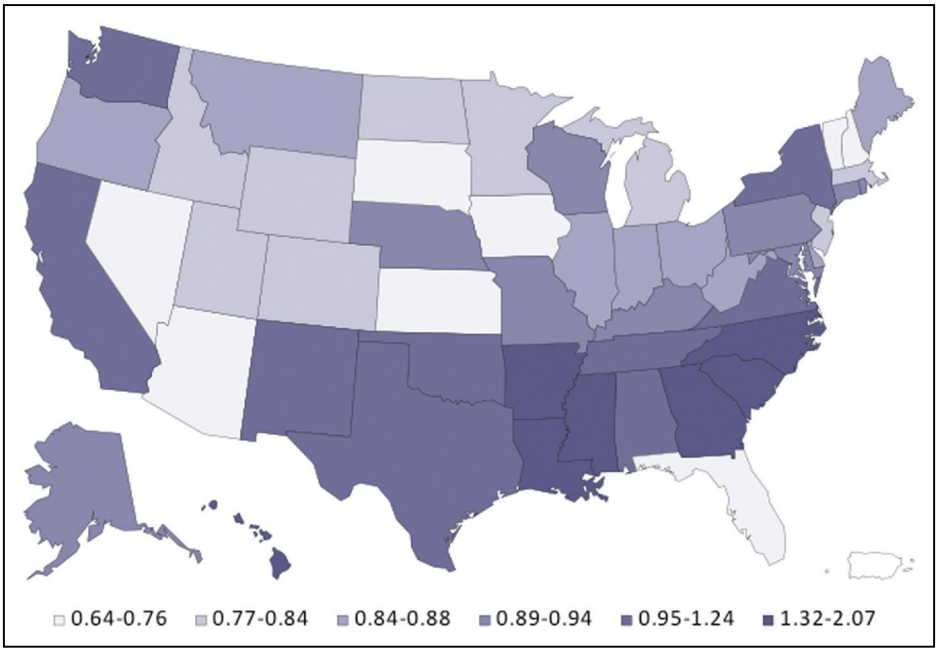

Chart 24-3. Geographic variation in rates of lower-extremity amputation in the United States based on Centers for Medicare & Medicaid Services data from 2000 to 2008.
Source: Reprinted from Jones et al[14] with permission from the American College of Cardiology Foundation. Copyright © 2012, the American College of Cardiology Foundation.

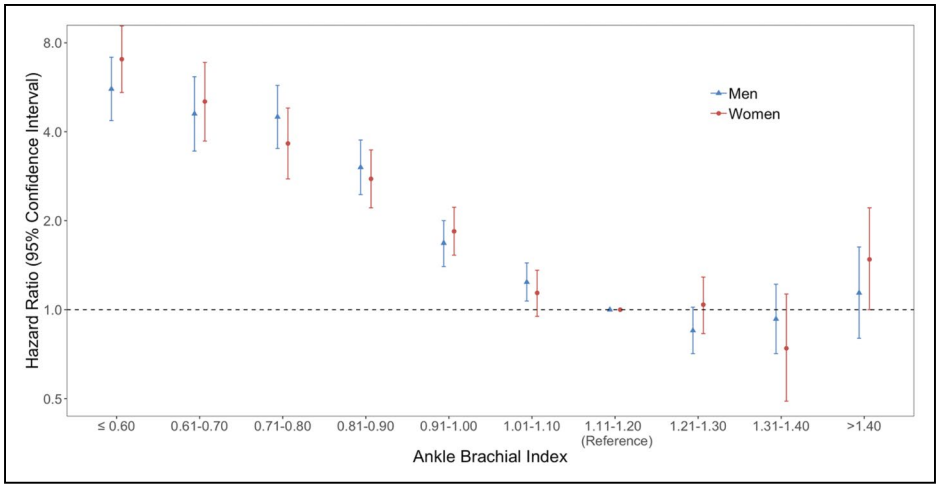

Chart 24-4. Hazard ratios of global cardiovascular mortality with 95% CI by categories, 1976 to 2000 (baseline years).
Source: Data derived from Fowkes et al.[64]

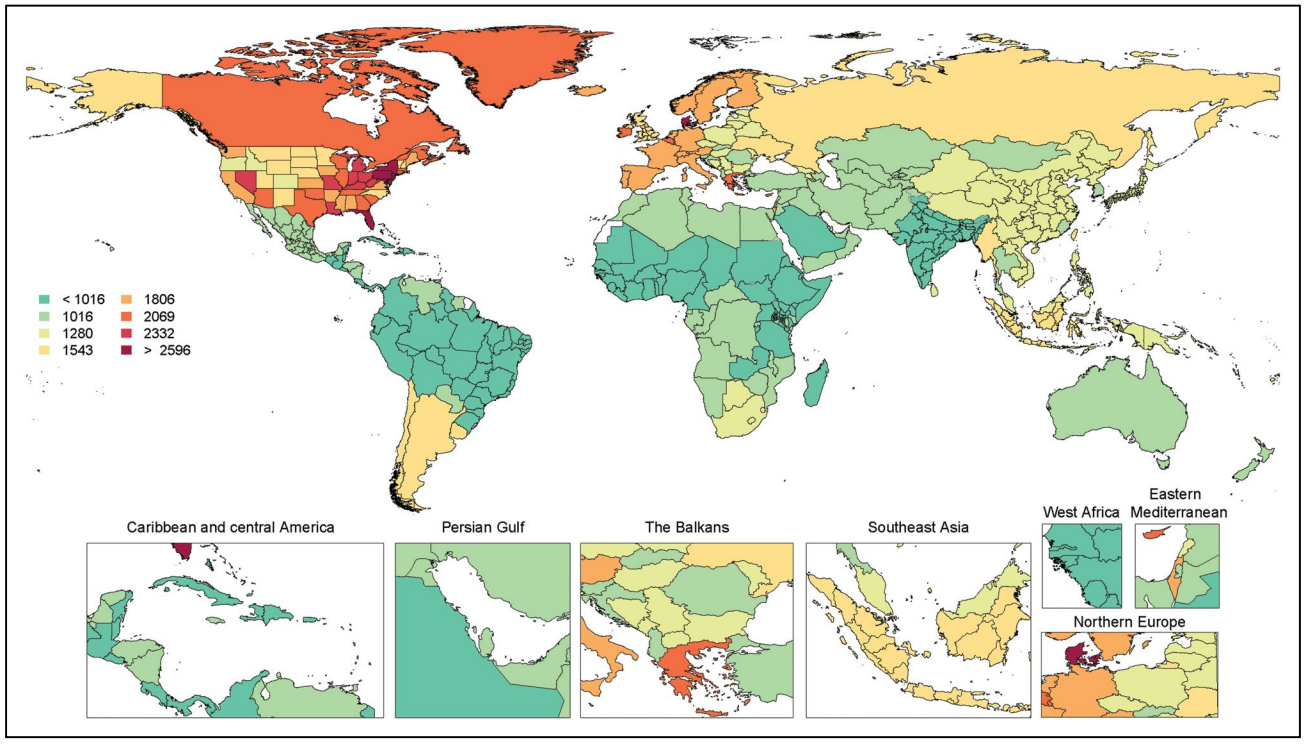

Chart 24-5. Age-standardized prevalence of peripheral artery disease per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[88] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[171]

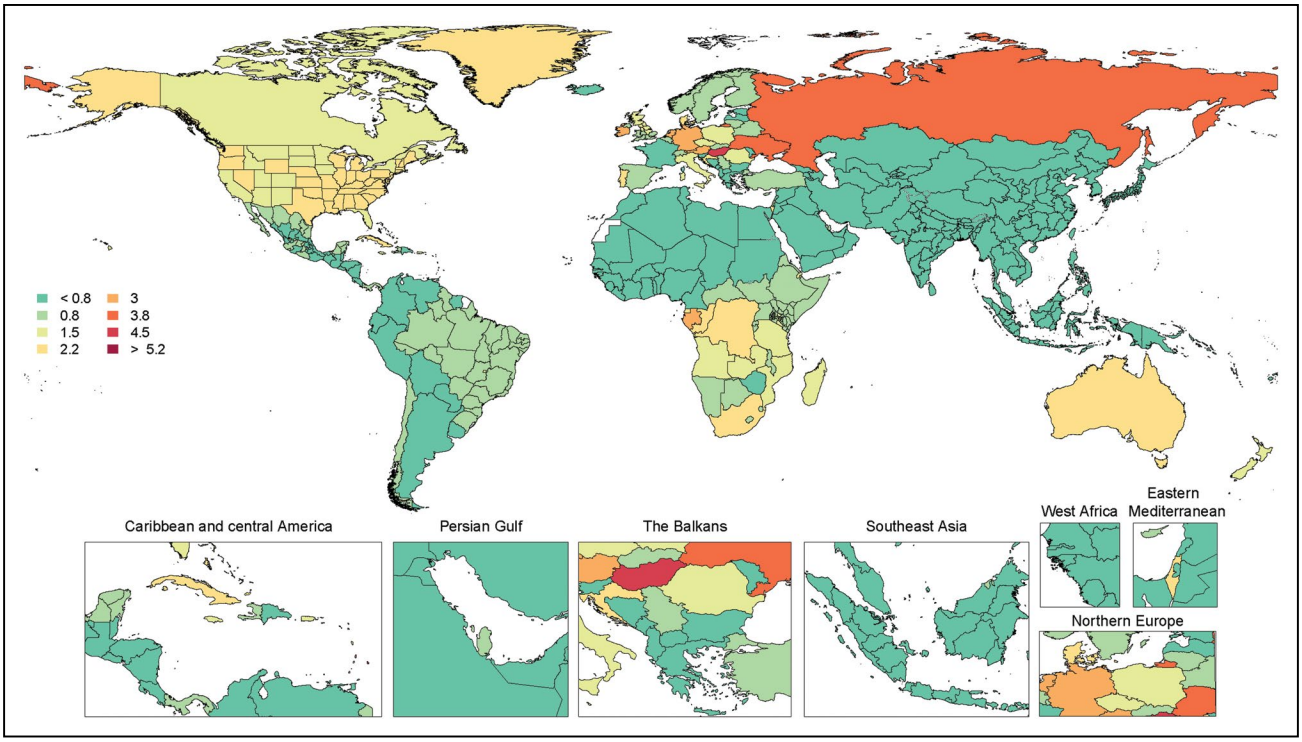

Chart 24-6. Age-standardized mortality rates of peripheral artery disease per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[88] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[171]

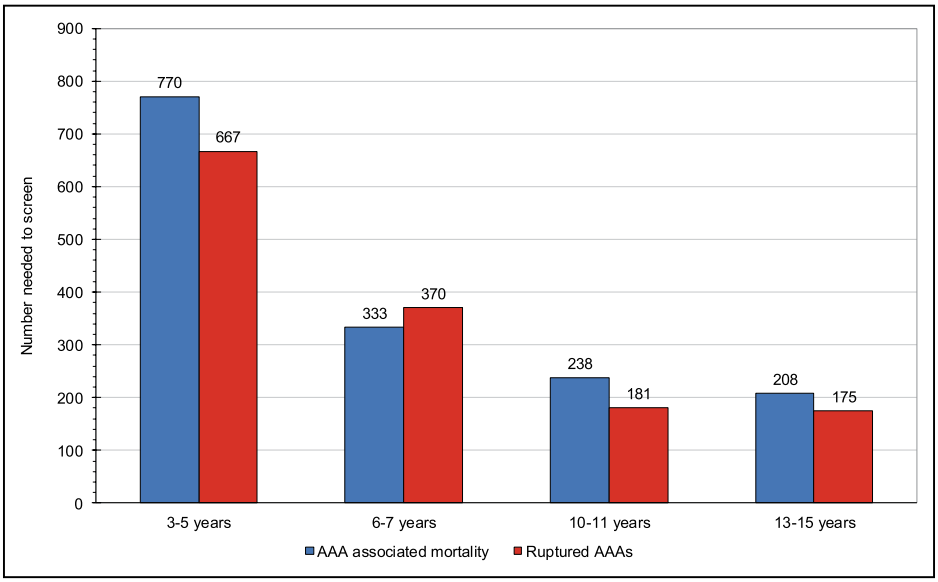

Chart 24-7. Numbers needed to screen to avoid an AAA-associated death and a ruptured AAA, 1988 to 1999 (baseline years), with average follow-up of 4 to 15 years.
Global data. AAA indicates abdominal aortic aneurysm. Source: Data derived from Eckstein et al.[122]

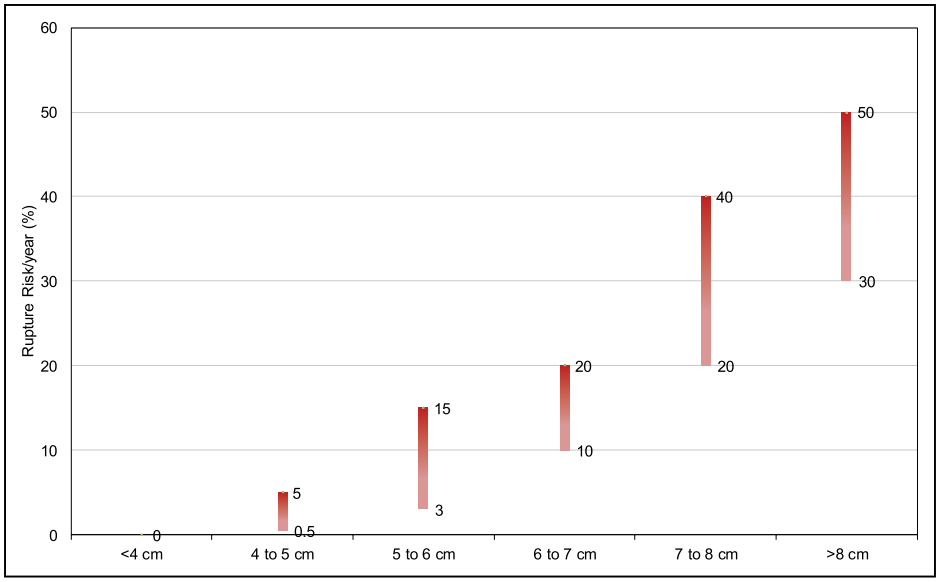

Chart 24-8. Association between diameter and minimum and maximum risk of abdominal aortic aneurysm rupture per year.
Source: Data derived from Brewster et al.[158]

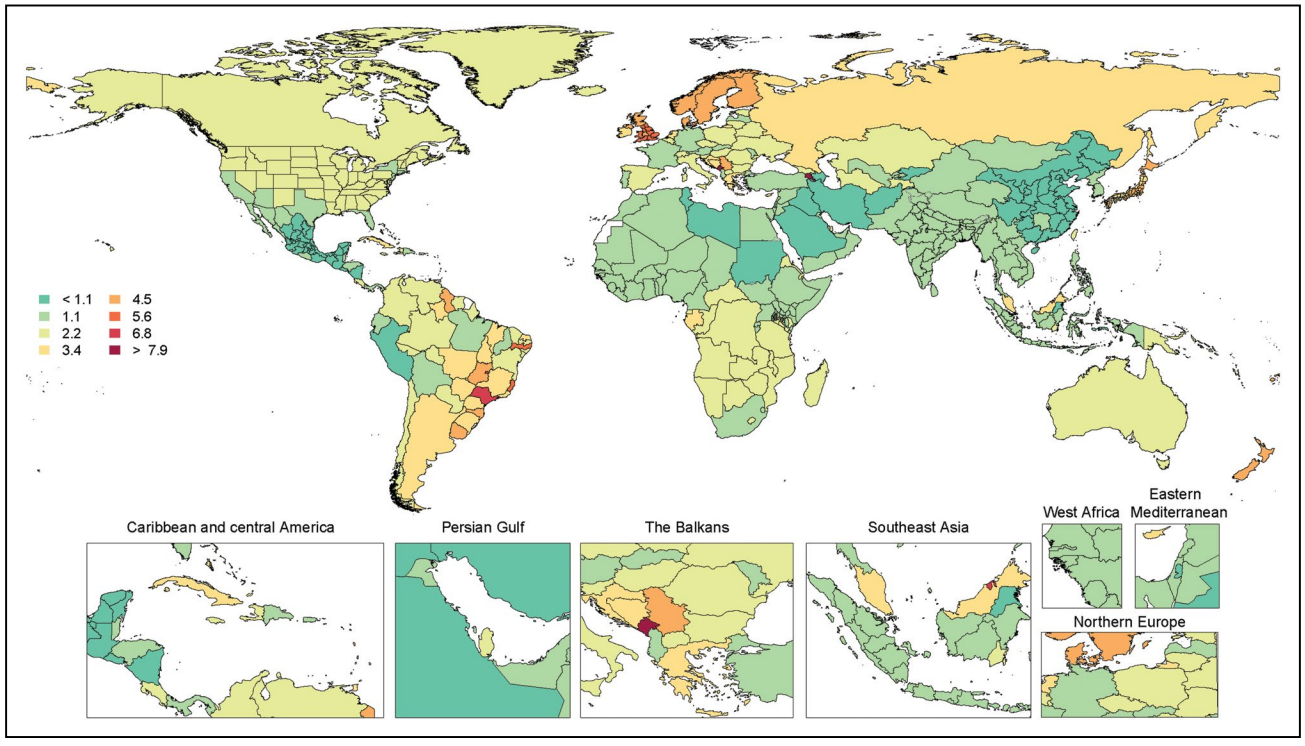

Chart 24-9. Age-standardized mortality rates of aortic aneurysm per 100 000, both sexes, 2019.
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.[88] Printed with permission. Copyright © 2020, University of Washington. Detailed results are available on the Global Burden of Disease Study website.[171]

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25. QUALITY OF CARE

See Tables 25-1 through 25-8

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The Institute of Medicine defines 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] identifying 6 specific domains for improving health care: safety, effectiveness, patient- or people-centeredness, timeliness, efficiency, and equity.

Abbreviations Used in Chapter 25

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
ACTION	Acute Coronary Treatment and Intervention Outcomes Network
AF	atrial fibrillation
AHA	American Heart Association
aHR	adjusted hazard ratio
AIS	acute ischemic stroke
AMI	acute myocardial infarction
aOR	adjusted odds ratio
ARB	angiotensin receptor blocker
ARIC	Atherosclerosis Risk in Communities study
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
CI	confidence interval
CKD	chronic kidney disease
CMS	Centers for Medicare & Medicaid Services

(*Continued*)

Abbreviations Used in Chapter 25 Continued

CPR	cardiopulmonary resuscitation
CT	computed tomography
CVD	cardiovascular disease
DOAC	direct oral anticoagulant
ECG	electrocardiogram
EMS	emergency medical services
ERR	excess readmission ratio
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
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HMO	health maintenance organization
HR	hazard ratio
HRRP	Hospital Readmissions Reduction Program
IHCA	in-hospital cardiac arrest
IQR	interquartile range
IV	intravenous
LDL-C	low-density lipoprotein cholesterol
LV	left ventricular
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MACE	major adverse cardiovascular event
MEPS	Medical Expenditure Panel Survey
MI	myocardial infarction
N/A	not available or not applicable
NCDR	National Cardiovascular Data Registry
NHANES	National Health and Nutrition Examination Survey
NIHSS	National Institutes of Health Stroke Scale
NIS	National (Nationwide) Inpatient Sample
NSTEMI	non–ST-segment–elevation myocardial infarction
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
PA	physical activity
PCI	percutaneous coronary intervention
PINNACLE	Practice Innovation and Clinical Excellence
PPO	preferred provider organization
RR	relative risk
RSMR	risk-standardized mortality rate
SD	standard deviation
SES	socioeconomic status
STEMI	ST-segment–elevation myocardial infarction
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist
tPA	tissue-type plasminogen activator
UFH	unfractionated heparin
VTE	venous thromboembolism

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Quality-of-care assessment requires the use of performance measures, explicit standards against which care delivery can be judged.[2] This differs from guidelines, which provide clinical recommendations to inform usual clinical scenarios but ultimately leave decisions to reasonable clinician discretion. Measuring performance

requires a robust process for data collection across care facilities and clinicians and data transfer, analysis, and dissemination.

Decades of clinical registries in the United States and worldwide have helped to better understand and improve quality, performance, and outcomes. Early registries focused 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 run principally by the ACC's NCDR[3] and the AHA's GWTG program.[4] Elective procedural registries were also developed by the AHA and ACC such as those for AF ablation and left atrial appendage occlusion. In addition, outpatient registries such as the ACC's PINNACLE Registry use electronic health record data transfer rather than case report form data 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 health care systems (Veterans Affairs) have also examined quality.

In the following sections, data on quality of care are presented across these 6 domains, grouped by disease or therapeutic area. When possible, data are reported from recently published literature or as standardized quality indicators drawn from quality-improvement registries with methods that 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 included to supplement performance measures data. 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.

Acute Myocardial Infarction (See Tables 25-1 through 25-3)

- The ACC's Chest Pain – MI Registry (formerly the ACTION Registry)[7] is currently the largest US-based hospital registry of inpatient AMI care (Tables 25-1 through 25-3).
- Wadhera and colleagues[5] examined a large cohort of Medicare beneficiaries with 642 105 index hospitalizations for AMI. Higher 30-day payments were associated with lower 30-day mortality after adjustment for patient characteristics and comorbidities (aOR for additional $1000 payments, 0.986 [95% CI, 0.979–0.992]; $P<0.001$).
- In propensity-matched analysis of 40 870 STEMI hospitalizations in the NIS from 2012 to 2015, Medicaid beneficiaries had lower rates of revascularization (89.1% versus 91.1%; OR, 0.80 [95% CI, 0.76–0.84]) and higher in-hospital mortality (4.9% versus 3.7%; OR, 1.35 [95% CI, 1.26–1.45]) compared with privately insured individuals ($P<0.001$ for both).[8]
- The association of state Medicaid expansion with quality of AMI care and outcomes was investigated in 55 737 low-income patients <65 years of age across 765 sites using NCDR data from January 1, 2012, to December 31, 2016.[9] During this period, Medicaid coverage increased from 7.5% to 14.4% in expansion states compared with 6.2% to 6.6% in nonexpansion states ($P<0.001$). In expansion compared with nonexpansion states, there was no change in use of procedures such as PCI for NSTEMI, and delivery of defect-free care increased to a lesser extent in expansion states. In-hospital mortality improved to a similar extent in expansion and nonexpansion states: 3.2% to 2.8% (aOR, 0.93 [95% CI, 0.77–1.12]) versus 3.3% to 3.0% (aOR, 0.85 [95% CI, 0.73–0.99]; $P_{interaction}=0.48$).
- Chatterjee and Joynt Maddox[6] examined patterns in 30-day mortality from AMI in relation to public outcome reporting from 2009 to 2015 across 2751 hospitals. They showed that 30-day mortality was highest among baseline poor performers (worst quartile in 2009 and 2010 in public reporting, before value-based payment) but improved more over time compared with other hospitals (from 18.6% in 2009 to 14.6% in 2015 [–0.74% per year; $P<0.001$] versus from 15.7% in 2009 to 14.0% in 2015 [–0.26% per year; $P<0.001$]; $P_{interaction}<0.001$).
- Examining hospitals with higher-than-expected risk-adjusted 30-day readmission rates (ERR >1) after AMI, Pandey and colleagues[10] found no association of risk-adjusted 30-day readmission rates with in-hospital quality of AMI care (aOR, 0.94 [95% CI, 0.81–1.08] per 0.1-unit increase in AMI ERR for overall defect-free care). Among 51 453 patients with 1-year outcomes data, higher AMI ERR was associated with higher all-cause readmission within 1 year of discharge; however, this association was driven largely by readmissions early after discharge and was not present in landmark analyses beginning 30 days after discharge. The AMI ERR was not associated with 1-year mortality.
- In 119 735 patients with AMI who were admitted to 1824 hospitals, Bucholz and colleagues[11] showed that patients admitted to high-performing hospitals after AMI had longer life expectancies than patients treated at low-performing hospitals. This signal appeared in the first 30 days and persisted over 17 years of follow-up. Patients treated at high-performing hospitals lived on average 0.74 to 1.14 years longer than patients treated at low-performing hospitals.
- Makam and Nguyen[12] reported that cardiac biomarker testing 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, biomarkers were tested in 35.4% of visits in this group despite the absence of ACS-related symptoms.

- The CMS and Hospital Quality Alliance started to publicly report 30-day mortality measures for AMI and HF in 2007, subsequently expanding to include 30-day readmission rates. 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%).[13]
- Mathews and colleagues[14] examined post-MI medication adherence as a hospital-level variable using data from 347 US hospitals participating in the ACTION Registry–GWTG. Postdischarge use of secondary prevention medications varied significantly across US hospitals and was inversely associated with 2-year outcomes at the hospital level.
- The study by Wadhera et al[15] spanned 2005 to 2015 and included 1.8 million hospitalizations for AMI. Evaluating outcomes in relation to announcement and implementation of the HRRP, the study evaluated 4 time periods. Periods 1 and 2 were before the HRRP: April 2005 to September 2007 and October 2007 to March 2010. Periods 3 and 4 were after HRRP announcement (April 2010–September 2012) and HRRP implementation (October 2012–March 2015). The HRRP announcement was associated with a reduction in 30-day postdischarge mortality in patients with AMI (0.18% pre-HRRP increase versus 0.08% post-HRRP announcement decrease; difference in change, –0.26%; *P*=0.01) and did not significantly change after HRRP implementation.
- A 20-year evaluation from January 1, 1995, to December 31, 2014, evaluated AMI outcomes in older adults.[16] The sample included 4 367 485 Medicare fee-for-service beneficiaries ≥65 years of age cared for at 5680 US hospitals. The rate of AMI hospitalization decreased from 914 to 566 per 100 000 beneficiary-years, with improvements in 30-day mortality from 20.0% to 12.4%, 30-day all-cause readmissions from 21.0% to 15.3%, and 1-year recurrent AMI from 7.1% to 5.1%.
- In the ARIC study, 28 732 weighted hospitalizations from 1995 to 2014 for AMI were sampled among patients 35 to 74 years of age. The proportion of AMI hospitalizations occurring in young individuals 35 to 54 years of age increased steadily over the 20-year period, from 27% in 1995 to 1999 to 32% in 2010 to 2014 (*P* for trend=0.002). Notably, the increase was seen in young females but not in young males. Compared with young males, young females with AMI were more often Black and presented with a higher comorbidity burden. Young females were less likely to have received guideline-directed medical therapies. However, 1-year all-cause mortality was comparable for females and males (HR, 1.10 [95% CI, 0.83–1.45]).[17]

Heart Failure (See Tables 25-4 and 25-5)

- Current US HF quality data are best captured by the widespread but voluntary GWTG-HF program (Tables 25-4 and 25-5).
- In a study based on the GWTG-HF program linked with Medicare data, the association between 30-day readmission rates and 3-year mortality and median survival was not significant at the hospital level. The HR for 3-year mortality comparing the top and bottom quartiles for readmission was 0.9 (95% CI, 0.90–1.01), whereas median survival time was highest for the bottom quartile.[18]
- In an evaluation of the validity of use of hospital volume as a structural metric for quality of HF care, Kumbhani and colleagues[19] examined the relationship among 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 correlated with process measures but not with 30-day outcomes and only marginally with outcomes in 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).
- In a national cohort study including 241 533 patients admitted with HF at all 591 acute care institutions in Canada, investigators found inverse associations between inpatient mortality and hospital volume, with 11.3% mortality in low-volume centers versus 17.3% in high-volume centers, with an aOR of 0.90 (95% CI, 0.80–1.00) and with a similar trend for 30-day readmissions (OR, 0.91 [95% CI, 0.85–0.97]).[20]
- Gupta and colleagues[21] examined the association of the HRRP 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 HRRP implementation.

- In a longitudinal cohort study of 48 million hospitalizations among 20 million Medicare fee-for-service patients across 3497 hospitals, Desai and colleagues[22] showed that patients at hospitals subject to penalties under the HRRP 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.
- 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 that 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%/y; $P<0.001$), but mean mortality among all other HF hospitals increased during the study period (from 10.9% to 12.0%; 0.17%/y; $P<0.001$, $P_{interaction}<0.001$).
- In a secondary analysis of the TOPCAT and HF-ACTION trials focused on patient-reported outcomes, Pokharel and colleagues[23] observed that the most recent of a series of Kansas City Cardiomyopathy Questionnaire scores was most strongly associated with subsequent death and cardiovascular hospitalization.
- Among 106 304 patients hospitalized with HF at 317 centers in the GWTG-HF registry, there was a graded inverse association between 30-day RSMR and long-term mortality (quartile 1 versus 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.[24]
- Pandey et al[25] 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.
- 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%).[13]
- Krumholz and colleagues[26] 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[27] 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.
- In a multicenter study involving 3677 patients in 24 hospitals in France, admission of acute HF episodes to a cardiology inpatient service was associated with lower in-hospital mortality (OR, 0.61 [95% CI, 0.44–0.84]) after propensity matching for individual patient characteristics.[28]
- In a Spanish study including 77 652 patients admitted with acute HF, the hospital-level aspects associated with lower in-hospital mortality were larger hospital size and the availability of a cardiology service.[29]
- In data from the GWTG-HF registry from 2007 to 2012, early follow-up visits with a specialist or primary care physician were associated with a reduction in readmissions and mortality for patients with HF. For individuals with CKD, an early visit was associated with a 35% reduction in readmissions; for those with chronic pulmonary obstructive disease,

an early pneumologist visit was associated with a 29% reduction in readmissions; whereas for those individuals with HF and diabetes, an early visit was associated with a 42% reduction in mortality. Finally, an early follow-up with the cardiologist or primary care physician for those with no comorbidities was associated with a reduction in 90-day mortality.[30]

- Home time after admission for HF may be calculated as the time spent alive outside a hospital, skilled nursing facility, or rehabilitation facility after discharge. In a study using GWTG-HF data between 2011 and 2014, home time 30 days and 1 year after discharge was highly correlated with survival and survival free from HF readmissions.[31]
- In the GWTG-HF registry, discharge to hospice after HF admissions increased from 2.0% in 2005 to 4.9% in 2014. For individuals discharged to hospice, the median postdischarge survival was 11 days, with 34.1% mortality within 3 days and a 15.0% survival after 6 months. Among those discharged to hospice, the readmission rate (4.1%) was significantly lower than for other patients with advanced HF (27.2%) or other HF in the registry (22.2%).[32]

Prevention and Risk Factor Modification (See Table 25-6)

- The National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set consists of established measures of quality of care related to CVD prevention in the United States (Table 25-6).[33]
- Pokharel and colleagues[34] examined practice-level variation in statin therapy among patients 40 to 75 years of age with diabetes 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 diabetes. Among 182 practices with ≥30 patients with diabetes, the median practice statin prescription rate was 62.3%, with no 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, suggesting that primarily practice- or clinician-related factors determined variation in statin use.
- Using data from MEPS, Salami and colleagues[35] described trends in statin use and related out-of-pocket expense from 2002 to 2013. Although statin use increased overall and among those with established ASCVD, 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.
- Hira and colleagues[36] showed in the PINNACLE Registry that among 68 808 patients receiving aspirin therapy for primary prevention, roughly 11.6% (7972) were receiving inappropriate 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).
- In an analysis of the US NHANES from 2001 to 2002 through 2015 to 2016, trends in cardiovascular risk factor control were assessed in 35 416 males and females 20 to 79 years of age. There were improvements in control of hypertension, diabetes, and dyslipidemia over time, but sex differences persisted. In 2013 to 2016, hypertension control in females versus males was observed in 30% versus 22%, diabetes control in 30% versus 20%, and dyslipidemia control in 51% versus 63%.[37]

Atrial Fibrillation

- The proportion of patients with AF receiving oral anticoagulants has increased over time,[38] with the highest uptake reported in US and European registries (90%) and the lowest in Asia (58%). However, methodological factors likely explain differences in estimates, including selection bias of both the 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%.[39]
- An analysis of data from the AHA GWTG-AF program examined prescription of oral anticoagulation therapy at discharge in 33 235 patients with a CHA_2DS_2-VASc score ≥2 hospitalized for AF at 1 of 115 sites from 2013 to 2017. Oral anticoagulation use increased over time, and there was high adherence, with 93.5% of eligible patients without contraindications being prescribed oral anticoagulation therapy for stroke prevention in AF.[40]
- An AHA GWTG-Stroke study compared outcomes with DOAC therapy (dabigatran, rivaroxaban, or apixaban) versus warfarin in 11 662 patients ≥65

years of age with AF who were anticoagulation naive and discharged from 1041 hospitals after AIS in October 2011 to December 2014. Patients discharged on DOAC therapy had more favorable outcomes compared with those discharged on warfarin, including more days at home during the first year after discharge (mean±SD, 287.2±114.7 days versus 263.0±127.3 days [adjusted difference, 15.6; 99% CI, 9.0–22.1]), fewer MACEs (aHR, 0.89 [99% CI, 0.83–0.96]), and fewer deaths (aHR, 0.88 [95% CI, 0.82–0.95]; $P<0.001$).[41]

- 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.[42]
- Treating specialty can influence therapy and outcomes. In the Veterans Health Administration, the largest integrated health care system in the United States, provision of 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]) but with an increased risk of arrhythmia-related hospitalization (HR, 1.38 [95% CI, 1.35–1.42]).[43] This finding was statistically mediated by an increase in 90-day oral anticoagulant prescription.
- In 340 127 patients with nonvalvular AF and HF in the NCDR PINNACLE-AF Registry, use of anticoagulation was lower in patients with HFpEF versus HFrEF (60.6% versus 64.2%), a difference that persisted after risk adjustment (RR, 0.93 [95% CI, 0.91–0.94]). These findings suggest that clinicians may underaccount for the risk associated with HFpEF in prescribing anticoagulation for patients with AF.[44]

Stroke (See Tables 25-3 and 25-7)

- The AHA GWTG-Stroke program (Tables 25-3 and 25-7) 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 of the quality data for acute stroke care.
- A study of 2083 patients with ischemic stroke from 82 hospitals with data in both the AVAIL registry and GWTG-Stroke found that one-third of patients with acute stroke 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 to improve poststroke functional outcomes.[45]
- 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, and 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.[46]
- 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 patients with stroke fail to use EMS.[47]
- Because of the poor survival after stroke, interventions related to improvement in end-of-life care are desirable to improve quality of care for those patients. In a study using GWTG-Stroke data, it was demonstrated that discharge from a Medicare Shared Savings Program hospital or alignment with a related organization was associated with a 16% increase in the odds of hospice enrollment (OR, 1.16 [95% CI, 1.06–1.26]) for patients with high mortality risk, with absolute rates of 20% versus 22%. However, a reduction in patient conform measures or hospice enrollment in individuals at lower mortality risk, from 9% to 8%, was noted in the same organizations (OR, 0.82 [95% CI, 0.74–0.91]).[48]
- In an analysis comparing individuals presenting with stroke at institutions participating in the GWTG-Stroke program versus institutions not enrolled in the program, those in the GWTG-Stroke program were more likely to receive intravenous tPA (RR, 3.74 [95% CI, 1.65–8.50]), to receive education on risk factors (RR, 1.54 [95% CI, 1.16–2.05]), to be evaluated for swallowing (RR, 1.25 [95% CI, 1.04–1.50]), to receive a lipid evaluation (RR, 1.18 [95% CI, 1.05–1.32]), and to be evaluated by a neurologist (RR, 1.12 [95% CI, 1.05–1.20]).[49]
- Early supported discharge with continued home rehabilitation resulted in improvement of patient-reported outcome measures in a large Swedish registry of 30 232 patients included from 2010 to 2013.

Patients in the early supported discharge group were more satisfied with rehabilitation (OR, 1.78 [95% CI, 1.17 – 2.49]), presented with a lower prevalence of dysthymia or depression (OR, 0.68 [95% CI, 0.55 – 0.84]), and showed more independence for activities such as toileting, dressing, and mobility.[50]

Implantable Defibrillators and Cardiac Resynchronization Therapy

- In a comparative-effectiveness study of single- versus dual-chamber implantable cardioverter-defibrillators using data from the ACC's Implantable Cardioverter Defibrillator Registry, Peterson and colleagues[51] 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).
- In an analysis from the GWTG-HF including >18 000 patients, the timeliness of cardiac resynchronization therapy was associated with outcomes. Implantation of cardiac resynchronization therapy during the acute HF hospitalization was associated with lower mortality (aHR, 0.63; *P*=0.048) and lower rehospitalization (aHR, 0.67; *P*<0.001).[52]

Resuscitation (See Table 25-8)

- 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 (Table 25-8). GWTG-Resuscitation is a voluntary hospital registry and performance-improvement initiative for IHCA.
- 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 IHCA has increased modestly over the past decade.[53] However, despite an overall improvement in survival, there remains lower survival in IHCA during off-hours (nights and weekends) compared with on-hours events.[54]
- Of 103 932 IHCAs 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 a reduction in this process measure could improve outcomes has not yet been demonstrated.[55]
- A composite performance score for IHCA 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.[56]
- Data from the GWTG-Resuscitation including 268 031 patients demonstrated a longitudinal reduction in time to receiving each medication, including epinephrine, vasopressin, amiodarone, lidocaine, atropine, and other medications, from 2001 to 2016 in IHCA.[57]
- Stub et al[58] 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: aOR of survival, 1.64 [95% CI, 1.13–2.38]).[58]
- In a French study of 8754 OHCAs in the greater Paris area, the neighborhoods with a higher density of ambulances were associated with a higher aOR for return of spontaneous circulation (OR, 1.31 [95% CI, 1.14–1.51]) and higher survival (aOR, 1.30 [95% CI, 1.06–1.59]).[59]

Social Determinants

- In NCDR data collected at 586 hospitals from July 2008 to December 2013, Udell et al[60] examined AMI care in 390692 patients stratified by neighborhood SES. They reported longer median arrival-to-angiography time in lower-SES neighborhoods (lowest, 8.0 hours; low, 5.5 hours; medium, 4.8 hours; high, 4.5 hours; and highest, 3.4 hours; $P<0.0001$) and a higher proportion of patients with STEMI treated with fibrinolysis (lowest, 23.1%; low, 20.2%; medium, 18.0%; high, 14.2%; and highest, 5.9%; $P<0.0001$). Although overall defect-free acute care appeared similar after controlling for covariates, patients from lower-SES neighborhoods had greater independent risk of in-hospital mortality and major bleeding and a lower quality of discharge care. These results indicate further opportunities to improve the quality of AMI care in patients from the most disadvantaged neighborhoods.
- Graham et al[61] assessed the degree to which nonrace characteristics explain survival differences between White and Black patients with AMI in a prospective registry study across 31 US hospitals from 2003 to 2008. Propensity scores associated with Black race were calculated with the use of 8 domains of patient characteristics. Among 6402 patients with AMI, 5-year mortality occurred in 28.9% of Black patients (476 of 1648) and 18.0% of White patients (856 of 4754; HR, 1.72 [95% CI, 1.54–1.92]; $P<0.001$). Controlling for propensity associated with being a Black patient, no difference in mortality by race was observed (aHR, 1.09 [95% CI, 0.93–1.26]; $P=0.37$). These findings suggest that most of the mortality rate difference between Black and White patients may be mediated by patient characteristics.
- Health care insurance coverage may influence oral anticoagulant and novel oral anticoagulant use. An analysis of 363309 patients with prevalent AF from the PINNACLE-AF outpatient registry found considerable variation in oral anticoagulant use across insurance plans.[62] Relative to Medicare, Medicaid insurance was associated with a lower odds of oral anticoagulant prescription and of novel oral anticoagulant use.
- Before HRRP implementation, there was a continuous trend in the reduction of racial disparities for MI and HF, particularly in safety-net hospitals. For example, although Black patients had 13% higher odds of readmission if treated in safety-net hospitals in 2007, this difference decreased to 5% in 2010. Data suggest that those improvements persisted after HRRP implementation.[63]
- Using NIS data, Ziaeian and colleagues[64] showed that 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 hospitalization rates that were 229% ($P_{trend}=0.141$) and 240% ($P_{trend}=0.725$) those of White individuals in 2013. Hispanic males had rates that were 32% greater in 2002, and the difference narrowed to 4% greater ($P_{trend}=0.047$) in 2013 relative to White males. For Hispanic females, the rate was 55% greater in 2002 and narrowed to 8% greater ($P_{trend}=0.004$) in 2013 relative to White females. Asian/Pacific Islander males had a 27% lower hospitalization rate in 2002, which improved to 43% lower ($P_{trend}=0.040$) in 2013 relative to White males. 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 White females.
- In a study including >15000 individuals with HFpEF, females had worse quality of life, although LV function was similar. Females also had lower mortality (aHR, 0.68 [95% CI, 0.62–0.74]) and lower risk of HF hospitalization (HR, 0.80 [95% CI, 0.72–0.89]).[65]
- In an analysis from GWTG-Stroke, Asian American individuals presented with more severe strokes, with an OR of 1.35 (95% CI, 1.30–1.40; $P<0.001$) for an NIHSS score >16, and were less likely to receive intravenous tPA (OR, 0.95 [95% CI, 0.91–0.98]; $P=0.003$). They also had higher in-hospital mortality (OR, 1.14 [95% CI, 1.09–1.19]; $P<0.001$) and more symptomatic hemorrhage after tPA (OR, 1.36 [95% CI, 1.20–1.55]; $P<0.001$) than White patients, although the mortality was in fact lower after adjustment for stroke severity (OR, 0.95 [95% CI, 0.91–0.99]; $P=0.008$). In addition, Asian American patients had better adherence to rehabilitation (OR, 1.27 [95% CI, 1.18–1.36]; $P<0.001$) and intensive statin therapy (OR, 1.14 [95% CI, 1.10–1.18]; $P<0.001$).[66]
- Data from >3000 patients from Sweden suggest that in out-of-hospital stroke care, individuals with lower SES take longer to undergo brain CT and are less likely to receive highest priority in the ambulance. They are also less likely to have their stroke recognized in the prehospital setting.[67]
- In a temporal trend evaluation of survival to discharge after IHCA across races, there was a significant increase in survival in Black (11.3% in 2000 versus 21.4% in 2014) and in White (15.8% versus 23.2%) patients, although a reduction in the difference between races was noted ($P_{interaction}<0.001$).[68]
- French data on OHCA from 123 municipalities suggest that municipalities with lower SES are associated with a higher incidence of OHCA.[69]

Table 25-1. Time Trends in the Chest Pain – MI Registry's CAD Quality-of-Care Measures, United States, 2010 to 2019

Quality-of-care measure	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019*
Aspirin within 24 h of arrival†	97	97.6	97.8	95.4	98.1	98.6	98.5	98.5	98.7	97.6
Aspirin at discharge‡	98	98.3	98.4	98.4	98.7	98.7	98.7	98.7	98.9	98.3
β-Blockers at discharge	96	96.7	97.1	97.1	97.6	97.5	97.5	97.4	97.4	96.3
Statin use at discharge	92	98.4	98.8	98.8	99.1	99.2	99.4	99.4	99.5	99.4
High-intensity statin at discharge	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	88.1
ARB/ACE inhibitor at discharge for patients with LVEF <40%	86	87.8	89.7	90.0	91.2	90.2	91.0	90.3	90.9	81.4
Adult smoking cessation advice/ counseling	98	98.4	98.4	98.4	98.6	98.0	98.1	98.0	98.2	N/A
Cardiac rehabilitation referral for patients with AMI	75	76.5	77.3	77.2	79.4	77.8	78.6	80.4	83.3	82.7

Values are percentages. ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and N/A, not available.

*Quality of Care Metrics in 2019 were updated to align with the 2017 American Heart Association (AHA)/American College of Cardiology (ACC) Clinical Performance and Quality Measures for Adults With ST-Elevation and Non-ST–Elevation Myocardial Infarction.[69a] These updated measures did not consider a "patient reason" valid for not prescribing guideline medications. Consequently, the registry saw a decline in performance for the following: aspirin within 24 hours of arrival, aspirin at discharge, β-blockers at discharge, statin use at discharge, and ARB/ACE inhibitor at discharge for patients with LVEF <40%. In addition, the registry aligned cardiac rehabilitation referral at discharge with the 2018 ACC/AHA Clinical Performance and Quality Measures for Cardiac Rehabilitation, which has more stringent criteria.[69b]

†Effective January 1, 2015, this measure was updated in the Chest Pain – MI Registry to exclude patients taking dabigatran, rivaroxaban, or apixaban (novel oral anticoagulant medications) at home.

‡Effective January 1, 2015, this measure was updated in the Chest Pain – MI Registry to exclude patients who were prescribed dabigatran, rivaroxaban, or apixaban (novel oral anticoagulant medications) at discharge.

Source: Data from the American College of Cardiology's Chest Pain – MI Registry.[7]

Table 25-2. Additional Chest Pain – MI Registry Quality-of-Care Metrics for AMI Care, United States, 2018 and 2019

Quality metrics	2018	2019
ECG within 10 min of arrival	68.6	64.0
Aspirin within 24 h of arrival	98.7	97.6
Any anticoagulant use*	96.1	N/A
Dosing errors		
UFH dose	43.2	N/A
Enoxaparin dose	9.8	N/A
Glycoprotein IIb/IIIa inhibitor dose	4.3	N/A
Discharge		
Aspirin at discharge	98.9	98.3
Prescribed statins on discharge	99.5	N/A
High-intensity statin at discharge	N/A	88.1
Adult smoking cessation advice/ counseling	98.2	N/A
Cardiac rehabilitation referral	83.3	82.7
In-hospital mortality† (95% CI)	4.12 (3.96–4.39)	N/A

Values are percentages. Data reported include data from the first quarter of 2018 to the fourth quarter of 2018. AMI indicates acute myocardial infarction; MI, myocardial infarction; N/A, not available; and UFH, unfractionated heparin.

*Includes UFH, low-molecular-weight heparin, or direct thrombin inhibitor use.

†Includes all patients.

Source: Data from the American College of Cardiology's Chest Pain – MI Registry.[7]

Table 25-3. Timely Reperfusion for AMI and Stroke, United States

Quality-of-care measure	GWTG-Stroke (for stroke) July 1, 2018–June 30, 2019	Chest Pain – MI Registry: STEMI, 2019
STEMI		
PCI within 90 min*	N/A	94.0
Stroke		
IV tPA in patients who arrived <2 h after symptom onset, treated ≤3 h	88.2†	N/A
IV tPA in patients who arrived <3.5 h after symptom onset, treated ≤4.5 h	84.2†‡	N/A
IV tPA door-to-needle time ≤60 min	84.2†	N/A

Values are percentages. AMI indicates acute myocardial infarction; GWTG, Get With The Guidelines; IV, intravenous; MI, myocardial infarction; 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 the Heart Disease and Stroke Statistics–2020 Update.

‡The "IV tPA in patients who arrived <3.5 h after symptom onset, treated ≤4.5 h" measure was changed in 2016 to include in-hospital strokes in the denominator.

Source: Chest pain data from the American College of Cardiology's Chest Pain – MI Registry.[7] Stroke data from unpublished data, GWTG-Stroke, July 1, 2018, to June 30, 2019.

Table 25-4. HF Quality-of-Care Measures, July 1, 2018, to June 30, 2019

Quality-of-care measure	AHA GWTG-HF
LVEF assessment	99.2
ARB/ACE inhibitor at discharge for patients with LVSD	93.1
Complete discharge instructions	91.6
β-Blockers at discharge for patients with LVSD, no contraindications	98.1
Anticoagulation for AF or atrial flutter, no contraindications	89.2

Values are percentages. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; AHA, American Heart Association; ARB, angiotensin receptor blocker; GWTG-HF, Get With The Guidelines–Heart Failure; LVEF, left ventricular ejection fraction; and LVSD, left ventricular systolic dysfunction.

Source: Unpublished AHA tabulation, GWTG-HF, July 1, 2018, to June 30, 2019.

Table 25-5. Quality of Care by Race/Ethnicity and Sex in the GWTG-HF Program, United States, July 1, 2018, to June 30, 2019

	Race/ethnicity			Sex	
Quality-of-care measure	White	Black	Hispanic	Males	Females
Postdischarge appointment*	84.38	82.17	83.40	83.37	83.88
Complete set of discharge instructions	91.67	91.19	92.42	92.08	91.00
Measure of LV function*	99.28	99.23	99.00	99.26	99.13
ACE inhibitor or ARB at discharge for patients with LVSD, no contraindications*	92.35	93.47	94.23	93.09	92.55
Smoking cessation counseling, current smokers	90.25	90.26	88.36	89.78	90.60
Evidence-based specific β-blockers*	94.07	95.81	94.89	94.95	94.13
β-Blockers at discharge for patients with LVSD, no contraindications	98.07	98.12	97.89	98.14	97.97
Hydralazine/nitrates at discharge for patients with LVSD, no contraindications†	0.00	32.66	21.43	36.31	26.44
Anticoagulation for AF or atrial flutter, no contraindications	89.78	86.43	88.61	89.18	89.30
Composite quality-of-care measure (using discharge instructions and β-blocker at discharge)	96.15	95.81	96.25	96.08	95.99

Values are percentages. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; 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.

Source: Unpublished American Heart Association tabulation, GWTG-HF, July 1, 2018, to June 30, 2019.

Table 25-6. National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set on CVD, Diabetes, Tobacco, Nutrition, and Lifestyle, United States, 2018

	Commercial		Medicare		Medicaid
	HMO	PPO	HMO	PPO	HMO
CVD					
β-Blocker persistence after MI*	82.1	82.8	87.1	89.1	75.9
BP control†	61.3	48.8	69.7	68.8	58.9
Statin therapy for patients with CVD	80.7	80.4	81.1	80.4	76.3
Diabetes					
HbA_{1c} testing	91.3	90.2	94.4	93.9	87.8
HbA_{1c} >9.0%	30.3	37.8	22.5	19.9	41.2
Eye examination performed	55.9	49.6	74.2	72.7	57.4
Monitoring nephropathy	90.3	88.6	95.5	94.9	89.9
BP <140/90 mm Hg	64.2	53.6	69.5	67.3	62.1
Statin therapy for patients with diabetes	63.0	61.0	74.4	71.3	62.3
Tobacco, nutrition, and lifestyle					
Advising smokers and tobacco users to quit	77.8	70.1	86.5	83.2	76.7
BMI percentile assessment in children and adolescents (3–17 y of age)	72.6	60.9	N/A	N/A	74.3
Nutrition counseling (children and adolescents [3–17 y of age])	66.5	56.0	N/A	N/A	67.3
Counseling for PA (children and adolescents [3–17 y of age])	62.3	51.0	N/A	N/A	62.4
BMI assessment for adults 18–74 y of age	82.5	71.4	96.2	96.3	86.6
PA discussion in older adults (≥65 y of age) (2016 data)	N/A		55.3	57.7	N/A
PA advice in older adults (≥65 y of age) (2016 data)	N/A		52.3	51.1	N/A

Values are percentages. BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; HbA_{1c}, hemoglobin A_{1c}; HMO, health maintenance organization; MI, myocardial infarction; N/A, not available or not applicable; PA, physical activity; and PPO, preferred provider organization.

*β-Blocker persistence: received persistent β-blocker treatment for 6 mo after hospital discharge for acute myocardial infarction.

†Adults 18 to 59 years of age with BP <140/90 mm Hg, adults 60 to 85 years of age with a diagnosis of diabetes and BP <140/90 mm Hg, and adults 60 to 85 years of age without a diagnosis of diabetes and BP <150/90 mm Hg.

Source: Healthcare Effectiveness Data and Information Set, 2018.[33]

Table 25-7. Quality of Care by Race/Ethnicity and Sex in the GWTG-Stroke Program, United States, July 1, 2018, to June 30, 2019

	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*	88.00	88.13	88.22	88.68	87.67
IV tPA in patients who arrived <3.5 h after symptom onset, treated ≤4.5 h†	83.96	83.83	85.26	84.53	83.9
IV tPA door-to-needle time ≤60 min	84.32	83.20	83.51	84.91	83.47
Thrombolytic complications: IV tPA and life-threatening, serious systemic hemorrhage	8.29	8.29	7.05	7.76	8.80
Antithrombotic agents <48 h after admission*	97.13	96.66	96.90	97.19	96.83
VTE prophylaxis by second hospital day*	99.25	99.06	99.04	99.20	99.19
Antithrombotic agents at discharge*	99.01	98.84	98.50	99.04	98.75
Anticoagulation for AF at discharge*	96.58	95.78	96.05	96.61	96.36
Therapy at discharge if LDL-C >100 mg/dL, LDL-C not measured, or on therapy at admission*	97.46	97.87	97.62	97.97	97.09
Counseling for smoking cessation*	97.36	97.02	96.56	97.27	97.17
Lifestyle changes recommended for BMI >25 kg/m^2	51.41	55.64	56.09	53.07	52.62
Composite quality-of-care measure	98.04	97.91	97.86	98.14	97.85

Values are percentages. AF indicates atrial fibrillation; BMI, body mass index; GWTG, Get With The Guidelines; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; tPA, tissue-type plasminogen activator; and VTE, venous thromboembolism.

*Indicates the 7 key achievement measures targeted in GWTG-Stroke.

†This measure was changed in 2016 to include in-hospital strokes in the denominator.

Source: Unpublished American Heart Association tabulation, GWTG-Stroke, July 1, 2018, to June 30, 2019.

Table 25-8. Quality of Care of Patients With IHCA Among GWTG-Resuscitation Hospitals, United States, 2019

	Adults	Children
Event outside critical care setting	45.4	14.3
All objective CPR data collected	98.7	99.5
End-tidal CO_2 monitoring used during arrest	13.1	35.1
Induced hypothermia after resuscitation from shockable rhythm	10.0	13.9

Values are mean percentages. CPR indicates cardiopulmonary resuscitation; GWTG, Get With The Guidelines; and IHCA, in-hospital cardiac arrest.

Source: GWTG-Resuscitation Registry unpublished data, 2019.

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26. MEDICAL PROCEDURES

See Tables 26-1 and 26-2 and Charts 26-1 through 26-4

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Trends in Operations and Procedures (See Tables 26-1 and 26-2 and Charts 26-1 and 26-2)

- The mean hospital charges for cardiovascular procedures in 2014 ranged from $43 484 for CEA to $808 770 for heart transplantations (Table 26-1).
- The trends in the numbers of 5 common cardiovascular procedures in the United States from 1993 to 2014 are presented in Chart 26-1. Of the 5 procedures, cardiac catheterization was the most common procedure for all years presented (Chart 26-1).
- Of the 10 leading diagnostic groups in the United States, the greatest number of surgical procedures were cardiovascular and obstetric procedures (Chart 26-2).
- The total number of inpatient cardiovascular operations and procedures decreased 6%, from 8 461 000 in 2004 to 7 971 000 in 2014 (Table 26-2).
- Data from the HCUP were examined by the NHLBI for trends from 1997 to 2014 for use of PCI and CABG,[1] as discussed in this chapter.

Abbreviations Used in Chapter 26

ASD	atrial septal defect
CABG	coronary artery bypass graft
CEA	carotid endarterectomy
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
STS	Society of Thoracic Surgeons
VSD	ventricular septal defect

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

Coronary Artery Bypass Grafting

- The number of inpatient discharges for CABG decreased from 683 000 in 1997 to 371 000 in 2014 (Chart 26-1).
- In 1997, the number of inpatient discharges for CABG was 484 000 for males and 199 000 for females; these numbers declined to 276 000 and 94 000, respectively, in 2014 (Table 26-2).[1]

Inpatient Cardiac Catheterization and PCI (See Tables 26-1 and 26-2 and Chart 26-1)

- 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 (Table 26-2).
- 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 26-1).
- From 2004 to 2014, the number of inpatient cardiac catheterizations decreased from 1 486 000 to 1 016 000 annually (Chart 26-1).
- In 2014, an estimated 480 000 inpatient PCI (previously referred to as percutaneous transluminal coronary angioplasty) procedures were performed in the United States (Chart 26-1).
- In 2014, ≈68% of PCI procedures were performed on males, and ≈50% were performed on people ≥65 years of age (Table 26-2).
- Inpatient hospital deaths for PCI increased from 0.8% in 2004 to 2.1% in 2014 (Table 26-1). In 2014, ≈82% of stents implanted during PCI were drug-eluting stents compared with 18% that were bare-metal stents.
- The rate of any cardiac stent procedure per 10 000 population rose by 61% from 1999 to 2006 and 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

Circulation. 2021;143:e254–e743. DOI: 10.1161/CIR.0000000000000950

States, indicate that a total of 159 869 procedures involved isolated CABG in 2016.[4]

- Among other major procedures in 2016, 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, 2015 to 2018

According to data from the STS Congenital Heart Surgery Database[5]:

- There were 123 777 congenital heart surgeries performed from January 2015 to December 2018. The in-hospital mortality rate was 2.8% during that time period. The 5 most common diagnoses were type 2 VSD (6.2%), open sternum with open skin (6.1%), HLHS (5.8%), patent ductus arteriosus (4.0%), and secundum ASD (4.0%).
- The 5 most common primary procedures were delayed sternal closure (8.3%), patch VSD repair (6.4%), mediastinal exploration (3.5%), patch ASD repair (3.2%), and complete atrioventricular canal (ASD) repair (2.8%).

Heart Transplantations (See Charts 26-3 and 26-4)

According to data from the Organ Procurement and Transplantation Network[6]:

- In 2019, 3552 heart transplantations were performed in the United States, the most ever (Chart 26-3).
- Of the recipients in 2019, 69.5% were male, 61.2% were White, 22.4% were Black, 11.2% were Hispanic, and 3.5% were Asian. Heart transplantations by recipient age are shown in Chart 26-4.
- For transplantations that occurred between 2008 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 2015 transplantations were 78.4% for males and 77.7% for females. The 1- and 5-year survival rates for White patients undergoing cardiac transplantation were 90.7% and 79.1%, respectively. For Black patients, they were 90.7% and 74.1%, respectively. For Hispanic patients, they were 90.1% and 80.0%, respectively. For Asian patients, they were 91.4% and 80.1%, respectively.
- As of March 11, 2020, 3661 patients were on the transplant waiting list for a heart transplant, and 52 patients were on the list for a heart/lung transplant.

Table 26-1. Mean Hospital Charges, In-Hospital Death Rates, and Mean Length of Stay for Various Cardiovascular Procedures, United States, 2014

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
CABG	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
CEA	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. CABG indicates coronary artery bypass graft; CEA, carotid endarterectomy; *ICD-9-CM*, *International Classification of Diseases, Clinical Modification, 9th Revision*; and PCI, percutaneous coronary intervention.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project, 2014.[1]

Table 26-2. Estimated* Inpatient Cardiovascular Operations, Procedures, and Patient Data, by Sex and Age (in Thousands), United States, 2014

Operation/procedure/patients	*ICD-9-CM* procedure codes	All	Sex		Age, y			
			Male	Female	18–44	45–64	65–84	≥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
CABG	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
CEA	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. CABG indicates coronary artery bypass graft; CEA, carotid endarterectomy; *ICD-9-CM*, *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.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project, 2014.[1]

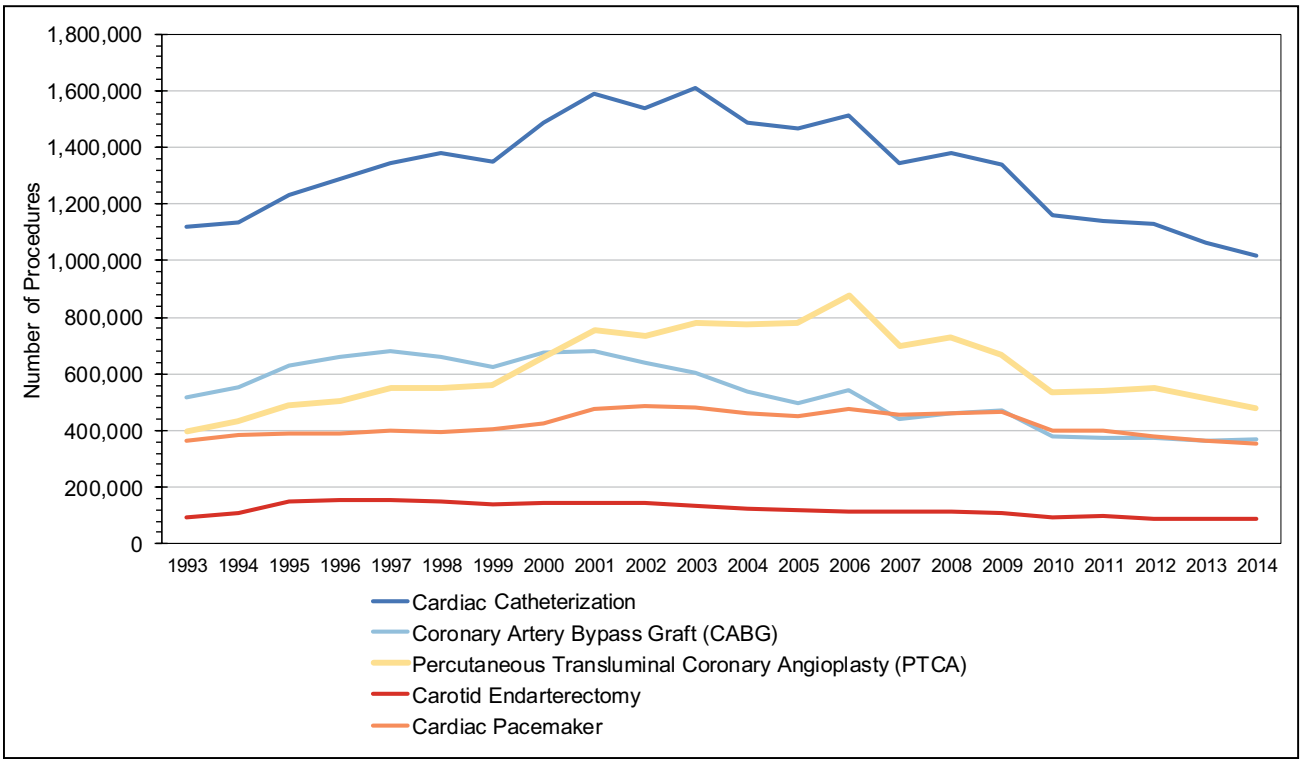

Chart 26-1. Trends in cardiovascular procedures, United States, 1993 to 2014, inpatient procedures only.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project, 1993 to 2014.[1]

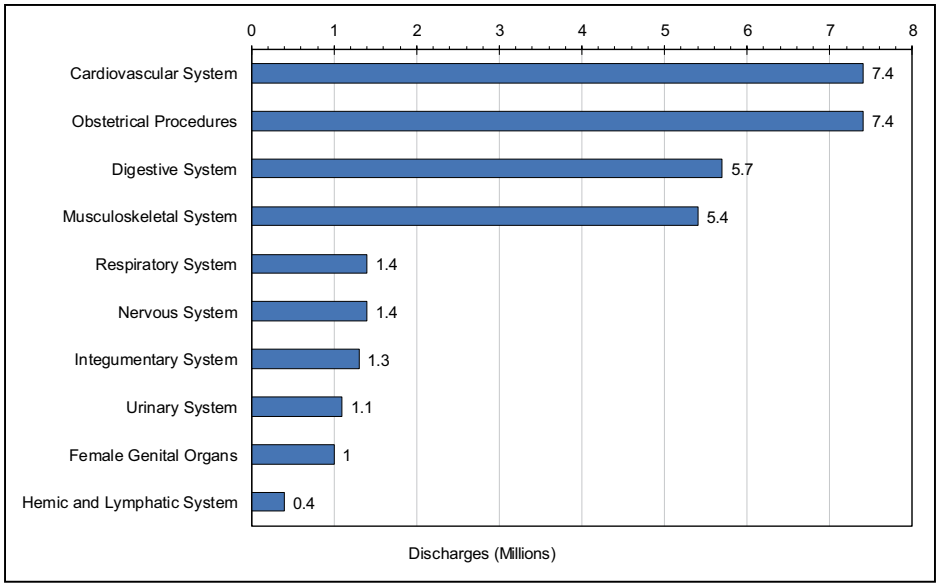

Chart 26-2. Number of surgical procedures in the 10 leading diagnostic groups, United States, 2014.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project, 2014.[1]

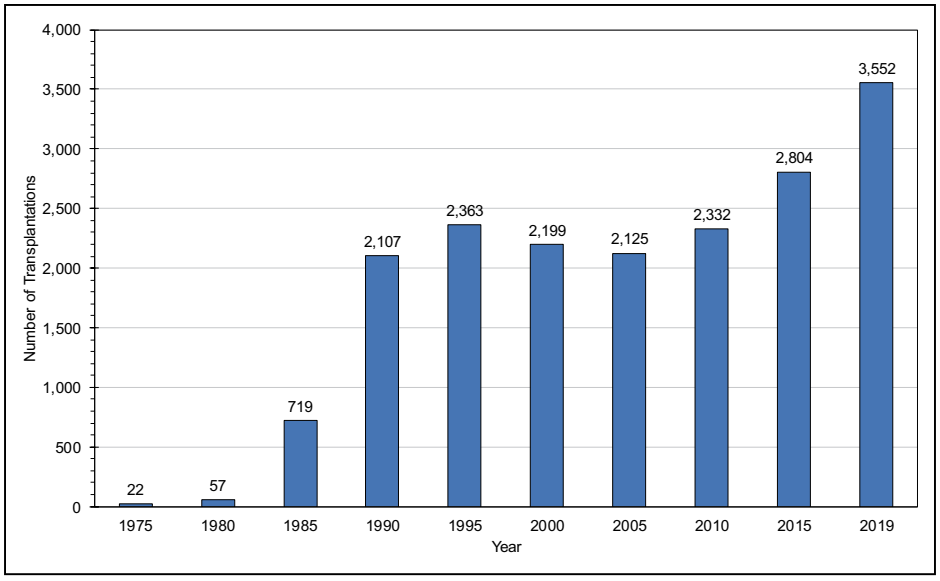

Chart 26-3. Trends in heart transplantations, United States, 1975 to 2019.
Source: Data derived from the Organ Procurement and Transplantation Network, 1975 to 2019.[6]

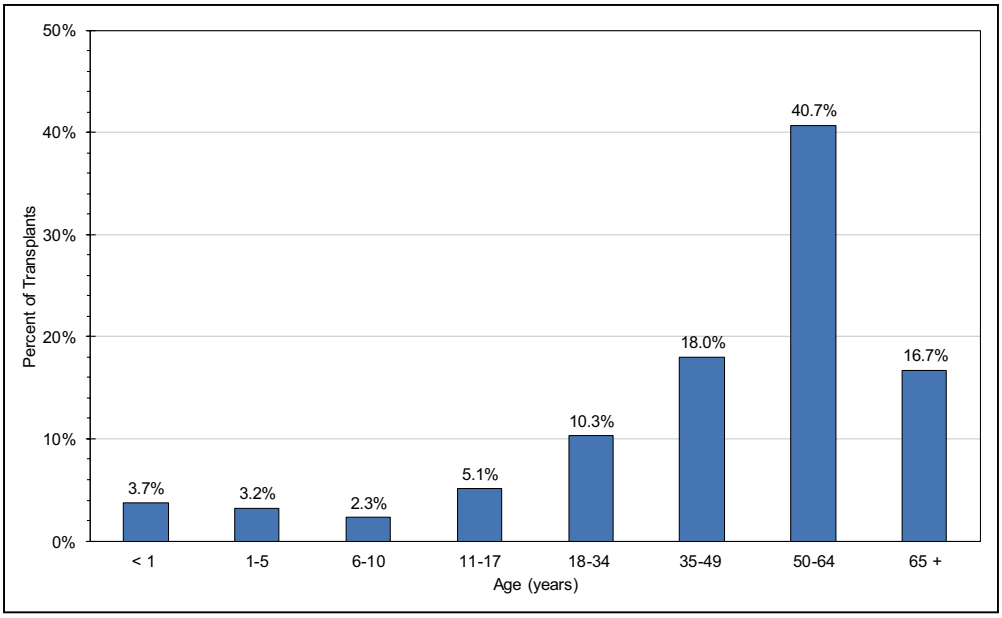

Chart 26-4. Heart transplantations by recipient age, United States, 2019.
Source: Data derived from the Organ Procurement and Transplantation Network, 2019.[6]

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27. ECONOMIC COST OF CARDIOVASCULAR DISEASE

See Tables 27-1 and 27-2 and Charts 27-1 through 27-3

Click here to return to the Table of Contents

According to data from MEPS (2016–2017),[1] the annual direct and indirect cost of CVD in the United States is an estimated $363.4 billion (Table 27-1 and Chart 27-1). This figure includes $216.0 billion in expenditures (direct costs, which include the cost of physicians and other professionals, hospital services, prescribed medications, and home health care but not the cost of nursing home care) and $147.4 billion in lost future productivity (indirect costs) attributed to premature CVD mortality in 2016 to 2017.

The direct costs for CVD for 2016 to 2017 (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 2016 to 2017 (average annual) by multiplying the number of deaths for those years attributable to CVD, in age and sex groups, by estimates of the present value of lifetime earnings for those age and sex groups as of 2016 to 2017. Mortality data are from the NVSS 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 2017 to account for the 2014 to 2017 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 illness during 2016 to 2017 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 27

COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
ED	emergency department
HD	heart disease
MEPS	Medical Expenditure Panel Survey
NCHS	National Center for Health Statistics
NVSS	National Vital Statistics System

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Most Costly Diseases (See Tables 27-1 and 27-2 and Charts 27-2 and 27-3)

CVD accounted for 13% of total US health expenditures in 2016 to 2017, more than any major diagnostic group.[1] By way of comparison, CVD total direct costs shown in Table 27-1 are higher than the 2016 to 2017 Agency for Healthcare Research and Quality estimates for cancer, which were $105.6 billion (55% for outpatient or office-based events, 25% for inpatient stays, and 14% for prescription drugs).[1]

Table 27-2 shows direct and indirect costs for CVD by sex and by 2 broad age groups. Chart 27-2 shows total direct costs for the 20 leading chronic diseases on the MEPS list. HD is the fourth most costly condition.[1]

The estimated direct costs of CVD in the United States increased from $103.5 billion in 1996 to 1997 to $216.0 billion in 2016 to 2017 (Chart 27-3).

Economic Value of CVD Risk Factor Control

Cutler et al[6] analyzed individual-level Medicare and non-Medicare health care spending captured by Medicare Current Beneficiary Survey data from 1999 to 2012. Overall, increased use of lipid-lowering, antihypertensive, and antidiabetes medications over time accounted for a combined 51% of the reduction in individual spending on CVD.

Table 27-1. Estimated Direct and Indirect Costs (in Billions of Dollars) of CVD, United States, Average Annual, 2016 to 2017

	HD*	Stroke	Hypertensive disease†	Other circulatory conditions‡	Total CVD
Direct costs§					
Hospital inpatient stays	54.9	17.1	6.4	17.8	96.2
Hospital ED visits	5.7	1.1	1.8	1.8	10.4
Hospital outpatient or office-based provider visits	21.4	2.9	13.1	10.4	47.8
Home health care	9.4	8.6	5.9	2.2	26.1
Prescribed medicines	11.8	1.1	19.9	2.7	35.5
Total expenditures	103.2	30.8	47.1	34.9	216.0
Indirect costs‖					
Lost productivity/mortality	116.4	19.0	5.3	6.7	147.4
Grand totals	219.6	49.8	52.4	41.6	363.4

Numbers do not add to total because of rounding. CVD indicates cardiovascular disease; ED, emergency department; and HD, heart disease.

*This category includes coronary HD, heart failure, part of hypertensive disease, cardiac dysrhythmias, rheumatic HD, cardiomyopathy, pulmonary HD, and other or ill-defined HDs.

†Costs attributable to hypertensive disease are limited to hypertension without HD.

‡Other circulatory conditions include arteries, veins, and lymphatics.

§ MEPS (Medical Expenditure Panel Survey) health care 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 2016 to 2017, discounted at 3%.

Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using Household Component of the MEPS for direct costs (average annual 2016 to 2017). [1] Indirect mortality costs are based on 2016 to 2017 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 2017 from change in worker compensation reported by the US Bureau of Labor Statistics.[5]

Table 27-2. Costs of CVD in Billions of Dollars by Age and Sex, United States, Average Annual, 2016 to 2017

	Total	Males	Females	Age <65 y	Age ≥65 y
All direct	216.0	118.8	97.2	92.4	123.6
Indirect: mortality only	147.4	109.8	37.6	122.6	24.8
Total	363.4	228.6	134.8	215.0	148.4

Numbers may not add to total because of rounding. CVD indicates cardiovascular disease.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey, average annual 2016 to 2017 (direct costs) and mortality data from the National Vital Statistics System and present value of lifetime earnings from the Institute for Health and Aging, University of California, San Francisco (indirect costs).[1,3]

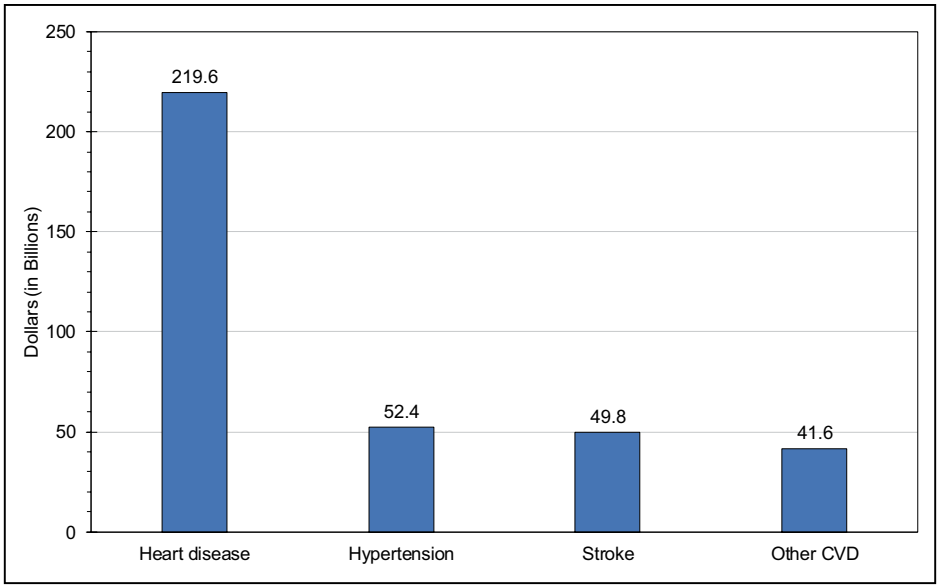

Chart 27-1. Direct and indirect costs of CVD (in billions of dollars), United States, average annual 2016 to 2017.
CVD indicates cardiovascular disease.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey data and mortality data from the National Vital Statistics System.[1,3]

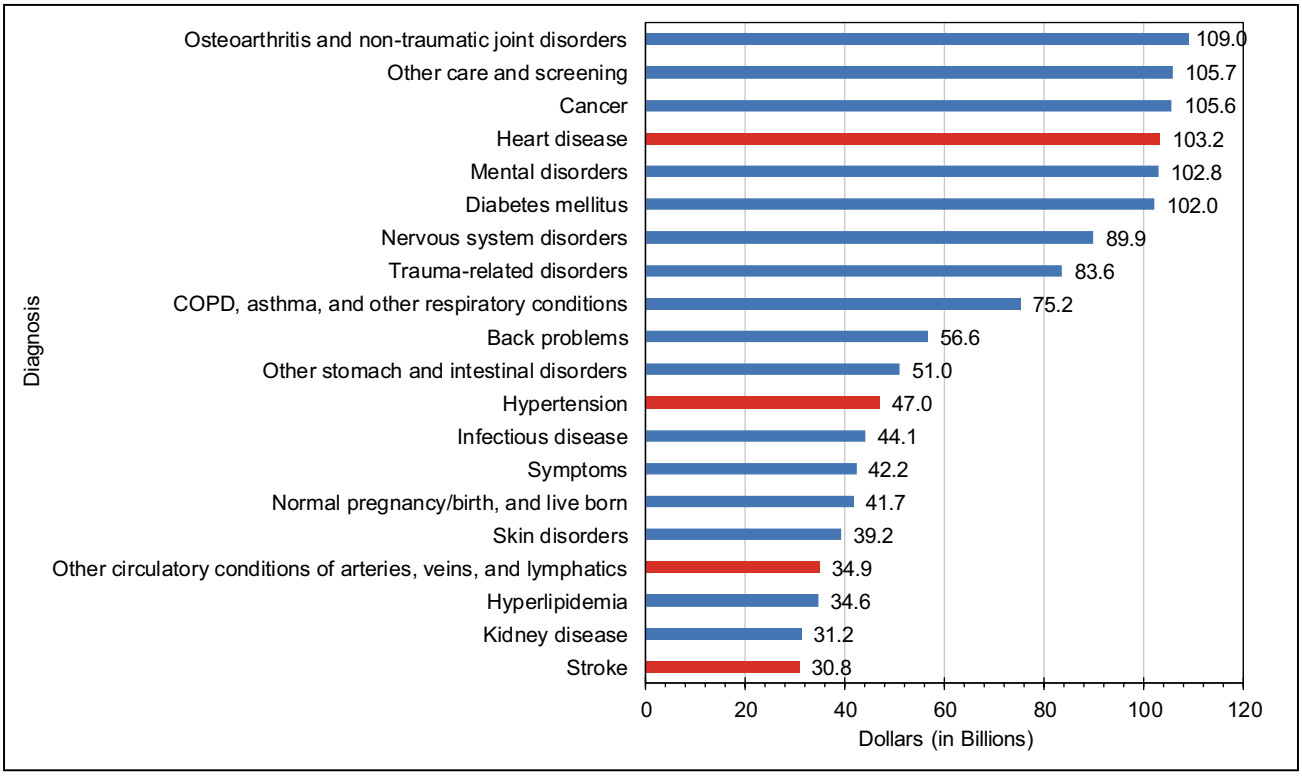

Chart 27-2. The 20 leading diagnoses for direct health expenditures, United States, average annual 2016 to 2017 (in billions of dollars).
COPD indicates chronic obstructive pulmonary disease.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey data and excluding nursing home costs.[1]

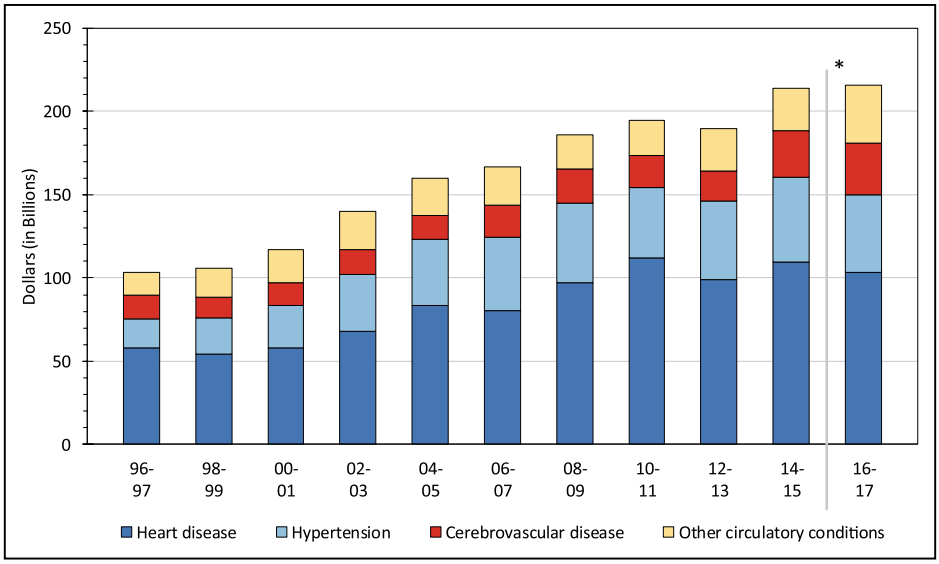

Chart 27-3. Estimated direct cost (in billions of dollars) of cardiovascular disease, United States, average annual (1996–1997 to 2016–2017).
**International Classification of Diseases*-9 coding for 1996 to 2015; *International Classification of Diseases*-10 coding for 2016 to 2017.
Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey for direct costs (average annual 1996–1997 to 2016–2017).[1]

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28. AT-A-GLANCE SUMMARY TABLES

See Tables 28-1 through 28-3

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Sources: See the following summary tables for complete details:

- Prevalence of Overweight, Obesity, and Severe Obesity in Youth and Adults, United States, 2015 to 2018—Table 6-1
- High TC and LDL-C and Low HDL-C, United States—Table 7-1
- HBP in the United States—Table 8-1
- Diabetes in the United States—Table 9-1
- CVDs in the United States—Table 14-1
- Stroke in the United States—Table 15-1
- CCDs in the United States—Table 16-1
- CHD in the United States—Table 20–1; Angina Pectoris in the United States—Table 20–2
- HF in the United States—Table 21–2

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Table 28-1. 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, 2015–2018							
Overweight and obesity, BMI ≥25.0 kg/m²†	170.1 M (71.3%)	85.3 M (74.8%)	73.9%	69.9%	84.8%	55.9%	…
Obesity, BMI ≥30.0 kg/m²†	96.4 M (40.6%)	45.4 M (39.9%)	40.7%	38.2%	44.0%	13.5%	…
Blood cholesterol							
Prevalence, years vary below							
TC ≥200 mg/dL,‡ 2015–2018	93.9 M (38.1%)	41.6 M (35.3%)	35.0%	31.0%	37.7%	38.6%	…
TC ≥240 mg/dL,‡ 2015–2018	28.0 M (11.5%)	12.2 M (10.5%)	10.1%	9.2%	12.4%	13.0%	…
LDL-C ≥130 mg/dL,‡ 2013–2016	69.6 M (28.9%)	34.8 M (30.1%)	29.4%	29.5%	33.5%	32.2%	…
HDL-C <40 mg/dL,‡ 2015–2018	41.9 M (17.2%)	31.6 M (26.6%)	26.3%	17.0%	32.0%	26.4%	…
HBP							
Prevalence, 2015–2018†	121.5 M (47.3%)	63.1 M (51.7%)	51.0%	58.3%	50.6%	51.0%	…
Mortality, 2018§‖	95 876	46 124 (48.1%)¶	31 094	9249	3764	1389#	671
Diabetes							
Prevalence, 2013–2016							
Diagnosed diabetes†	26.0 M (9.8%)	13.7 M (10.9%)	9.4%	14.7%	15.1%	12.8%	…
Undiagnosed diabetes†	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 diabetes, 2015**	1.5 M	…	…	…	…	…	…
Mortality, 2018§‖	84 946	47 551 (56.0%)¶	32 182	7802	5115	1695#	1073
Total CVD							
Prevalence, 2015–2018†	126.9 M (49.2%)	66.1 M (54.1%)	53.6%	60.1%	52.3%	52.0%	…
Mortality, 2018§‖	868 662	448 498 (51.6%)¶	344 013	56 945	30 584	12 596#	4642
Stroke							
Prevalence, 2015–2018†	7.6 M (2.7%)	3.5 M (2.6%)	2.3%	4.1%	2.4%	1.4%	…
New and recurrent strokes§	795.0 K	370.0 K (46.5%)¶	325.0 K††	45.0 K††	…	…	…
Mortality, 2018§	147 810	62 844 (42.5%)¶	45 741	8851	5260	2524#	703‡‡

(*Continued*)

Table 28-1. 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*
CHD							
Prevalence, CHD, 2015–2018†	20.1 M (7.2%)	11.0 M (8.3%)	8.7%	6.7%	6.8%	5.0%	…
Prevalence, MI, 2015–2018†	8.8 M (3.1%)	5.8 M (4.3%)	4.4%	3.9%	3.7%	2.7%	…
Prevalence, AP, 2015–2018†	11.0 M (4.1%)	5.3 M (4.2%)	4.5%	3.3%	3.5%	2.1%	…
New and recurrent MI and fatal CHD, 2005–2014§§	1.05 M	610.0 K	520.0 K††	90.0K††	…	…	…
New and recurrent MI, 2005–2014§§	805.0 K	470.0 K	…	…	…	…	…
Mortality, 2018, CHD§‖	365 744	215 032 (58.8%)¶	169 211	22 699	14 755	6084	2058
Mortality, 2018, MI§‖	108 610	64 079 (59.0%)¶	50 465	6650	4584	1835#	612
HF							
Prevalence, 2015–2018†	6.0 M (2.1%)	3.4 M (2.5%)	2.4%	3.6%	2.4%	1.9%	…
Incidence, 2014‖‖	1.0 M	495.0 K	430.0 K††	65.0 K††	…	…	…
Mortality, 2018§‖	83 616	38 487 (46.0%)¶	31 246	4354	1950	718#	300

AP indicates angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes MI, AP, or both); CVD, cardiovascular disease; 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); NH, non-Hispanic; and TC, total cholesterol.

*Both sexes.

†Age ≥20 years.

‡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.

§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 people.

**Age ≥18 years.

††Estimates include Hispanic and NH individuals. Estimates for White individuals include other non-Black races.

‡‡Estimate considered unreliable or does not meet standards of reliability or precision.

§§Age ≥35 years.

‖‖Age ≥55 years.

Table 28-2. 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, 2015–2018							
Overweight and obesity, BMI ≥25.0 kg/m²†	170.1 M (71.3%)	84.8 M (68.1%)	65.4%	78.4%	77.8%	42.9%	…
Obesity, BMI ≥30.0 kg/m²†	96.4 M (40.6%)	51.0 M (41.1%)	38.7%	55.2%	46.2%	15.9%	…
Blood cholesterol							
Prevalence, years vary below							
TC ≥200 mg/dL,‡ 2015–2018	93.9 M (38.1%)	52.3 M (40.4%)	41.8%	33.4%	37.3%	38.6%	…
TC ≥240 mg/dL,‡ 2015–2018	28.0 M (11.5%)	15.8 M (12.1%)	13.1%	10.5%	9.2%	10.3%	…
LDL-C ≥130 mg/dL,‡ 2013–2016	69.6 M (28.9%)	34.8 M (27.6%)	29.7%	23.4%	23.8%	25.1%	…
HDL-C <40 mg/dL,‡ 2015–2018	41.9 M (17.2%)	10.3 M (8.5%)	7.4%	7.9%	12.3%	6.7%	…
HBP							
Prevalence, 2015–2018†	121.5 M (47.3%)	58.4 M (42.8%)	40.5%	57.6%	40.8%	42.1%	…
Mortality, 2018§‖	95 876	49 752 (51.9%)¶	35 763	8546	3373	1629#	671
Diabetes							
Prevalence, 2013–2016							
Diagnosed diabetes†	26.0 M (9.8%)	12.3 M (8.9%)	7.3%	13.4%	14.1%	9.9%	…
Undiagnosed diabetes†	9.4 M (3.7%)	3.9 M (2.8%)	2.6%	3.3%	4.0%	2.1%	…

(*Continued*)

Table 28-2. 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*
Prediabetes†	91.8 M (37.6%)	40.1 M (31.3%)	32.2%	24.0%	31.7%	29.4%	…
Incidence, diagnosed diabetes, 2015**	1.5 M	…	…	…	…	…	…
Mortality, 2018§‖	84 946	37 395 (44.0%)¶	23 591	7463	4271	1490#	1073
Total CVD							
Prevalence, 2015–2018†	126.9 M (49.2%)	60.8 M (44.4%)	42.1%	58.8%	42.7%	42.5%	…
Mortality, 2018§‖	868 662	420 164 (48.4%)¶	326 069	53 641	25 983	11 421#	4642
Stroke							
Prevalence, 2015–2018†	7.6 M (2.7%)	4.1 M (2.8%)	2.5%	4.9%	1.7%	1.0%	…
New and recurrent strokes§	795.0 K	425.0 K (53.5%)¶	365.0 K††	60.0 K††	…	…	…
Mortality, 2018§	147 810	84 966 (57.5%)¶	64 789	10 622	5986	3043#	703‡‡
CHD							
Prevalence, CHD, 2015–2018†	20.1 M (7.2%)	9.1 M (6.2%)	6.0%	7.2%	6.4%	3.2%	…
Prevalence, MI, 2015–2018†	8.8 M (3.1%)	3.0 M (2.1%)	2.0%	2.3%	2.1%	0.7%	…
Prevalence, AP, 2015–2018†	11.0 M (4.1%)	5.7 M (4.0%)	4.0%	4.7%	4.3%	2.2%	…
New and recurrent MI and fatal CHD, 2005–2014§§	1.05 M	445.0 K	370.0 K††	75.0 K††	…	…	…
New and recurrent MI, 2005–2014§§	805.0 K	335.0 K	…	…	…	…	…
Mortality, 2018, CHD§‖	365 744	150 712 (41.2%)¶	117 194	18 118	10 105	4054	2058
Mortality, 2018, MI§‖	108 610	44 531 (41.0%)¶	34 447	5476	3099	1166#	612
HF							
Prevalence, 2015–2018†	6.0 M (2.1%)	2.6 M (1.7%)	1.4%	3.3%	1.7%	0.7%	…
Incidence, 2014‖‖	1.0 M	505.0K	425.0 K‡‡	80.0 K‡‡	…	…	…
Mortality, 2018§‖	83 616	45 129 (54.0%)¶	37 112	4961	2035	793#	300

AP indicates angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes MI, AP, or both); CVD, cardiovascular disease; 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); NH, non-Hispanic; and TC, total cholesterol.

*Both sexes.

†Age ≥20 years.

‡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.

§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 people.

**Age ≥18 years.

††Estimates include Hispanic and NH individuals. Estimates for White individuals include other non-Black races.

‡‡Estimate considered unreliable or does not meet standards of reliability or precision.

§§Age ≥35 years.

‖‖Age ≥55 years.

Table 28-3. Children, Youth, and CVD: At-a-Glance Table

Diseases and risk factors	Both sexes	Total males	Total females	NH White		NH Black		Hispanic		NH Asian	
				Males	Females	Males	Females	Males	Females	Males	Females
Overweight and obesity											
Prevalence, 2015–2018											
Overweight and obesity, 2–19 y of age*	25.9 M (35.4%)	13.1 M (35.0%)	12.8 M (35.8%)	30.9%	31.7%	31.5%	45.2%	45.9%	43.8%	26.4%	18.8%
Obesity, 2–19 y of age*	13.8 M (19.0%)	7.3 M (20.0%)	6.5 M (18.0%)	16.2%	14.2%	19.1%	27.1%	28.6%	23.4%	11.3%	7.4%
Blood cholesterol, years vary below											
Mean TC, 2015–2018, mg/dL											
6–11 y of age	157.3	157.4	157.1	156.1	157.8	157.1	156.3	157.6	154.8	167.5	159.0
12–19 y of age	155.1	152.7	157.5	151.2	158.0	155.8	157.1	152.3	153.8	155.2	165.0
Mean HDL-C, 2015–2018, mg/dL											
6–11 y of age	56.3	57.6	54.9	57.3	55.1	60.6	58.2	55.9	52.5	60.7	56.0
12–19 y of age	52.4	50.2	54.8	50.2	55.0	54.8	57.4	49.1	52.9	51.9	54.6
Mean LDL-C, 2013–2016, mg/dL											
12–19 y of age	86.7	85.6	87.8	86.7	87.9	81.7	88.4	85.0	84.2	81.7	103.3
Congenital cardiovascular defects (all age groups: children and adults)											
Mortality, 2018†‡§‖	2903	1574 (54.2%)§	1329 (45.8%)§	937	809	292	231	254	213	57	53

CVD indicates cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; M, millions; NH, non-Hispanic; and TC, total cholesterol.

*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: 42.

29. 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, to reduce the cost of health care, to improve patient safety, to decrease the number of medical errors, and to broaden access to essential services. The AHRQ sponsors and conducts research that provides evidence-based information on health care outcomes, quality, cost, use, and access. The information helps health care decision makers (patients, clinicians, health system leaders, and policy makers) make more informed decisions and improve the quality of health care services. The AHRQ conducts the Medical Expenditure Panel Survey (MEPS; ongoing).
- *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)*—The 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); certain current complications after acute myocardial infarction (I23); 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

The 2021 American Heart Association (AHA) Statistical Update uses updated language surrounding race and ethnicity to honor the people belonging to each group. Instead of referring to a specific group with only the name of their race or ethnicity, we have identified each race or ethnic classification with terms such as "Asian people," "Black adults," "Hispanic youth," "White females," or similar terms.

As the AHA continues its focus on health equity to address structural racism, we are working actively to reconcile language used in previously published data sources and studies as we compile this information in the annual Statistical Update. We strive to use the racial and ethnic terms from the original data sources or published studies (mostly from the past 5 years), which may not be as inclusive as the terms now used in 2021. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Update publications.

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).
- *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 (I30–I49, 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 all Hispanic people, as reported by government agencies or specific studies. In certain time-trend charts and tables, data for Mexican American people are shown because data are not available for all Hispanic people.
- *Hospital discharges*—The number of inpatients (including newborn infants) discharged from short-stay hospitals for whom some type of disease was the principal 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.
- *Infective endocarditis*—An infection of the inner lining (endocardium) of the heart or of the heart valves. The bacteria that most often cause endocarditis are streptococci, staphylococci, and enterococci.
- *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*—Both incidence and prevalence rates are 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, is 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; 1965–2002)
  - Cardiovascular Health Study (CHS; 1989 to…) (ongoing)
  - Atherosclerosis Risk in Communities (ARIC) study (1987 to…) (ongoing)
  - Strong Heart Study (SHS; 1989 to…) (ongoing)

— Multi-Ethnic Study of Atherosclerosis (MESA; 2000 to…) (ongoing)

- *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 White, Black, American Indian or Alaska Native, and Asian or Pacific Islander people 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)*—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).
- *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.