

AHA STATISTICAL UPDATE

# Heart Disease and Stroke Statistics—2022 Update: A Report From the American Heart Association

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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 2022 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 and an enhanced focus on social determinants of health, adverse pregnancy outcomes, vascular contributions to brain health, and the global burden of cardiovascular disease and healthy life expectancy.

**Results:** Each of the 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, policymakers, media professionals, clinicians, health care administrators, researchers, health advocates, and others seeking the best available data on these factors and conditions.

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

The 2022 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 2022. 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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## SUMMARY

Each year, the American Heart Association (AHA), in conjunction with the National Institutes of Health and other government agencies, brings together in a single document the most up-to-date statistics related to heart disease, stroke, and cardiovascular risk factors



**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.<sup>1</sup> AHA indicates American Heart Association; HDL, high-density lipoprotein cholesterol; and LDL, low-density lipoprotein cholesterol.

in the AHA's My Life Check—Life's Simple 7 (Figure),<sup>1</sup> which include core health behaviors (smoking, physical activity [PA], diet, and weight) and health factors (cholesterol, blood pressure [BP], and glucose control) that contribute to cardiovascular health (CVH). The Statistical Update represents a critical resource for the lay public, policymakers, 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 heart disease, rhythm disorders, subclinical atherosclerosis, coronary heart disease, heart failure [HF], valvular heart disease, 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, CIs for statistics reported below, and additional information.

### Cardiovascular Health (Chapter 2)

- A report pooled NHANES (National Health and Nutrition Examination Survey) 2011 to 2016 data and individual-level data from 7 US community-based cohort studies and estimated that 70.0% of major CVD events in the United States were attributable to low and moderate CVH; 2.0 million major CVD events could potentially be prevented each year if all US adults attain high CVH; and even a partial improvement in CVH scores to the moderate level among all US adults with low overall CVH could lead to a reduction of 1.2 million major CVD events annually.
- The large number of individuals in the United States who contracted severe illness because of coronavirus disease 2019 (COVID-19) resulted in a huge mortality toll. As of March 2021, the cumulative number of COVID-19 deaths in the United States was ≈545 000, which equates to ≈166 cases per 100 000 people, with higher rates of deaths occurring among US counties with metropolitan areas (≈185 deaths per 100 000), with a high percentage (>45.5%) of the population that is non-Hispanic (NH) Black (≈200 deaths per 100 000), with a high proportion (>37%) of the population that is Hispanic (≈219 deaths per 100 000), or with a high percentage (>17.3%) of the population that are living in poverty (≈211 deaths per 100 000 people).
- Because of the high COVID-19 mortality rates, life expectancy in the United States for the year 2020 has been estimated to decline with disproportionate impacts on populations with high COVID-19 mortality rates. Provisional US life expectancy estimates for January to June 2020 indicate that between 2019 and the first half of 2020, life expectancy decreased from 74.7 to 72.0 years for NH Black individuals, from 81.8 to 79.9 years for Hispanic individuals, and from 78.8 to 78.0 years for NH White individuals.

### 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 1.6% and 4.6%, respectively, in 2020.
- Although there has been a consistent decline in adult and youth cigarette use in the United States

in the past 2 decades, significant disparities persist. Substantially higher tobacco use prevalence rates are observed in American Indian/Alaska Native adults and youth and lesbian, gay, and bisexual adults.

- Over the past 9 years, there has been a sharp increase in electronic cigarette use among adolescents, increasing from 1.5% to 19.6% between 2011 and 2020; electronic cigarettes are now the most commonly used tobacco product in this demographic.

### Physical Activity and Sedentary Behavior (Chapter 4)

- According to nationwide self-reported PA (YRBSS [Youth Risk Behavior Surveillance System], 2019), the prevalence of high school students who engaged in ≥60 minutes of PA on at least 5 days of the week was 44.1% and was lower with each successive grade (from 9th [49.1%]–12th [40.0%] grades).
- From nationwide self-reported PA (NHIS, 2018), the age-adjusted proportion who reported meeting the 2018 aerobic PA guidelines for Americans was 54.2%.
- An umbrella review of 24 systematic reviews of adults ≥60 years of age concluded that those who are physically active are at a reduced risk of CVD mortality (25%–40% risk reduction), all-cause mortality (22%–35%), breast cancer (12%–17%), prostate cancer (9%–10%), and depression (17%–31%) while experiencing better quality of life, healthier aging trajectories, and improved cognitive functioning.

### Nutrition (Chapter 5)

- Data from the Nurses' Health Study (1984–2014) and Health Professionals Follow-up Study showed that daily intake of 5 servings of fruit and vegetables (versus 2 servings/d) was associated with 13% lower total mortality, 12% lower CVD mortality, 10% lower cancer mortality, and 35% lower respiratory disease mortality.
- NHANES data and meta-analyses of prospective cohort studies show that higher intakes of total fat, polyunsaturated fatty acids, and monounsaturated fatty acids are associated with lower total mortality. However, the evidence for saturated fatty acid intake as a risk or protective factor for total and CVD mortality remains controversial.
- Meta-analytic evidence from randomized clinical trials does not support vitamin D supplementation for improving cardiometabolic health in children and adolescents between 4 and 19 years of age.

## Overweight and Obesity (Chapter 6)

- From NHANES data, the overall prevalence of obesity and severe obesity in youth 2 to 19 years of age increased from 13.9% to 19.3% and 2.6% to 6.1% between 1999 to 2000 and 2017 to 2018. Over the same period, the prevalence of obesity and severe obesity increased from 14.0% to 20.5% and from 3.7% to 6.9% for males and from 13.8% to 18.0% and from 3.6% to 5.2% for females.
- From NHANES data, among adults, from 1999 to 2000 through 2017 to 2018, the prevalence of obesity among males increased from 27.5% to 43.0% and severe obesity increased from 3.1% to 6.9%. The prevalence of obesity among females increased from 33.4% to 41.9% and severe obesity from 6.2% to 11.5%.
- Significant increases in the prevalence of obesity were seen between 1999 to 2000 through 2017 to 2018 in all age-race and ethnicity groups except for NH Black males, in whom the prevalence increased from 1999 through 2006.

## High Blood Cholesterol and Other Lipids (Chapter 7)

- In 2015 to 2018, unfavorable lipid measures of low-density lipoprotein cholesterol  $\geq 130$  mg/dL were present in 6.1% of male adolescents and 3.0% of female adolescents 12 to 19 years of age, triglycerides  $\geq 130$  mg/dL were present in 9.7% of male adolescents and 6.6% of female adolescents, and high-density lipoprotein cholesterol measures  $< 40$  mg/dL were present in 18.4% of male adolescents and 7.4% of female adolescents.
- In 2015 to 2018, total cholesterol  $\geq 200$  mg/dL was present in 38.1% of adults, low-density lipoprotein cholesterol  $\geq 130$  mg/dL was present in 27.8% of adults, triglycerides  $\geq 150$  mg/dL were present in 21.1% of adults, high-density lipoprotein cholesterol  $< 40$  mg/dL was present in 17.2% of adults.

## High Blood Pressure (Chapter 8)

- From 2009 to 2019, the death rate attributable to high BP increased 34.2%, and the actual number of deaths attributable to high BP rose 65.3%.
- The 2019 age-adjusted death rate attributable primarily to high BP was 25.1 per 100 000 people. Age-adjusted death rates attributable to high BP (per 100 000 people) in 2019 were 25.7 for NH White males, 56.7 for NH Black males, 23.1 for Hispanic males, 17.4 for NH Asian/Pacific Islander males, 31.9 for NH American Indian/Alaska Native males, 20.6 for NH White females, 38.7 for NH Black females, 17.4 for Hispanic females, 14.5 for

NH Asian/Pacific Islander females, and 22.4 for NH American Indian/Alaska Native females.

- In an analysis of 18 262 adults  $\geq 18$  years of age with hypertension (defined as 140/90 mmHg) in NHANES, the estimated age-adjusted proportion with controlled BP increased from 31.8% in 1999 to 2000 to 48.5% in 2007 to 2008, remained relatively stable at 53.8% in 2013 to 2014, but declined to 43.7% in 2017 to 2018.

## Diabetes (Chapter 9)

- In NHANES 2015 to 2018, an estimated 28.2 million adults (10.4%) had diagnosed diabetes, 9.8 million adults (3.8%) had undiagnosed diabetes, and 113.6 million adults (45.8%) had prediabetes.
- In NHANES 2003 through 2016, among adults with diagnosed and undiagnosed diabetes, the proportion taking any medication increased from 58% in 2003 through 2004 to 67% in 2015 through 2016, with an increase in the use of metformin and insulin analogs and decrease in sulfonylureas, thiazolidinediones, and human insulin.
- In NHANES 1988 through 2018, among adults with newly diagnosed type 2 diabetes, there was a significant increase in the proportion of individuals with hemoglobin A1c  $< 7\%$  (59.8% for 1998–1994 and 73.7% for 2009–2018) and decreases in mean hemoglobin A1c (7.0% and 6.7%), mean BP (130.1/77.5 and 126.0/72.1 mmHg), and mean total cholesterol (219.4 and 182.4 mg/dL). The proportion with hemoglobin A1c  $< 7.0\%$ , BP  $< 140/90$  mmHg, and total cholesterol  $< 240$  mg/dL improved from 31.6% to 56.2%.

## Metabolic Syndrome (Chapter 10)

- In the HELENA study (Healthy Lifestyle in Europe by Nutrition in Adolescence) among 1037 European adolescents 12.5 to 17.5 years of age, those with mothers with low education showed a higher metabolic syndrome (MetS) risk score ( $\beta$  estimate, 0.54) compared with those with highly educated mothers. Adolescents who accumulated  $> 3$  disadvantages (defined as parents with low education, low family affluence, migrant origin, unemployed parents, or nontraditional families) had a higher MetS risk score compared with those who did not experience disadvantage ( $\beta$  estimate, 0.69).
- In HCHS/SOL (Hispanic Community Health Study/Study of Latinos), socioeconomic status was inversely associated with prevalent MetS among Hispanic/Latino adults of diverse ancestry groups. Higher income and education and full-time employment status versus unemployed status were associated with a 4%, 3%, and 24% decreased odds



of having MetS, respectively. The association with income was significant only among females and those with current health insurance.

- In combined analysis from ARIC (Atherosclerosis Risk in Communities) and JHS (Jackson Heart Study), among 13 141 White and Black individuals with a mean follow-up of 18.6 years, risk of ischemic stroke increased consistently with MetS severity z score (hazard ratio [HR], 1.75) for those above the 75th percentile compared with those below the 25th percentile. Risk was highest for White females (HR, 2.63), although without significant interaction by sex and race.

### 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.
- Among 2304 female-newborn dyads in the multinational HAPO study (Hyperglycemia and Adverse Pregnancy Outcome), lower CVH (based on 5 metrics: body mass index, BP, cholesterol, glucose, and smoking) at 28 weeks' gestation was associated with a higher risk of preeclampsia; adjusted relative risks were 3.13, 5.34, and 9.30 for females with  $\geq 1$  intermediate, 1 poor, or  $\geq 2$  poor (versus all ideal) CVH metrics during pregnancy, respectively.
- In analyses of Swedish national birth register data ( $>2$  million– $>4$  million individuals), gestational age at birth was inversely associated with the risks for type 1 diabetes, type 2 diabetes, hypertension, and lipid disorders among individuals born preterm versus term.

### Kidney Disease (Chapter 12)

- Overall prevalence of chronic kidney disease (estimated glomerular filtration rate  $<60$  mL $\cdot$ min $^{-1}$  $\cdot$ 1.73 m $^{-2}$  or albumin-to-creatinine ratio  $\geq 30$  mg/g) was 14.9% (2015–2018).
- Age-, race-, and sex-adjusted prevalence of end-stage renal disease in the United States was 2242 per million people (in 2018) with highest rates among Black adults followed by American Indian/Alaska Native adults, Asian adults, and White adults.
- Medicare spent \$81 billion caring for people with chronic kidney disease and \$49.2 billion on those with end-stage renal disease in 2018.

### Sleep (Chapter 13)

- In data from the 2014 BRFSS (Behavioral Risk Factor Surveillance System), 11.8% of people

reported a sleep duration  $\leq 5$  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  $\geq 10$  hours. Overall, 65.2% met the recommended sleep duration of  $\geq 7$  hours.

- Analysis of the UK Biobank study (N=468941) found that participants who reported short sleep ( $<7$  h/d) or long sleep ( $>9$  h/d) had an increased risk of incident HF compared with normal sleepers (7–9 h/d). In males, the adjusted HR was 1.24 for short sleep and 2.48 for long sleep. In females, the adjusted HR was 1.39 for short sleep and 1.99 for long sleep.
- 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).

### Total Cardiovascular Diseases (Chapter 14)

- In the Cardiovascular Lifetime Risk Pooling Project among 30 447 participants from 7 US cohort studies, among individuals  $\geq 60$  years of age with low CVH, the 35-year risk of CVD was highest in White males (65.5%), followed by White females (57.1%), Black females (51.9%), and Black males (48.4%). These estimated risks accounted for competing risks of death caused by non-CVD causes.
- In a meta-analysis of 14 studies that focused on CVD among individuals diagnosed with COVID-19, preexisting CVD had a relative risk of 2.25 for death resulting from COVID-19.
- In 2020,  $\approx 19$  million deaths were attributed to CVD globally, which amounted to an increase of 18.7% from 2010.

### Stroke (Cerebrovascular Diseases) (Chapter 15)

- In the Greater Cincinnati Northern Kentucky Stroke Study, sex-specific ischemic stroke incidence rates declined significantly between 1993 to 1994 and 2015 for both males and females. In males, there was a decline from 282 to 211 per 100 000. In females, the decline was from 229 to 174 per 100 000. This trend was not observed for intracerebral hemorrhage or subarachnoid hemorrhage.
- In the Northern Manhattan Study, among 3298 stroke-free participants followed up through 2019, Black and Hispanic females  $\geq 70$  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; Hispanic females/White females: HR, 1.77). This increased risk was not present among elderly Black or Hispanic males compared with White males.

- Among adults treated for hypertension in an ambulatory setting in the United States, tight BP control (<130 mmHg) was associated with a 42% lower incidence of stroke compared with standard BP control (130–139 mmHg).

### Brain Health (Chapter 16)

- A systematic analysis of data from the GBD study (Global Burden of Disease) showed that, in 2017, Alzheimer disease/Alzheimer disease and related dementia was the fourth most prevalent neurological disorder in the United States (2.9 million people). Among neurological disorders, Alzheimer disease/Alzheimer disease and related dementia was the leading cause of mortality in the United States (38 deaths per 100 000 population per year) ahead of stroke.
- In 2017, Alzheimer disease/Alzheimer disease and related dementia had the fifth leading incidence rate of neurological disorders in the United States according to the GBD study data. The US age-standardized incidence rate of Alzheimer disease/Alzheimer disease and related dementia was 85 cases per 100 000 people).
- In a meta-analysis of 12 randomized controlled trials (>92 000 participants; mean age, 69 years; 42% females), BP lowering with antihypertensive agents, compared with control, was associated with a lower risk of incident dementia or cognitive impairment (7.0% versus 7.5% of patients over a mean trial follow-up of 4.1 years; odds ratio [OR], 0.93; absolute risk reduction, 0.39%).

### Congenital Cardiovascular Defects and Kawasaki Disease (Chapter 17)

- The 2017 all-age prevalence of congenital cardiovascular defects in the United States was estimated at 466 566 individuals, with 279 320 (60%) of these under the age of <20 years of age. The 2017 global prevalence of congenital cardiovascular defects was estimated at 157 per 100 000 people, with the highest prevalence estimates in countries with a low sustainable development index (238 per 100 000 people) and the lowest in those with a high-middle or high sustainable development index (112 and 135 per 100 000 people, respectively).
- Congenital cardiovascular defects appear to be more common among infants born to mothers with low socioeconomic status. In Ontario, mothers who lived in the lowest-income neighborhoods had higher risk of having an infant with a congenital cardiovascular defect compared with mothers living in the highest-income neighborhoods (OR, 1.29). Furthermore, this discrepancy between low and

high was also found across measures of neighborhood education (OR, 1.34) and employment rate (OR, 1.18).

- Since May 2020, the Centers for Disease Control and Prevention has been tracking reports of multisystem inflammatory syndrome in children. As of June 28, 2021, 4196 cases and 37 attributable deaths (0.89%) have been reported. Median age of cases was 9 years; 62% of cases have occurred in children who are Hispanic or Latino (1246 cases) or Black (1175 cases); 99% tested positive for severe acute respiratory syndrome coronavirus 2 (*reverse transcription–polymerase chain reaction*, serology, or antigen test); and 60% of reported patients were male.

### Disorders of Heart Rhythm (Chapter 18)

- A systematic review and meta-analysis of 18 published studies reported short-term and long-term associations of air pollution with atrial fibrillation (AF). For 10-mg/m<sup>3</sup> increases in PM<sub>2.5</sub> and PM<sub>10</sub> concentrations, the OR of AF was 1.01 and 1.03, respectively. The corresponding ORs for long-term exposure were 1.07 for PM<sub>2.5</sub> and 1.03 for PM<sub>10</sub>. SO<sub>2</sub> and NO<sub>2</sub> were also associated with AF in the short term: ORs for 10-ppb increments were 1.05 and 1.03, respectively.
- A multicenter, open-label, randomized trial evaluated a 2-week continuous electrocardiographic patch and an automated home BP machine with oscillometric AF screening capability for the detection of AF compared with usual care over a 6-month period in participants ≥75 years of age with hypertension. AF detection was 5.3% in the screening group compared with 0.5% in the control group (risk difference, 4.8%; number needed to screen, 21). By 6 months, anticoagulation was more frequently prescribed in the intervention group (4.1% versus 0.9%; risk difference, 3.2%).
- AF has been associated with increased mortality in patients with COVID-19. A meta-analysis of studies published in 2020, including 23 studies and 108 745 patients with COVID-19, showed that AF was associated with increased mortality (pooled effect size, 1.14).

### Sudden Cardiac Arrest, Ventricular Arrhythmias, and Inherited Channelopathies (Chapter 19)

- There was a 119% increase in out-of-hospital cardiac arrest during the pandemic compared with earlier control periods in a meta-analysis in 10 countries. For the patients with known outcomes (n=10 992), mortality was 85% compared with 62% for the control periods.

- Coinciding with timing of the pandemic in the United States, CARES Registry (Cardiac Arrest Registry to Enhance Survival) data indicate increased delays to initiation of cardiopulmonary resuscitation for out-of-hospital cardiac arrest and reduced survival after out-of-hospital cardiac arrest. Accompanying these effects were reductions in the frequency of shockable rhythms, out-of-hospital cardiac arrest in public locations, and bystander automated external defibrillator use, whereas field termination of resuscitation efforts increased. There was no significant alteration in frequency of bystander cardiopulmonary resuscitation.
- Survival to hospital discharge was 22.4% of 33 874 adult pulseless in-hospital cardiac arrests at 328 hospitals in Get With The Guidelines 2020 data. Among survivors, 79.5% had good functional status (Cerebral Performance Category 1 or 2) at hospital discharge.

### Subclinical Atherosclerosis (Chapter 20)

- In 3116 MESA (Multi-Ethnic Study of Atherosclerosis) participants (58±9 years of age, 63% females) who had no detectable coronary artery calcification (CAC) at baseline and were followed up over 10 years, CAC score >0, CAC score >10, and CAC score >100 were seen in 53%, 36%, and 8% of individuals at 10 years, respectively.
- In a study with 12.3 years of mean follow-up, cancer-related mortality was 1.55-fold higher in individuals who had a CAC score ≥1000 at baseline compared with those who had a CAC score of 0 at baseline, after adjustment for age, sex, and risk factors.
- In 9388 US and Finnish individuals with longitudinal measurement of CVD risk factors and carotid intima-media thickness, CVH declined from childhood to adulthood and was associated with thickening of the intima-media thickness.

### Coronary Heart Disease, Acute Coronary Syndrome, and Angina Pectoris (Chapter 21)

- In a European registry of high-volume percutaneous coronary intervention centers, the COVID-19 pandemic was associated with a significant increase in door-to-balloon and total ischemia times. Door-to-balloon time >30 minutes was 57.0% in the period of March to April 2020 compared with 52.9% in March to April 2019 ( $P=0.003$ ), whereas total ischemia time >12 hours was 11.7% in the 2020 period compared with 9.1% in 2019 ( $P=0.001$ ).
- In a retrospective cohort study of Medicare fee-for-service patients (N=453 783) who were

diagnosed with coronary artery disease, patients that received care at the most socioeconomically deprived practices had higher odds of being admitted for unstable angina (adjusted OR, 1.46) and higher 30-day mortality rates after acute myocardial infarction (adjusted OR, 1.31). After additional adjustment for patient-level area deprivation index, these associations were attenuated (unstable angina adjusted OR, 1.20; 30-day mortality after myocardial infarction adjusted OR, 1.31).

- A pooled analysis of 21 randomized percutaneous coronary intervention trials including 32 877 patients (28% females) found that female sex was an independent risk factor for major adverse cardiovascular events (HR, 1.14) and ischemia-driven target lesion vascularization (HR, 1.23) but not of all-cause or cardiovascular mortality (HR, 0.91 and 0.97, respectively).

### Cardiomyopathy and Heart Failure (Chapter 22)

- The lifetime risk of HF remains high, with variation across racial and ethnic groups ranging from 20% to 45% after 45 years of age.
- Secular trends show that the incidence of HF with preserved ejection fraction is increasing and, in contrast, the incidence of HF with reduced ejection fraction is decreasing, whereas both HF subtypes have similar all-cause mortality rates.
- Contemporary HF with reduced ejection fraction guideline-directed medical therapy is estimated to reduce the hazard of cardiovascular death or HF hospitalization by up to 62% compared with limited conventional therapy.

### Valvular Diseases (Chapter 23)

- 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.
- The pooled prevalence of all aortic stenosis in the elderly is 12.4%, and the prevalence of severe aortic stenosis is 3.4%. The annual volume of transcatheter aortic valve replacement (TAVR) has increased each year since 2011. After the US Food and Drug Administration approval of TAVR for low-risk patients in 2019, the TAVR volume exceeded all forms of surgical aortic valve replacement ( $n=72\,991$  versus  $n=57\,626$ ). From 2011 through 2018, extreme- and high-risk patients remained the largest cohort undergoing TAVR, but in 2019, the intermediate-risk cohort was the largest, and low-risk patients with a median 75 years of age increased to 8395, making up 11.5% of all patients undergoing TAVR.

## Venous Thromboembolism (Deep Vein Thrombosis and Pulmonary Embolism), Chronic Venous Insufficiency, Pulmonary Hypertension (Chapter 24)

- In 2018, there were an estimated  $\approx 1\,015\,000$  total venous thromboembolism cases in the United States.
- In addition, 2019 data show that 37 571 deaths (any mention) resulted from pulmonary embolism and 27 574 deaths (any mention) resulted from pulmonary hypertension.
- In the COVID-19 scenario, the incidence of venous thromboembolism was up to 31% in hospitalized patients. Among them, those who were admitted to the intensive care unit had a 2- to 3-fold greater risk of developing deep vein thrombosis or pulmonary embolism.

## Peripheral Artery Disease and Aortic Diseases (Chapter 25)

- From 2011 to 2019, the global prevalence of peripheral artery disease was 5.56% with a higher prevalence in high- compared with low- to middle-income countries (7.37% versus 5.09%, respectively). In 2015, it was estimated that 236.62 million people  $\geq 25$  years of age were living with peripheral artery disease.
- In an analysis of 393 017 patients who underwent lower extremity arterial revascularization, 50 750 (12.9%) had at least 1 subsequent hospitalization for major adverse limb events.
- In a population-based screening study of 14 989 participants 60 to 74 years of age, male sex (OR, 1.9), hypertension (OR, 1.8), and family history (OR, 1.6) were associated with a heightened risk of ascending thoracic aortic aneurysm. Diabetes was associated with a lower risk (OR, 0.8).

## Quality of Care (Chapter 26)

- Compared with 2019, a lower proportion of cases received bystander cardiopulmonary resuscitation in 2020, and use of automated external defibrillators was lower. There were also longer emergency medical services response times and lower survival to hospital discharge. Those are likely related to the COVID-19 pandemic.
- In a Get With The Guidelines—HF study, inclusion in Medicare Advantage led to a higher proportion of discharge to home with no difference in mortality compared with fee-for-service programs.
- In data from the PINNACLE Registry (Practice Innovation and Clinical Excellence), only about two-thirds of the individuals were treated with appropriate statin therapy as recommended in the American

College of Cardiology/AHA guidelines. In addition, higher income was associated with higher likelihood of appropriate statin therapy.

## Medical Procedures (Chapter 27)

- As per the Society of Thoracic Surgeons/American College of Cardiology transcatheter valve therapy registry data, TAVR volumes continue to grow, with 13 723 TAVR procedures in 2011 to 2013 and 72 991 TAVR procedures in 2019. In 2019, 669 sites were performing TAVR. In 2019, TAVR volumes ( $n=72\,991$ ) exceeded the volumes for all forms of surgical aortic valve replacement ( $n=57\,626$ ).
- In 2020, 3658 heart transplantations were performed in the United States, the most ever. The highest number of heart transplantations were performed in the states of California (496), Texas (302), Florida (288), and New York (250).
- A global survey of 909 inpatient and outpatient centers performing cardiovascular diagnostic procedures in 108 countries compared procedural volumes for common cardiovascular diagnostic procedures between March 2019 and March 2020/April 2020. This survey indicated that cardiovascular diagnostic procedures decreased by 64% from March 2019 to April 2020.

## Economic Cost of Cardiovascular Disease (Chapter 28)

- The average annual direct and indirect cost of CVD in the United States was an estimated \$378.0 billion in 2017 to 2018.
- The estimated direct costs of CVD in the United States increased from \$103.5 billion in 1996 to 1997 to \$226.2 billion in 2017 to 2018.
- By event type, hospital inpatient stays accounted for the highest direct cost (\$99.6 billion) in 2017 to 2018 in the United States.

## Conclusions

The AHA, through its Statistics Committee, continuously monitors and evaluates sources of data on heart disease and stroke in the United States to provide the most current information available in the Statistical Update. The 2022 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.

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ARTICLE INFORMATION

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\*Modest.

†Significant.

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1. American Heart Association. My Life Check—Life's Simple 7. Accessed July 28, 2021. <https://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check--lifes-simple-7>



## ABBREVIATIONS TABLE

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6MWD	6-minute walk distance
AAA	abdominal aortic aneurysm
ABI	ankle-brachial index
ACC	American College of Cardiology
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACR	albumin-to-creatinine ratio
ACS	acute coronary syndrome
ACTION	Acute Coronary Treatment and Intervention Outcomes Network
AD	Alzheimer disease
ADAMS	Aging, Demographics, and Memory Study
ADRD	Alzheimer disease and related dementia
AF	atrial fibrillation or atriofibrillation
AGES	Age, Gene/Environment Susceptibility
AHA	American Heart Association
AHEI	Alternative Health Eating Index
AHI	apnea-hypopnea index
aHR	adjusted hazard ratio
AHS-2	Adventist Health Study 2
AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes
aIRR	adjusted incidence rate ratio
AIS	acute ischemic stroke
AMI	acute myocardial infarction
ANOVA	analysis of variance
ANP	atrial natriuretic peptide
aOR	adjusted odds ratio
AP	angina pectoris
APO	adverse pregnancy outcome
ARGEN-IAM-ST	Pilot Study on ST Elevation Acute Myocardial Infarction
ARIC	Atherosclerosis Risk in Communities
ARIC-NCS	Atherosclerosis Risk in Communities Neurocognitive Study
ARIC-PET	Atherosclerosis Risk in Communities—Positron Emission Tomography
aRR	adjusted relative risk
ARVC	arrhythmogenic right ventricular cardiomyopathy
ASB	artificially sweetened beverage
ASCVD	atherosclerotic cardiovascular disease
ASD	atrial septal defect
ASPIRE	Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre Registry
ATP III	Adult Treatment Panel III
AUC	area under the curve
AVAIL	Adherence Evaluation After Ischemic Stroke Longitudinal
AWHS	Aragon Workers Health Study
BASIC	Brain Attack Surveillance in Corpus Christi
BEST	Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease
BiomarCaRE	Biomarker for Cardiovascular Risk Assessment in Europe

BioSHaRe	Biobank Standardization and Harmonization for Research Excellence in the European Union
BIOSTAT-CHF	Biology Study to Tailored Treatment in Chronic Heart Failure
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CABG	coronary artery bypass graft
CAC	coronary artery calcification
CAD	coronary artery disease
CAIDE	Cardiovascular Risk Factors, Aging and Dementia
CANHEART	Cardiovascular Health in Ambulatory Care Research Team
CARDIA	Coronary Artery Risk Development in Young Adults
CARDIoGRAM	Coronary Artery Disease Genome-Wide Replication and Meta-Analysis
CARDIoGRAMplusC4D	Coronary Artery Disease Genome-Wide Replication and Meta-Analysis (CARDIoGRAM) plus the Coronary Artery Disease Genetics (C4D)
CARES	Cardiac Arrest Registry to Enhance Survival
CAS	carotid artery stenting
CASCADE FH	Cascade Screening for Awareness and Detection of Familial Hypercholesterolemia
CASQ2	calsequestrin 2
CCD	congenital cardiovascular defect
CDC	Centers for Disease Control and Prevention
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CEA	carotid endarterectomy
CHADS2	clinical prediction rule for estimating the risk of stroke based on congestive heart failure, hypertension, age $\geq 75$ years, diabetes (1 point each), and prior stroke/transient ischemic attack/thromboembolism (2 points)
CHA2DS2-VASc	clinical prediction rule for estimating the risk of stroke based on congestive heart failure, hypertension, diabetes, and sex (1 point each); age $\geq 75$ years and stroke/transient ischemic attack/thromboembolism (2 points each); plus history of vascular disease, age 65 to 74 years, and (female) sex category
CHAMP-HF	Change the Management of Patients With Heart Failure
CHAP	Chicago Health and Aging Project
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
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COAPT	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
CONFIRM	Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry
CORAL	Cardiovascular Outcomes in Renal Atherosclerotic Lesions
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
CPR	cardiopulmonary resuscitation
CPS-II	Cancer Prevention Study II

CPVT	catecholaminergic polymorphic ventricular tachycardia
CROMIS-2	Clinical Relevance of Microbleeds in Stroke
CRP	C-reactive protein
CRUSADE	Can Rapid Risk Stratification of Unstable Angina Patient Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines
CSA	community-supported agriculture
CSC	comprehensive stroke center
CT	computed tomography
CTEPH	chronic thromboembolic pulmonary hypertension
CVD	cardiovascular disease
CVD PREDICT	Cardiovascular Disease Policy Model for Risk, Events, Detection, Interventions, Costs, and Trends
CVH	cardiovascular health
CVI	chronic venous insufficiency
DALY	disability-adjusted life-year
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
DCCT/EDIC	Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications
DCM	dilated cardiomyopathy
DHA	docosahexaenoic acid
DII	Dietary Inflammatory Index
DNA	deoxyribonucleic acid
DPP	Diabetes Prevention Program
DVT	deep vein thrombosis
EAGLES	Study Evaluating the Safety and Efficacy of Varenicline and Bupropion for Smoking Cessation in Subjects With and Without a History of Psychiatric Disorders
ECG	electrocardiogram
e-cigarette	electronic cigarette
ED	emergency department
EF	ejection fraction
eGFR	estimated glomerular filtration rate
e-hookah	electronic hookah
ELSA	English Longitudinal Study of Ageing
EMPHASIS-HF	Epleren in Mild Patients Hospitalization and Survival Study in Heart Failure
EMS	emergency medical services
EPA	eicosapentaenoic acid
EPIC	European Prospective Investigation Into Cancer and Nutrition
ERICA	Study of Cardiovascular Risks in Adolescents
ERP	early repolarization pattern
ERR	excess readmission ratio
ESRD	end-stage renal disease
EUCLID	Examining Use of Ticagrelor in PAD
EVEREST	Endovascular Valve Edge-to-edge Repair
EVEREST II HRS	Endovascular Valve Edge-to-Edge Repair High-Risk Study
EVITA	Effect of Vitamin D on Mortality in Heart Failure
EVITA	Evaluation of Varenicline in Smoking Cessation for Patients Post-Acute Coronary Syndrome
e-waterpipe	electronic waterpipe
EXAMINE	Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care
FANTASIA	Atrial fibrillation: influence of the level and type of anticoagulation on the incidence of ischemic and hemorrhagic stroke

FDA	US Food and Drug Administration
FH	familial hypercholesterolemia
FHS	Framingham Heart Study
FINRISK	Finnish Population Survey on Risk Factors for Chronic, Noncommunicable Diseases
FMD	flow-mediated dilation
FOURIER	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk
FPG	fasting plasma glucose
FRS	Framingham Risk Score
FUTURE	Follow-up of TIA and Stroke Patients and Unelucidated Risk Factor Evaluation
FVL	factor V Leiden
GARFIELD-VTE	Global Anticoagulant Registry in the Field—Venous Thromboembolism
GBD	Global Burden of Disease
GCKSS	Greater Cincinnati/Northern Kentucky Stroke Study
GFR	glomerular filtration rate
GISSI-3	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
GLORIA-AF	Global Registry on Long-term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation
GRS	genetic risk score
GWAS	genome-wide association studies
GWG	gestational weight gain
GWTG	Get With The Guidelines
HANDLS	Health Aging in Neighborhoods of Diversity Across the Life Span
HAPIEE	Health, Alcohol and Psychosocial Factors in Eastern Europe
HAPO	Hyperglycemia and Adverse Pregnancy Outcome
HbA1c	hemoglobin A1c (glycosylated hemoglobin)
HBP	high blood pressure
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
HCM	hypertrophic cardiomyopathy
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HDP	hypertensive disorders of pregnancy
Health ABC	Health, Aging, and Body Composition
HEI	Healthy Eating Index
HELENA	Healthy Lifestyle in Europe by Nutrition in Adolescence
HF	heart failure
HF-ACTION	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
HFmrEF	heart failure with midrange ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrfEF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
HLHS	hypoplastic left-heart syndrome
HPFS	Health Professionals Follow-Up Study
HPS	Heart Protection Study
HR	hazard ratio
HRRP	Hospital Readmissions Reduction Program
HRS	Health and Retirement Study
HYVET	Hypertension in the Very Elderly Trial
ICAD	International Children's Accelerometry Database

ICD	International Classification of Diseases
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
ICE-PCS	International Collaboration on Endocarditis—Prospective Cohort Study
ICE-PLUS	International Collaboration on Endocarditis—PLUS
ICH	intracerebral hemorrhage
ICU	intensive care unit
IDACO	International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes
IE	infective endocarditis
IE After TAVI	Infective Endocarditis After Transcatheter Aortic Valve Implantation and SwissTAVI as Swiss Transcatheter Aortic Valve Implantation
IHCA	in-hospital cardiac arrest
IHD	ischemic heart disease
IL	interleukin
IMPACT	International Model for Policy Analysis of Agricultural Commodities and Trade
IMPROVE	Carotid Intima–Media Thickness (IMT) and IMT–Progression as Predictors of Vascular Events in a High–Risk European Population
IMT	intima-media thickness
INTER-CHF	International Congestive Heart Failure
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IQR	interquartile range
IRAD	International Registry of Acute Aortic Dissection
IRR	incidence rate ratio
IVIG	intravenous immunoglobulin
JHS	Jackson Heart Study
KD	Kawasaki disease
LBW	low birth weight
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
LIBRA	Lifestyle for Brain Health
LIFE	Lifestyle Interventions and Independence for Elders
LOAD	late-onset Alzheimer disease
Look AHEAD	Look: Action for Health in Diabetes
LV	left ventricular
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LQTS	long QT syndrome
MACE	major adverse cardiovascular event
MAP	Memory and Aging Project
MARS	Minority Aging Research Study
MCI	mild cognitive impairment
MDCS	Malmö Diet and Cancer Study
MEPS	Medical Expenditure Panel Survey
MESA	Multi-Ethnic Study of Atherosclerosis

MET	metabolic equivalent
MetS	metabolic syndrome
MHO	metabolically healthy obesity
MI	myocardial infarction
MIDA	Mitral Regurgitation International Database
MIDAS	Myocardial Infarction Data Acquisition System
MI-GENES	Myocardial Infarction Genes Study
MIND-China	Multimodal Interventions to Delay Dementia and Disability in Rural China
MIS-C	multisystem inflammatory syndrome in children
MITRA-FR	Percutaneous Repair With the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation
MONICA	Monitoring Trends and Determinants of Cardiovascular Disease
MR	mitral regurgitation
MRI	magnetic resonance imaging
MTF	Monitoring the Future
MUSIC	Muerte Súbita en Insuficiencia Cardiaca
NAFLD	nonalcoholic fatty liver disease
NAMCS	National Ambulatory Medical Care Survey
NCDR	National Cardiovascular Data Registry
NCHS	National Center for Health Statistics
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHDS	National Hospital Discharge Survey
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NIH-AARP	National Institutes of Health–American Association of Retired Persons
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institutes of Neurological Disorders and Stroke
NIPPON DATA	National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in Aged
NIS	National (Nationwide) Inpatient Sample
NOMAS	Northern Manhattan Study
NOTION	Nordic Aortic Valve Intervention
NSDUH	National Survey on Drug Use and Health
NSHDS	Northern Sweden Health and Disease Study
NSTEMI	non–ST-segment–elevation myocardial infarction
NT-proBNP	N-terminal pro-B-type natriuretic peptide
nuMoM2b	Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be
NVSS	National Vital Statistics System
ODYSSEY	Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
ORBIT-AF	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
OSA	obstructive sleep apnea
OVER	Open Versus Endovascular Repair
PA	physical activity
PAD	peripheral artery disease
PAF	population attributable fraction
PAH	pulmonary arterial hypertension
PALM	Patient and Provider Assessment of Lipid Management Registry

PAR	population attributable risk
PARADIGM	Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging
PARTNER	Placement of Aortic Transcatheter Valve
PATH	Population Assessment of Tobacco and Health
PCE	Pooled Cohort Equations
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PE	pulmonary embolism
PESA	Progression of Early Subclinical Atherosclerosis
PH	pulmonary hypertension
PHS	Physicians' Health Study
PHIRST	Pulmonary Arterial Hypertension and Response to Tadalafil Study
PINNACLE	Practice Innovation and Clinical Excellence
PM2.5	fine particulate matter <2.5- $\mu$ m diameter
POINT	Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke
PPCM	peripartum cardiomyopathy
PPSW	Prospective Population Study of Women in Gothenburg
PR	prevalence ratio
PRECOMBAT	Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus Stents in Patients With Left Main Coronary Artery Disease
PREDIMED	Prevención con Dieta Mediterránea
PREMA	Prediction of Metabolic Syndrome in Adolescence
PREMIER	Lifestyle Interventions for Blood Pressure Control
PREVEND	Prevention of Renal and Vascular End-Stage Disease
PROFESS	Prevention Regimen for Effectively Avoiding Second Stroke
PTB	preterm birth
PTS	postthrombotic syndrome
PUFA	polyunsaturated fatty acid
PURE	Prospective Urban Rural Epidemiology
PWV	pulse-wave velocity
QALY	quality-adjusted life-year
QTc	corrected QT interval
RCT	randomized controlled trial
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
REACH	Reduction of Atherothrombosis for Continued Health
REDINSCOR	Red Española de Insuficiencia Cardiaca
REGARDS	Reasons for Geographic and Racial Differences in Stroke
REMEDY	Global Rheumatic Heart Disease Registry
RENIS-T6	Renal Iohexol Clearance Survey in Tromsø 6
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
REVEAL	Registry to Evaluate Early and Long-term PAH Disease Management
ROADMAP	Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device (LVAD) and Medical Management in Ambulatory Heart Failure Patients
ROC	Resuscitation Outcomes Consortium
ROS	Religious Orders Study
RR	relative risk
RSMR	risk-standardized mortality rate

RV	right ventricular
RYR2	ryanodine receptor 2
SAFEHEART	Spanish Familial Hypercholesterolemia Cohort Study
SAGE	Study on Global Ageing and Adult Health
S.AGES	Sujets AGÉS—Aged Subjects
SAH	subarachnoid hemorrhage
SAVE	Sleep Apnea Cardiovascular Endpoints
SAVR	surgical aortic valve replacement
SBP	systolic blood pressure
SCA	sudden cardiac arrest
SCD	sudden cardiac death
SCORE	Systematic Coronary Risk Evaluation
SD	standard deviation
SDB	sleep disordered breathing
SE	standard error
SEARCH	Search for Diabetes in Youth
SEMI-COVID-19	Sociedad Española de Medicina Interna Coronavirus Disease 2019
SES	socioeconomic status
SFA	saturated fatty acid
SGA	small for gestational age
SHIP	Study of Health in Pomerania
SHS	Strong Heart Study
SILVER-AMI	Comprehensive Evaluation of Risk Factors in Older Patients With Acute Myocardial Infarction
SNAC-K	Swedish National Study on Aging and Care in Kungsholmen
SND	sinus node dysfunction
SNP	single-nucleotide polymorphism
SOF	Study of Osteoporotic Fractures
SPRINT	Systolic Blood Pressure Intervention Trial
SPS3	Secondary Prevention of Small Subcortical Strokes
SSB	sugar-sweetened beverage
START	South Asian Birth Cohort
STEMI	ST-segment-elevation myocardial infarction
STS	Society of Thoracic Surgeons
SUN	Seguimiento Universidad de Navarra
SURTAVI	Surgical Replacement and Transcatheter Aortic Valve Implantation
SVT	supraventricular tachycardia
SWAN	Study of Women's Health Across the Nation
SWIFT PRIME	Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment
SwissTAVI	Swiss Transcatheter Aortic Valve Implantation
SYNTAX	Synergy Between PCI With Taxus and Cardiac Surgery
TAA	thoracic aortic aneurysm
TAVR	transcatheter aortic valve replacement
TC	total cholesterol
TdP	torsade de pointes
TECOS	Trial Evaluating Cardiovascular Outcomes With Sitagliptin
TGA	transposition of the great arteries
TGF	transforming growth factor
3C	Three City Study
TIA	transient ischemic attack
TODAY	Treatment Options for Type 2 Diabetes in Adolescents and Youth



TOF	tetralogy of Fallot
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist
tPA	tissue-type plasminogen activator
TRIUMPH	Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension
TVT	transcatheter valve therapy
UA	unstable angina
UI	uncertainty interval
UK	United Kingdom
USRDS	US Renal Data System
VBI	vascular brain injury
VF	ventricular fibrillation
VITAL	Vitamin D and Omega-3 Trial
VOYAGER	Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects With Symptomatic Peripheral Artery Disease Undergoing Peripheral Revascularization Procedures of the Lower Extremities

VSD	ventricular septal defect
VT	ventricular tachycardia
VTE	venous thromboembolism
WC	waist circumference
WHI	Women's Health Initiative
WHICAP	Washington Heights-Hamilton Heights-Inwood Community Aging Project
WHO	World Health Organization
WHS	Women's Health Study
WMD	weighted mean difference
WMH	white matter hyperintensity
WPW	Wolff-Parkinson-White
YLD	years of life lived with disability or injury
YLL	years of life lost to premature mortality
YRBS	Youth Risk Behavior Survey
YRBSS	Youth Risk Behavior Surveillance System

Abbreviations used only in charts and tables do not appear in this table.

## 1. ABOUT THESE STATISTICS

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The AHA works with the NHLBI to derive the annual statistics in the AHA Statistical Update. This chapter describes the most important sources and the types of data used from them. For more details, see Chapter 30 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
- GBD—global disease prevalence, mortality, and healthy life expectancy
- 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 the United States
- USRDS—kidney disease prevalence
- WHO—mortality rates by country
- YRBS—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 2022 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 (most-ly from the past 5 years), which may not be as inclusive as the terms now used in 2022. 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 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 the 2022 Statistical Update is to present the latest estimates of the number of people in the United States who have specific conditions to provide a realistic estimate of burden. Most estimates based on NHANES prevalence rates are based on data collected from 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 2022 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 2015 to 2018 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 are used to present estimates of the percentage of people with overweight, obesity, and high total cholesterol and HDL-C. BRFSS 2019 data are used for the prevalence of sleep issues. The NHIS 2019 data, BRFSS 2019, and NYTS 2020 are used for the prevalence of cigarette smoking. The prevalence of physical inactivity is obtained from 2019 YRBS 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 AHA Statistical 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 the 2022 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 22 (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.<sup>1</sup> Any-mention numbers of deaths were tabulated from the CDC WONDER website or CDC NVSS mortality file.<sup>2</sup>

## Population Estimates

In this publication, we have used national population estimates from the US Census Bureau for 2018<sup>2</sup> in the computation of morbidity data. CDC/NCHS population estimates<sup>3</sup> 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 2018 HCUP NIS. Ambulatory care visit data include patient visits to primary health care professionals' offices and EDs. Ambulatory care visit data reflect the primary (first-listed) diagnosis. Primary health care professional office visit estimates are from the 2018 NAMCS of the CDC/NCHS. ED visit estimates are from the 2018 HCUP National ED Sample. 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 ninth and 10th *ICD* revisions, comparability ratios computed by the CDC/NCHS are applied as noted.<sup>4</sup> Effective with mortality data for 1999, *ICD-10* is used.<sup>5</sup> Beginning in 2016, *ICD-10-CM* is used for hospital inpatient stays and ambulatory care visit data.<sup>6</sup>

## 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.<sup>7</sup> 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 the 2022 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 2019. 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 of hospital inpatient discharges for the United States are for

2018. The numbers of visits to primary health care professionals' offices and hospital EDs are for 2018. Except as noted, economic cost estimates are for 2017 to 2018.

### Cardiovascular Disease

For data on hospitalizations, primary health care professional 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 and 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 AHA works with the Institute for Health Metrics and Evaluation to help derive annual statistics for the AHA Statistical Update. The Global Burden of Diseases, Injuries, and Risk Factors Study is an ongoing global effort to quantify health loss from hundreds of causes and risks from 1990 to the present for all countries. The study seeks to produce consistent and comparable estimates of population health over time and across locations, including summary metrics such as DALYs and healthy life expectancy. Results are made available to policymakers, researchers, governments, and the public with the overarching goals of improving population health and reducing health disparities.

GBD 2020, the most recent iteration of the study, was produced by the collective efforts of more than 7500 researchers in more than 150 countries. Estimates were produced for 370 causes and 88 risk factors.

During each annual GBD Study cycle, population health estimates are reproduced for the full time series. For GBD 2020, estimates were produced for 1990 to 2020 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 GBD and to access GBD resources, data visualizations, and most recent publications, please visit the study website.<sup>8–10</sup>

### 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 the 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 CVH of all Americans by 20%, while reducing deaths from CVDs and stroke by 20%.<sup>1</sup>

The concept of CVH was introduced in this goal and characterized by 7 components (Life’s Simple 7)<sup>2</sup> 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.<sup>1</sup> Table 2-1 provides the specific definitions for these categories for each CVH component in both adults and youth.

From 2011 to 2021, this chapter in the annual Statistical Update published national prevalence estimates for CVH based on released NHANES data to inform progress toward improvements in the prevalence of CVH. In 2021, 10-year differences in the leading causes and risk factors for YLDs and YLLs, which highlight the influence of the components of CVH on premature death and disability in populations, were also added.

### 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.<sup>3–8</sup> Similar relationships have also been seen in non-US populations.<sup>3,4,9–22</sup>

- 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.<sup>4</sup>
- A study of Black people found that risk of incident HF was 61% lower among those with  $\geq 4$  ideal CVH components than among those with 0 to 2 ideal components.<sup>5</sup>
- 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.<sup>23</sup>
- 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.<sup>24</sup>
- 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 having the lowest number of ideal components.<sup>25</sup>
- The adjusted PAFs for CVD mortality for individual components of CVH have been reported as follows<sup>26</sup>:
  - 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

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used to demonstrate an inverse stepwise association between a higher CVH score component and a 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.<sup>27</sup> CVH score and components were also shown to predict MACEs (first occurrence of MI, stroke, acute ischemic syndrome, coronary revascularization, or death) over a median follow-up of 12 years in a biracial community-based population.<sup>28</sup>

- By combining the 7 CVH component scores and categorizing the total score to define overall CVH (low, 0–8 points; moderate, 9–11 points; high, 12–14 points), a report pooled NHANES 2011 to 2016 data and individual-level data from 7 US community-based cohort studies to estimate the age-, sex-, and race and ethnicity-adjusted PAF of major CVD events (nonfatal MI, stroke, HF, or CVD death) associated with CVH and found that 70.0% (95% CI, 56.5%–79.9%) of major CVD events in the United States were attributable to low and moderate CVH.<sup>29</sup> According to the authors' estimates, 2.0 (95% CI, 1.6–2.3) million major CVD events could potentially be prevented each year if all US adults attain high CVH, and even a partial improvement in CVH scores to the moderate level among all US adults with low overall CVH could lead to a reduction of 1.2 (95% CI, 1.0–1.4) million major CVD events annually.
- A report from the Framingham Offspring Study showed increased risks of subsequent hypertension, diabetes, CKD, CVD, and mortality associated with having a shorter duration of ideal CVH in adulthood.<sup>30</sup>
- 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  $\geq 1$  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  $\geq 2$  risk factors.<sup>31</sup>
- Better CVH as defined by the AHA is associated with lower incidence of HF,<sup>35–7,22</sup> less subclinical vascular disease,<sup>8,15,17,33,34</sup> better global cognitive performance and cognitive function,<sup>16,35,36</sup> lower hazard of subsequent dementia,<sup>37,38</sup> lower prevalence<sup>39</sup> and incidence<sup>40</sup> of depressive symptoms, lower loss of physical functional status,<sup>41</sup> longer leukocyte telomere length,<sup>42</sup> less ESRD,<sup>43</sup> less pneumonia, less chronic obstructive pulmonary disease,<sup>44</sup> less VTE/PE,<sup>45</sup> lower prevalence of aortic sclerosis and stenosis,<sup>46</sup> lower risk of calcific aortic valve stenosis,<sup>47</sup> better prognosis after MI,<sup>48</sup> lower risk of AF,<sup>49</sup> and lower odds of having elevated resting heart rate.<sup>50</sup> Using the CVH scoring approach, the FHS demonstrated significantly lower odds of prevalent hepatic steatosis associated with more favorable CVH scores, and the decrease of liver fat associated with more favorable CVH scores was greater among people with a higher GRS for NAFLD.<sup>51</sup> In addition, a study based on NHANES data showed significantly decreased odds of ocular diseases (OR, 0.91 [95% CI, 0.87–0.95]), defined as age-related macular degeneration, any retinopathy, and cataract or glaucoma, and odds of diabetic retinopathy (OR, 0.71 [95% CI, 0.66–0.76]) associated with each unit increase in CVH among US adults.<sup>52</sup>
- 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.<sup>53</sup> A study in college students found that both handgrip strength and muscle mass were positively associated with greater numbers of ideal CVH components,<sup>54</sup> and a cross-sectional study found that greater cardio-pulmonary fitness, upper-body flexibility, and lower-body muscular strength were associated with better CVH components in perimenopausal females.<sup>55</sup> Furthermore, higher quality of life scores were associated with better CVH metrics,<sup>56</sup> 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, underrepresented racial groups, and single-living status) were related to lower likelihood of attaining better CVH as measured by Life's Simple 7 scores.<sup>57</sup> 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.<sup>58</sup> A study focused on people with serious mental illness found that individuals of underrepresented races and ethnicities had significant lower CVH scores based on 5 of the Life's Simple 7 components.<sup>59</sup>
- Having more ideal CVH components in middle age has been associated with lower non-CVD and CVD health care costs in later life.<sup>60</sup> An investigation of 4906 participants in the Cooper Center Longitudinal Study reported that participants with  $\geq 5$  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  $\leq 2$  ideal CVH components.<sup>60</sup> 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.<sup>61</sup>

## CVH in the United States: Prevalence (NHANES 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 ( $\geq 20$  years of age) who meet ideal, intermediate, and poor levels of each of the 7 CVH components are displayed in Chart 2-1.<sup>62</sup> The most current estimates at the time of publication were based on data from NHANES 2017 to 2018. NHANES 2017 to 2018 survey changed the PA assessments for children, so the PA status for children was updated according to data from respondents who were 18 to 19 years of age.
- For most components of CVH, prevalence of ideal levels is higher in US children (12–19 years of age) than in US adults ( $\geq 20$  years of age), except for the Healthy Diet Score, for which prevalence of ideal levels in children is lower than in adults. For PA, the contrast for adults versus children is not clear because the prevalence estimate for children was from a subgroup of children only.
- 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  $>79\%$  for smoking, BP, and diabetes components (95.7%, 89.1%, and 79.0% respectively; 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  $\geq 20$  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 2017 to 2018 are displayed in Table 2-2.
- In 2017 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 ( $\geq 60$  years of age), except smoking and the Healthy Diet Score, for which prevalence of ideal levels was highest in older adults. For the Healthy Diet Score, all age groups had a prevalence of ideal level  $<1\%$  according to the 2017 to 2018 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 and ethnicity.
  - The majority of US children 12 to 19 years of age met ideal criteria for smoking (93.7%–99.0%), BP (82.2%–91.5%), and TC (68.9%–79.5%) in 2017 to 2018 across race and ethnicity subgroups.
  - The majority of US children 12 to 19 years of age met ideal criteria for diabetes (71.3%–80.1%) in 2017 to 2018 across race and ethnicity groups.
  - Of US children 12 to 19 years of age, 49.2% to 75.0% met ideal criteria for BMI in 2017 to 2018. The ideal level of PA in the subgroup of 18 to 19 years of age ranged from 38.1% to 64.6% across race and ethnicity groups in 2017 to 2018.
  - Few US children 12 to 19 years of age ( $<1\%$ ) met ideal criteria for Healthy Diet Score in 2017 to 2018 across all race and ethnicity groups.
- Chart 2-3 displays the adjusted prevalence estimates of ideal levels of CVH components for the population of US adults  $\geq 20$  years of age by race and ethnicity.
  - The majority of US adults  $\geq 20$  years of age met ideal criteria for smoking (77.6%–91.6%) in 2017 to 2018 across race and ethnicity subgroups.
  - Fewer than a quarter to a little more than half of US adults  $\geq 20$  years of age met ideal criteria for BMI (14.2%–44.7%), TC (50.1%–58.3%), PA (29.6%–40.1%), and BP (31.0%–43.2%) in 2017 to 2018 across race and ethnicity groups.
  - Of US adults  $\geq 20$  years of age, 43.6% to 53.4% met ideal criteria for diabetes in 2017 to 2018 across race and ethnicity categories.
  - Few US adults  $\geq 20$  years of age (0.0%–1.5%) met ideal criteria for Healthy Diet Score in 2017 to 2018 across all race and ethnicity groups.

## CVH in the United States: 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 2017–2018) are shown in Chart 2-4 for children (12–19 years of age) and in Chart 2-5 for adults ( $\geq 20$  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% (95% CI, 72.5%–79.8%) to 95.7% (95% CI, 92.9%–97.4%) for nonsmoking and from 83.6% (95% CI, 80.2%–86.6%) to 89.1% (95% CI, 86.3%–91.5%) for ideal BP. For ideal TC, the prevalence increased from 72.0% (95% CI, 68.4%–75.4%) to 77.2% (95% CI, 73.6%–80.5%). However, a decline in prevalence of ideal levels was observed for BMI, from 69.8% (95% CI, 66.8%–72.7%) in 1999 to 2000 to 60.1% (95% CI, 56.2%–63.8%) in 2015 to 2016, although it rebounded slightly to 63.3% (95% CI, 59.8%–66.7%) in 2017 to 2018. Declines in prevalence of ideal levels were observed for diabetes (92.4% [95% CI, 89.7%–94.4%]) to 79.0% [95% CI, 74.8%–82.7%]) from 1999 to 2000 to 2017 to 2018 among children.
- Because of changes in the PA questionnaire between NHANES cycles 1999 to 2006 and 2007 to 2016 and then again in the 2017 to 2018 cycle, interpretation of prevalence trends over time for this CVH component in children warrants caution. Ideal level of PA increased (38.4% [95% CI, 33.2%–44.0%]) to 47.8% [95% CI, 44.9%–50.8%]) from 1999 to 2000 to 2005 to 2006 and remained relatively unchanged (26.6% [95% CI, 23.8%–29.6%]) to 25.4% [95% CI, 22.4%–28.7%]) from 2007 to 2008 to 2015 to 2016 among children 12 to 19 years of age. The observed prevalence of ideal PA was 54.0% (95% CI, 45.8%–62.1%) in 2017 to 2018 in the subgroup of those 18 to 19 years of age.
- 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 age-adjusted prevalence of being a never smoker or having quit  $\geq 1$  year increased from 72.9% (95% CI, 69.6%–76.0%) to 79.8% (95% CI, 77.1%–82.3%). Over the 20-year period, the prevalence of meeting criteria for ideal TC increased from 45.1% (95% CI, 43.1%–47.1%) to 52.4% (95% CI, 49.4%–55.3%). However, declines in prevalence of ideal levels were observed for BMI (from 36.3% [95% CI, 33.0%–39.7%]) to 26.4% [95% CI, 23.9%–29.0%]) and diabetes (from 69.1% [95% CI, 66.1%–72.1%]) to 50.4% [95% CI, 48.0%–52.8%]) among adults during this period.
- Although the NHANES PA questionnaire changed over time, a slight upward trend in ideal level of PA was observed (40.2% [95% CI, 36.0%–44.6%]) to 45.1% [95% CI, 42.5%–47.8%]) from 1999 to 2000 to 2005 to 2006

and again (34.7% [95% CI, 30.7%–38.9%]) to 38.3% [95% CI, 35.8%–41.0%]) from 2007 to 2008 to 2017 to 2018.

## 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 AD and other dementias also rose from the 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%, and 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 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 2-10)

- 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 decreased 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.

## COVID-19 Mortality in the United States

- The large number of individuals in the United States who contracted severe illness attributable to COVID-19 resulted in a huge mortality toll, with disproportionate rates of deaths occurring among US counties with metropolitan areas and with higher proportions of the population who are NH Black and Hispanic people and in poverty.
  - As of March 2021, the cumulative number of COVID-19 deaths in the United States was ≈545 000, which equates to ≈166 deaths per 100 000 people.<sup>63</sup> In metropolitan areas in the United States, the cumulative COVID-19 death rate was ≈185 deaths per 100 000 compared with ≈162 deaths per 100 000 in nonmetropolitan areas.<sup>63</sup>
  - In US counties with a high percentage (>45.5%) of the population that is NH Black individuals, the COVID-19 death rate was ≈200 deaths per 100 000 compared with ≈158 deaths per 100 000 in counties with a low percentage (<2.5%) of the population that is NH Black individuals.<sup>63</sup>
  - In US counties with a high percentage (>37%) of the population that is Hispanic individuals, the cumulative COVID-19 death rate was ≈219 deaths per 100 000 compared with ≈153 deaths per 100 000 in counties with a low percentage (≤18.3%) of the population that is Hispanic individuals.<sup>63</sup>
  - In US counties with a high percentage (>17.3%) of the population in poverty, the cumulative COVID-19 death rate was ≈211 deaths per 100 000 compared with ≈139 deaths per 100 000 in counties with a low percentage (0.0–12.3%) of the population that is living in poverty.<sup>63</sup>

## Impact of COVID-19 on Life Expectancy in the United States

- As a result of the high COVID-19 mortality rates, life expectancy in the United States for 2020 has been estimated to decline with disproportionate impacts on populations with high COVID-19 mortality rates.

- Provisional US life expectancy estimates for January to June 2020<sup>64</sup> indicate that between 2019 and the first half of 2020, life expectancy (at birth) decreased from 74.7 to 72.0 years (−2.7 years) for NH Black individuals. Life expectancy decreased from 81.8 to 79.9 years (−1.9 years) for Hispanic individuals and decreased from 78.8 to 78.0 years (−0.8 year) for NH White individuals.

### 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 and YLD, including IHD,<sup>23</sup> Alzheimer disease,<sup>65</sup> stroke,<sup>66,67</sup> CKD,<sup>68</sup> diabetes,<sup>69,70</sup> and breast cancer<sup>71,72</sup> (Tables 2-4 and 2-6). 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 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.<sup>73</sup>

### 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 <sup>2</sup>	25–29.9 kg/m <sup>2</sup>	<25 kg/m <sup>2</sup>
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 HbA1c ≥6.5%	FPG 100–125 mg/dL or HbA1c 5.7%–6.4% or treated to goal	FPG <100 mg/dL or HbA1c <5.7%
Children 12–19 y of age	FPG ≥126 mg/dL or HbA1c ≥6.5%	FPG 100–125 mg/dL or HbA1c 5.7%–6.4% or treated to goal	FPG <100 mg/dL or HbA1c <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; HbA1c, glycosylated hemoglobin or hemoglobin A1c; 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, ie, 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 used solely to determine poor, intermediate, and ideal status for American Heart Association strategic Impact Goal monitoring purposes. For population surveillance purposes, use of HbA1c 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.<sup>1</sup> 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 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 (1.7)	25.5 (1.5)
BP	2017–2018	89.1 (1.3)	40.8 (1.4)	61.6 (1.9)	34.0 (2.6)	15.1 (1.3)
Diabetes	2017–2018	79.0 (2.0)	50.4 (1.2)	68.9 (1.8)	42.4 (2.5)	31.5 (2.0)
Ideal health behaviors						
PA	2017–2018	54.0 (4.2)†	38.3 (1.3)	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)	21.9 (2.0)	21.9 (1.1)
4 or 5 Healthy diet goals met‡	2017–2018	0.0 (0.0)	0.2 (0.1)	0.1 (0.1)	0.3 (0.2)	0.4 (0.1)
F&V ≥4.5 cups/d	2017–2018	5.5 (1.0)	9.8 (0.8)	8.7 (0.9)	9.3 (1.5)	12.0 (1.5)
Fish ≥2 svg/wk	2017–2018	8.4 (1.2)	18.3 (1.1)	16.4 (1.7)	18.2 (2.3)	23.7 (2.1)
Sodium <1500 mg/d	2017–2018	0.2 (0.1)	0.5 (0.2)	0.4 (0.2)	0.7 (0.3)	0.2 (0.1)
SSB <450 kcal/wk	2017–2018	39.3 (2.6)	55.1 (2.3)	49.7 (2.4)	55.2 (3.3)	64.0 (2.2)
Whole grains ≥3 one-ounce svg/d	2017–2018	6.2 (1.0)	6.4 (0.8)	5.6 (1.0)	5.5 (1.3)	8.6 (1.1)
Secondary diet metrics						
Nuts/legumes/seeds ≥4 svg/wk	2017–2018	34.2 (3.1)	49.6(1.7)	47.7 (2.2)	49.1 (2.3)	53.7 (2.9)
Processed meats ≤2 svg/wk	2017–2018	39.1 (2.3)	41.5 (0.8)	42.9 (1.9)	41.7 (2.3)	39.5 (1.9)
SFat <7% total kcal	2017–2018	6.8 (1.2)	7.0 (0.4)	7.4 (0.9)	8.0 (1.0)	5.3 (0.6)

Values are percent (standard error).

BMI indicates body mass index; BP, blood pressure; CVH, cardiovascular health; F&V, fruits and vegetables; 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.

†Data for 18 to 19 years of age only.

‡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.<sup>62</sup>

**Table 2-3. 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 −3.79%)	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-C	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 <i>trans</i> 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 −37.44%)	−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-C, low-density lipoprotein cholesterol; 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.<sup>24</sup> Printed with permission. Copyright © 2020, University of Washington.

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**Table 2-4. 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 (80.25 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.<sup>75</sup> Printed with permission. Copyright © 2020, University of Washington.

**Table 2-5. 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-C	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-C, low-density lipoprotein cholesterol; 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.<sup>74</sup> Printed with permission. Copyright © 2020, University of Washington.

**Table 2-6. 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 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	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 in the 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 in the 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 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.<sup>75</sup> Printed with permission. Copyright © 2020, University of Washington.

**Table 2-7. 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 No. of YLLs	Age-standardized YLL rate	1990	2019	Total No. of deaths	Age-standardized death rate
High SBP	6	1	143 603.62 (129 333.91 to 157 734.25)	214 260.28 (191 165.39 to 236 748.61)	49.2% (38.51% to 59.21%)	−28.96% (−33.93% to −24.37%)	6787.71 (6072.71 to 7495.92)	10 845.60 (9514.14 to 12 130.85)	59.78% (49.19% to 69.4%)	−29.81% (−34.25% to −25.76%)
Smoking	7	2	140 203.56 (132 792.85 to 147 036.56)	168 238.03 (155 801.16 to 180 393.21)	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	269 478.56 (250 822.80 to 288 996.54)	151 317.48 (128 528.30 to 179 613.60)	−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	221 314.76 (206 273.76 to 238 540.80)	128 741.23 (109 481.34 to 153 683.78)	−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	61 627.96 (51 459.07 to 74 728.01)	126 654.90 (104 234.74 to 153 148.03)	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	54 375.58 (30 163.43 to 84 361.01)	119 383.76 (79 596.11 to 163 875.52)	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	66 492.55 (44 569.97 to 94 108.79)	104 895.28 (84 911.25 to 123 445.01)	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-C	12	8	66 683.88 (56 074.15 to 79 392.34)	92 904.81 (75 590.22 to 111 436.78)	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	200 169.50 (154 731.29 to 248 560.54)	83 565.87 (60 754.11 to 108 481.62)	−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	292 012.74 (241 855.36 to 351 715.87)	79 87.22 (61 262.34 to 100 812.43)	−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 −65.74%)	−73.05% (−78.35% to −67.7%)
Alcohol use	15	11	55 971.37 (49 934.31 to 62 781.18)	75 813.95 (66 966.44 to 85 498.40)	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	37 087.06 (32 724.00 to 41 606.93)	65 204.46 (57 219.63 to 73 512.12)	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	153 905.20 (115 315.56 to 190 197.92)	57 641.09 (41.87 to 75 887.40)	−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	18 492.16 (14 813.00 to 23 832.65)	41 999.23 (37 398.24 to 49 078.72)	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	31 285.63 (10 435.19 to 63 583.27)	40 722.69 (11 550.13 to 86 326.74)	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 1194.71)	42.79% (4.76% to 61.05%)	−34.18% (−50.81% to −26.58%)
Diet low in whole grains	22	16	26 467.42 (12 815.63 to 33 041.82)	38 954.84 (19 130.31 to 49 094.51)	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	115 547.43 (92 118.35 to 138 980.27)	37 183.90 (29 008.07 to 48 393.08)	−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	80 929.22 (58 183.31 to 102 881.65)	32 224.40 (22 228.24 to 42 981.39)	−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	44 029.71 (31 252.42 to 57 353.06)	31 489.25 (24 218.79 to 38 792.35)	−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	26 827.37 (20 973.96 to 33 715.52)	25 954.68 (21 667.68 to 30 902.49)	−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-C, low-density lipoprotein cholesterol; 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.<sup>74</sup> Printed with permission. Copyright © 2020, University of Washington.

**Table 2-8. 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 −36.44%)	−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 (19.22 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 −39.9%)	788.32 (742.79 to 834.00)	957.19 (870.95 to 1034.65)	21.42% (10.17% to 36.33%)	−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.<sup>75</sup> Printed with permission. Copyright © 2020, University of Washington.



**Table 2-9. 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 (6 901.43 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 (7 295.78 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 (8 147.05 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 (8 098.99 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	3 985.80 (2 637.74 to 5 634.02)	13 320.10 (9 643.12 to 17 166.65)	234.19% (172.63% to 322.4%)	64.91% (34.85% to 107.76%)
Drug use	9	9	7 479.41 (5 163.69 to 10 042.08)	12 664.94 (8 804.75 to 16 725.98)	69.33% (60.93% to 78.15%)	14.49% (9.59% to 19.37%)
Kidney dysfunction	14	10	5 003.27 (3 651.06 to 5 080.3)	11 282.48 (8 232.55 to 14 676.40)	125.5% (118.26% to 132.74%)	20.24% (16.89% to 23.23%)
Short gestation	12	11	5 054.73 (3 854.95 to 6 433.30)	9 673.88 (7 598.43 to 12 021.19)	91.38% (75.26% to 106.94%)	43.44% (31.94% to 54.79%)
Low birth weight	13	12	5 054.73 (3 854.95 to 6 433.30)	9 673.88 (7 598.43 to 12 021.19)	91.38% (75.26% to 106.94%)	43.44% (31.94% to 54.79%)
Low bone mineral density	16	13	4 082.06 (2 923.34 to 5 511.96)	8 620.52 (6 115.78 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	8 277.99 (5 837.95 to 11 127.29)	7 908.60 (5 254.80 to 11 299.35)	−4.46% (−20.63% to 15.04%)	−52.14% (−60.18% to −42.55%)
Unsafe water source	11	15	6 054.63 (3 781.50 to 8 815.37)	7 455.38 (4 530.39 to 10 914.15)	23.14% (16.02% to 29.05%)	−11.82% (−16.58% to −8.1%)
Occupational noise	18	16	3 933.44 (2 688.10 to 5 599.97)	7 001.45 (4 760.56 to 10 059.34)	78% (71.39% to 83.61%)	−1.71% (−4.07% to 0.35%)
Occupational injuries	10	17	6 779.60 (4 833.81 to 9 123.27)	6 842.83 (4 831.64 to 9 300.85)	0.93% (−10.59% to 13.14%)	−39.26% (−46.08% to −31.85%)
High LDL-C	22	18	3 035.02 (1 990.11 to 4 342.73)	5 713.21 (3 677.82 to 8 268.24)	88.24% (82.75% to 94.36%)	−7.77% (−9.68% to −6.05%)
Secondhand smoke	24	19	2 652.31 (1 685.26 to 3 741.03)	5 512.81 (3 246.56 to 8 105.45)	107.85% (84.4% to 123.61%)	6.66% (−4.51% to 14.89%)
Unsafe sex	32	20	1 609.09 (1 135.71 to 2 172.24)	4 646.23 (3 296.41 to 6 215.68)	188.75% (161.84% to 225.83%)	80.75% (63.79% to 103.78%)

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

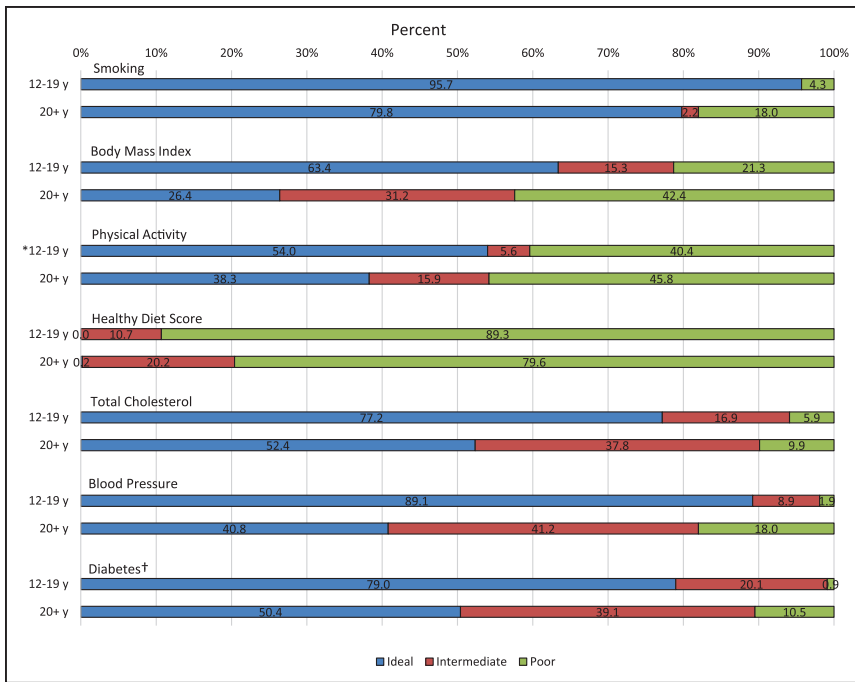
Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.<sup>74</sup> Printed with permission. Copyright © 2020, University of Washington.

**Table 2-10. 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 47.13)	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	9 131.34 (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	6 499.45 (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	5 184.78 (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	8 035.21 (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	7 875.53 (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	8 832.45 (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	5 054.73 (3854.95 to 6433.30)	9 673.88 (7598.43 to 12 021.19)	91.38% (75.26% to 106.94%)	43.44% (31.94% to 54.79%)

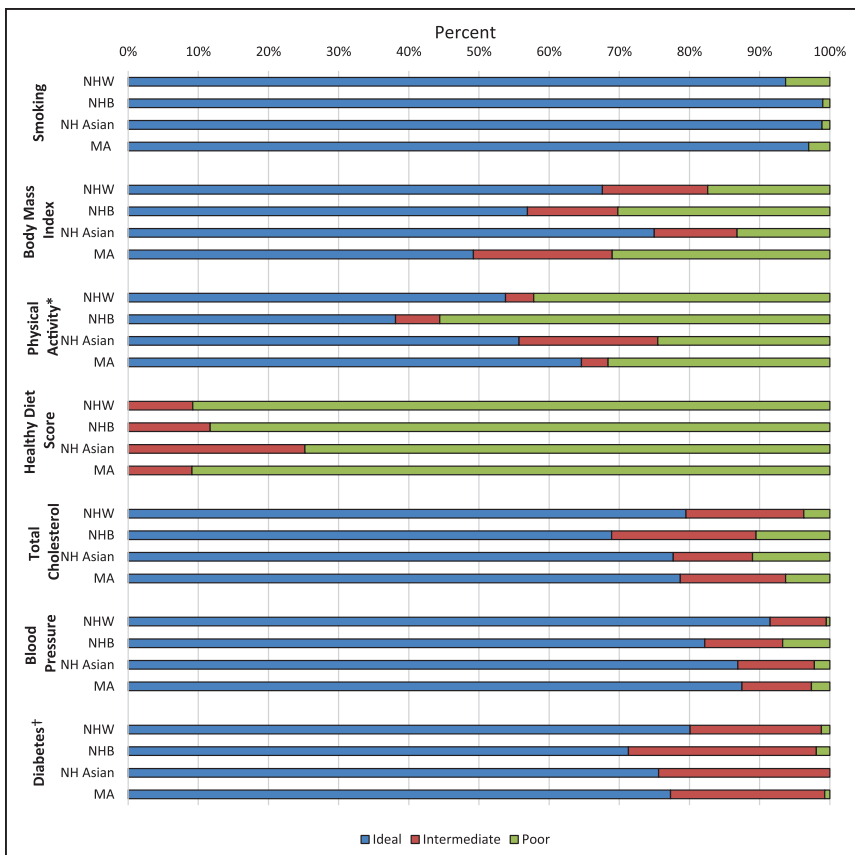
UI indicates uncertainty interval; and YLDs, years of life lived with disability or injury.

Source: Data derived from Global Burden of Disease Study 2019, Institute for Health Metrics and Evaluation, University of Washington.<sup>75</sup> Printed with permission. Copyright © 2020, University of Washington.



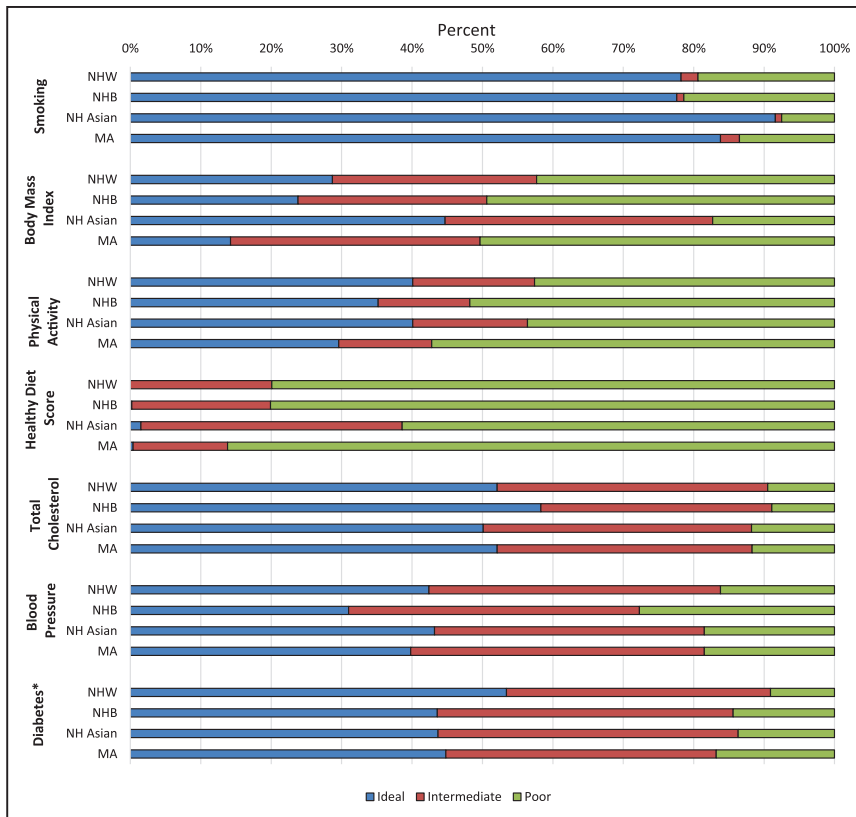
**Chart 2-1. Prevalence estimates of poor, intermediate, and ideal CVH for each component of CVH among US children 12 to 19 years of age and US adults ≥20 years of age, 2017 to 2018.**

CVH indicates cardiovascular health.  
 \*Data collection methodology for physical activity (PA) was changed in 2017 to 2018 for participants <18 years of age. Thus, prevalence of ideal PA levels in this age group during this cycle was based on data from 18 to 19 years of age only.  
 †Categories defined by either fasting plasma glucose or hemoglobin A1c 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.<sup>62</sup>



**Chart 2-2. Prevalence estimates of poor, intermediate, and ideal CVH for each component of CVH by race and ethnicity among US children 12 to 19 years of age, 2017 to 2018.**

CVH indicates cardiovascular health; MA, Mexican American; NH, non-Hispanic; NHB, non-Hispanic Black; and NHW, non-Hispanic White.  
 \*Data from 18 to 19 years of age only.  
 †Categories defined by either fasting plasma glucose or hemoglobin A1c 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.<sup>62</sup>

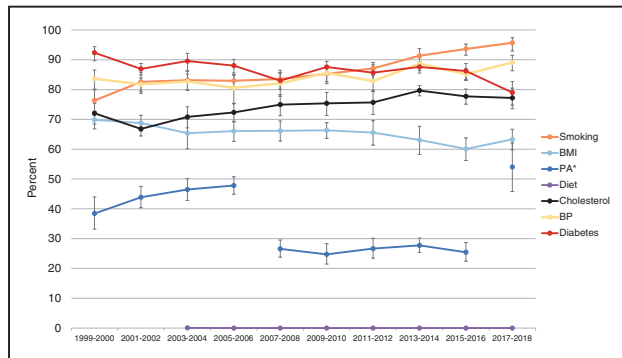


**Chart 2-3. Age-adjusted prevalence estimates of poor, intermediate, and ideal CVH for each component of CVH by race and ethnicity among US adults ≥20 years of age, 2017 to 2018.**

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

\*Categories defined by either fasting plasma glucose or hemoglobin A1c on the basis of data availability.

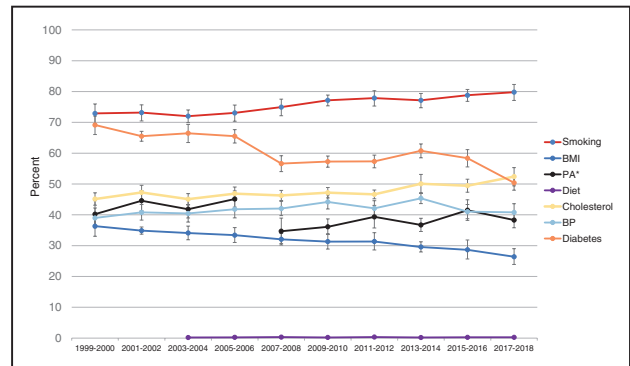
Source: Unpublished American Heart Association tabulation using National Health and Nutrition Examination Survey.<sup>62</sup>



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

BMI indicates body mass index; BP, blood pressure; CVH, cardiovascular health; and PA, physical activity. 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 through the 2017 to 2018 NHANES (National Health and Nutrition Examination Survey) cycles.

\*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. Thus, prevalence of ideal PA levels in this age group during this cycle was based on data from youth 18 to 19 years of age only. Please interpret the large increase in ideal PA levels with years of age in mind. Source: Unpublished American Heart Association tabulation using NHANES.<sup>62</sup>



**Chart 2-5. Age-standardized trends in prevalence of meeting ideal criteria for individual components of 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 through 2017 to 2018 NHANES (National Health and Nutrition Examination Survey) cycles.

BMI indicates body mass index; BP, blood pressure; CVH, cardiovascular health; 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.<sup>62</sup>

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### 3. SMOKING/TOBACCO USE

See Table 3-1 and Charts 3-1 through 3-5

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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, including stroke.<sup>1</sup> 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.<sup>2,3</sup> Unless otherwise stated, throughout the rest of this chapter, we report tobacco use and smoking estimates from the NYTS<sup>2</sup> for adolescents and from the NHIS<sup>4</sup> 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.<sup>2</sup>

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 adults and high school–aged children. The variety of e-cigarette–related products has increased exponentially, giving rise to the more general term *electronic nicotine delivery systems*.<sup>5</sup> 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 from nicotine salts in loose-leaf tobacco.<sup>6</sup> Use of cigars, cigarillos, filtered cigars, and hookah (ie, water pipe) 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.

The 2022 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 2022. 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 and ethnicity in 2020 is shown in Chart 3-1.
- In 2020<sup>7</sup>:
  - 23.6% (95% CI, 21.1%–26.4%) of high school students (corresponding to 3.7 million users) and 6.7% (95% CI, 5.5–8.2) of middle school students (corresponding to 800 000 users) used any tobacco products. In addition, 4.6% (95% CI, 3.6%–6.0%) of high school students (710 000 users) and 1.6% (95% CI, 1.2%–2.2%) of middle school students (190 000 users) smoked cigarettes in the past 30 days.
  - 3.1% (95% CI, 2.3%–4.1%) of high school students (480 000 users) and 1.2% (95% CI, 0.9%–1.6%) of middle school students (140 000) used smokeless tobacco in the past 30 days.
  - 5.0% (95% CI, 4.1%–6.2%) of high school students (770 000 users) and 1.5% (95% CI, 1.2%–2.0%) of middle school students (180 000 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.<sup>8</sup>
- In 2020, tobacco use within the past month for middle and high school students varied by race and ethnicity: The prevalence of past 30-day cigarette use was 3.7% (95% CI, 2.8%–4.8%) in NH White youth compared with 2.5% (95% CI, 1.8%–3.5%) in NH Black youth and 3.6% (95% CI, 2.6%–4.9%) in Hispanic youth. For cigars, the respective percentages were 2.8% (95% CI, 2.1%–3.7%), 6.5% (95% CI, 5.2%–8.2%), and 4.0% (95% CI, 2.9%–5.4%).<sup>7</sup>
- The percentage of high school (19.6% or 3 020 000 users) and middle school (4.7% or 550 000 users) students who used e-cigarettes in the past 30 days exceeded the proportion using cigarettes in 2020 (Chart 3-1).<sup>7</sup>

##### Adults

(See Charts 3-2 and 3-3)

- According to the NHIS 2019 data, among adults ≥18 years of age<sup>9</sup>:
  - 14.0% (95% CI, 13.5%–14.5%) of adults reported cigarette use every day or some days.
  - 15.3% (95% CI, 14.5%–16.1%) of males and 12.7% (95% CI, 12.0%–13.4%) of females reported cigarette use every day or some days.
  - 8.0% of those 18 to 24 years of age, 16.7% of those 25 to 44 years of age, 17.0% of those

- 45 to 64 years of age, and 8.2% of those  $\geq 65$  years of age reported cigarette use every day or some days.
- 20.9% of NH American Indian or Alaska Native adults, 14.9% of NH Black adults, 7.2% of NH Asian adults, 8.8% of Hispanic adults, and 15.5% 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 21.4% of people with  $< \$35\,000$  income compared with 15.7% of those with income of  $\$35\,000$  to  $\$74\,999$ , 11.4% of those with income of  $\$75\,000$  to  $\$99\,999$ , and 7.1% of those with income  $\geq \$100\,000$ .
  - In adults  $\geq 25$  years of age, the percentage reporting current cigarette use was 21.6% for those with  $< 12$  years of education, 35.3% in those with a General Educational Development high school equivalency, 19.6% among those with a high school diploma, 17.7% among those with some college, 14.0% among those with an associate's degree, and 6.9% among those with an undergraduate degree compared with 4.0% among those with a graduate degree.
  - 19.2% of lesbian/gay/bisexual individuals were current smokers compared with 13.8% of heterosexual/straight individuals.
  - By region, the prevalence of current cigarette smokers was highest in the Midwest (16.4%) and South (15.4%) and lowest in the Northeast (12.8%) and West (10.4%).<sup>9</sup>
  - According to data from BRFSS 2019, the state with the highest age-adjusted percentage of current cigarette smokers was West Virginia (25.4%). The states with the lowest age-adjusted percentage of current cigarette smokers were Utah (7.9%) and California (10.1%; Chart 3-2).<sup>10</sup>
  - In 2019, smoking prevalence was higher among adults  $\geq 18$  years of age who reported having a disability or activity limitation (21.1%) than among those reporting no disability or limitation (13.3%).<sup>9</sup>
  - Among individuals who reported cigarette use every day or some days, 34.5% reported having severe generalized anxiety disorder, 27.0% reported having moderate generalized anxiety disorder, and 21.5% reported having mild generalized anxiety disorder compared with 12.0% who reported having no/minimal generalized anxiety disorder.<sup>9</sup>
  - Among females who gave birth in 2017, 6.9% smoked cigarettes during pregnancy. Smoking prevalence during pregnancy was greatest for females 20 to 24 years of age (9.9%), followed by females 15 to 19 years of age (8.3%) and 25 to 29 years of age (7.9%).<sup>11</sup> Rates were highest among NH American Indian or Alaska Native females (15%)

and lowest in NH Asian females (1%). With respect to differences by education, cigarette smoking prevalence was highest among females who completed high school (12.2%), and lowest among females with a master's degree and higher (0.3%).

- 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.<sup>10</sup>

## Incidence

- According to the 2019 NSDUH,  $\approx 1.60$  million people  $\geq 12$  years of age had smoked cigarettes for the first time within the past 12 months compared with 1.83 million in 2018 (2019 NSDUH Table 4.2B).<sup>12</sup> Of new smokers in 2019, 541 000 were 12 to 17 years of age, 672 000 were 18 to 20 years of age, and 292 000 were 21 to 25 years of age; only 90 000 were  $\geq 26$  years of age when they first smoked cigarettes.
- The number of new smokers 12 to 17 years of age in 2019 (541 000) decreased from 2018 (571 000). The number of new smokers 18 to 25 years of age in 2019 (964 000) also decreased from 2018 (1.14 million) (2019 NSDUH Table 4.2B).<sup>12</sup>
- 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.<sup>13</sup>

## Lifetime Risk

### Youth

- Per NSDUH data for individuals 12 to 17 years of age, overall, the lifetime use of tobacco products declined from 13.4% to 12.8% between 2018 and 2019, with lifetime cigarette use declining from 9.6% to 9.0% during the same time period (2019 NSDUH Tables 2.1B and 2.2B).<sup>12</sup>
  - 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 (14.5%) than females (11.0%; 2019 NSDUH Table 2.8B).<sup>12</sup>



- Race and ethnicity: Lifetime use was highest among American Indian and Alaska Native adolescents (21.6%), followed by NH White adolescents (14.8%), Hispanic or Latino adolescents (12%), NH Black adolescents (8.8%), and NH Asian adolescents (3.5%; 2019 NSDUH Table 2.8B).<sup>12</sup>

### Adults

- According to NSDUH data, the lifetime use of tobacco products in individuals  $\geq 18$  years of age did not decline significantly between 2018 (66.3%) and 2019 (65.8%). Lifetime cigarette use declined in a similar interval from 60.3% to 59.5% (2019 NSDUH Tables 2.1B). Similar to the patterns in youth, lifetime risk of tobacco products varied by demographic factors (2019 NSDUH Table 2.8B)<sup>12</sup>:
  - Sex: Lifetime use was higher in males (74.4%) than females (57.7%).
  - Race and ethnicity: Lifetime use was highest in American Indian or Alaska Native adults (70.4%) and NH White adults (74.4%), followed by Native Hawaiian or Other Pacific Islander adults (48.9%), Hispanic or Latino adults (51.7%), NH Black adults (53.0%), and NH Asian adults (36.9%).
- In 2019, the lifetime use of smokeless tobacco for adults  $\geq 18$  years of age was 16.6% (2019 NSDUH Table 2.4B).<sup>12</sup>

## Secular Trends (See Chart 3-4)

### Youth

According to data from NSDUH (12–17 years of age) and MTF (8th and 10th grades combined), the percentage of adolescents who reported smoking cigarettes in the past month declined from 13.0% and 14.2% in 2002 to 2.3% and 2.9% in 2019, respectively (Chart 3-4).<sup>12,14</sup> The percentages for daily cigarette use among those with past-month cigarette smoking in individuals 12 to 17 years of age were 31.5% in 2002 and 13.2% in 2019.<sup>12,15</sup>

### 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.<sup>4</sup> 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.<sup>16</sup>

- On the basis of weighted NHIS data (2019), the current smoking status among males 18 to 24 years

of age declined from 28.0% in 2005 to 15.3% in 2019; for females 18 to 24 years of age, smoking declined from 20.7% to 12.7% over the same time period.<sup>9</sup>

- According to data from the BRFSS, the prevalence of e-cigarette use increased from 4.3% to 4.5% between 2016 and 2019 in US adults. Increases in e-cigarette use over this period were significant for middle-aged adults, females, and former smokers.<sup>17</sup>

## 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.<sup>18</sup> 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.<sup>19</sup>
- 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.<sup>18</sup>
- Cigarette smoking and other traditional CHD risk factors might have a synergistic interaction in HIV-positive individuals.<sup>20</sup>
- 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]).<sup>21</sup>
- A meta-analysis of 75 cohort studies ( $\approx 2.4$  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]).<sup>22</sup>
- 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.<sup>23</sup>
- A meta-analysis comparing pooled data of  $\approx 3.8$  million smokers and nonsmokers found a similar risk of stroke associated with current smoking in females and males.<sup>24</sup>
- Current smokers have a 2 to 4 times increased risk of stroke compared with nonsmokers or those who have quit for  $> 10$  years.<sup>23,25</sup> Among JHS participants without a history of stroke (N=4410), risk of stroke was higher among current smokers compared with individuals who never smoked (HR, 2.48; 95% CI, 1.60–3.83).<sup>26</sup>
- 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.<sup>27</sup> 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).<sup>28</sup>
- Short-term exposure to hookah smoking is associated with a significant increase in BP and heart rate and changes in cardiac function and blood flow, similar to those associated with cigarette smoking.<sup>29</sup> The short-term vascular impairment associated with hookah smoking is masked by the high levels of carbon monoxide—a vasodilator molecule—released from the charcoal briquettes used to heat the flavored tobacco product.<sup>30</sup> In a recent meta-analysis of 42 studies, compared with nonsmokers, hookah smokers had significantly lower HDL-C and higher LDL-C, triglycerides, and fasting glucose.<sup>31</sup> The long-term effects of hookah smoking 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.<sup>32</sup>
  - The long-term CVD risks associated with e-cigarette use are not known because of a lack of longitudinal data.<sup>33,34</sup> 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.<sup>35</sup> In addition, daily and some-day use of e-cigarettes may be associated with MI and CHD.<sup>36,37</sup>
  - 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.<sup>37</sup> 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.
  - In a pooled analysis of data collected from 10 randomized trials (N=2564), smokers had a higher risk of death or HF hospitalization (HR, 1.49 [95% CI, 1.09–2.02]), as well as reinfarction (HR, 1.97 [95% CI, 1.17–3.33]) after primary PCI in STEMI.<sup>38</sup>

### Family History and Genetics

- Genetic factors contribute to smoking behavior; in analyses of up to 346813 participants, common and rare variants in dozens of loci have been found to be

associated with smoking initiation, number of cigarettes smoked per day, and smoking cessation.<sup>39,40</sup>

- Genetics might also modify adverse CVH outcomes among smokers, with variation in *ADAMTS7* associated with loss of cardioprotection in smokers.<sup>41</sup>
- Mendelian randomization analysis has linked genetic liability to smoking to ASCVD, including increased risk of PAD (OR, 2.13 [95% CI, 1.78–2.56];  $P=3.6\times 10^{-16}$ ), CAD (OR, 1.48 [95% CI, 1.25–1.75];  $P=4.4\times 10^{-6}$ ), and stroke (OR, 1.40 [95% CI, 1.02–1.92];  $P=0.04$ ).<sup>42</sup>

### 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.<sup>43</sup>

- 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.<sup>44</sup>
  - In Massachusetts, investigators examined the associations between county-level tobacco 21 laws with adolescent cigarette and e-cigarette use. Increasing tobacco 21 laws were significantly ( $P=0.01$ ) associated with decreases in cigarette use only among adolescents 18 years of age.<sup>45</sup>
  - 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.<sup>46</sup>
- 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.<sup>47</sup> 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.<sup>47</sup>
- 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.<sup>48</sup>

## 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%).<sup>49</sup>
  - 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%.<sup>50</sup>
  - According to NHIS 2015 data, among all smokers, 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 professional advice to quit.<sup>51</sup> 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.<sup>52</sup>
- 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]).<sup>53</sup> 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.<sup>51</sup>
  - 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).<sup>51</sup>
- 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.<sup>54,55</sup>
  - Quitting smoking at any age significantly lowers mortality from smoking-related diseases, and the risk declines with the time since quitting smoking.<sup>1</sup> Cessation appears to have both short-term (weeks to months) and long-term (years) benefits for lowering CVD risk.<sup>56</sup>
  - 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.<sup>54</sup>
  - 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.<sup>57</sup>
- Among 726 smokers included in the Wisconsin Smokers Health Study, smoking cessation was associated with less progression of carotid plaque but not IMT.<sup>58</sup>
- Cessation medications (including sustained-release bupropion, varenicline, nicotine gum, lozenge, nasal spray, and patch) are effective for helping smokers quit.<sup>59,60</sup>
- 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 ( $\geq 50\%$  of daily cigarette consumption) were also higher in the varenicline group.<sup>61</sup>
- The EAGLES trial<sup>62</sup> 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.<sup>62</sup>
  - Extended use of a nicotine patch (24 compared with 8 weeks) has been demonstrated to be safe and efficacious in randomized clinical trials.<sup>63</sup>
  - An RCT demonstrated the effectiveness of individual- and group-oriented financial incentives for tobacco abstinence through at least 12 months of follow-up.<sup>64</sup>
  - 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.<sup>51,65</sup>
  - 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  $\approx 179\,099$  QALYs, and prevented  $\approx 17\,000$  premature deaths in the United States.<sup>66</sup>
  - 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.<sup>67</sup>
  - 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.<sup>68</sup>

- In a meta-analysis of 55 observational studies and 9 RCTs, e-cigarettes were not associated with increased smoking cessation, but e-cigarette provision was associated with increased smoking cessation.<sup>69</sup>

## 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,  $\approx 1$  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.<sup>70</sup> Overall mortality among US smokers is 3 times higher than that for never-smokers.<sup>54</sup>
- 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.<sup>16,71</sup>
- Increased CVD mortality risks persist for older ( $\geq 60$  years of age) smokers as well. A meta-analysis of 25 studies comparing CVD risks in 503 905 cohort participants  $\geq 60$  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.<sup>72</sup>
- 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.<sup>73</sup>
- 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.<sup>74</sup>
- If current smoking trends continue, 5.6 million US children will die of smoking prematurely during adulthood.<sup>18</sup>

## E-Cigarettes and Vaping Products

### (See Charts 3-1 and 3-3)

- Electronic nicotine delivery systems are battery-operated devices that deliver nicotine, flavors, and other chemicals to the user in an aerosol without any combustion. Although e-cigarettes—the most common form of electronic nicotine delivery systems—were introduced into the United States only around 2007, there are currently  $>450$  e-cigarette brands and vaping products on the market, and

sales in the United States were projected to be \$2 billion in 2014. Juul came on the market in 2015 and has rapidly become the most popular vaping 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.<sup>75</sup> Besides e-cigarettes and Juul, e-hookahs (ie, e-waterpipes) are a new category of vaping devices recently patented by Philip Morris in 2019.<sup>76,77</sup> Unlike e-cigarettes and Juul, e-hookahs are used through traditional water pipes, allowing the flavored aerosol to pass through the water-filled bowl before being inhaled.<sup>78</sup> The popularity of e-hookahs is driven in part by unsubstantiated claims that the presence of water “filters out toxins,” rendering e-hookahs as healthier tobacco alternatives.<sup>79,80</sup>

- 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.<sup>81</sup>
- Current e-cigarette user prevalence for 2017 in the United States is shown in Chart 3-3.
- According to the NYTS, in 2020, e-cigarettes were the most commonly used tobacco products in youth: In the past 30 days, 4.7% (550 000) of middle school and 19.6% (3.0 million) of high school students endorsed use (Chart 3-1).<sup>7</sup> An exponential increase in current e-cigarette use in high school students was observed between 2011 (1.5%) and 2020 (19.6%).<sup>7,82</sup> A significant increase in current e-cigarette use also was observed for middle school students, for whom the corresponding values were 0.6% and 4.7% in the 2 periods.<sup>2,7</sup> Among high school students, rates of use were slightly higher among males (20.4%) than females (18.7%) and most pronounced among NH White students (23.2%). In middle school students, rates of use were approximately equal between males (4.5%) and females (4.8%) and in Hispanic students (7.1%).<sup>7</sup>
- According to the NYTS, current exclusive e-cigarette use among US youth who have never used combustibles, including cigarettes, increased exponentially from 2014 to 2019.<sup>83</sup> Among high school students, current exclusive e-cigarette use increased from 1.4% (95% CI, 1.0%–2.1%) in 2014 to 9.2% (95% CI, 8.2%–10.2%) in 2019 and from 0.9% (95% CI, 0.6%–1.3%) in 2014 to 4.5% (95% CI, 3.7%–5.2%) in 2019 among middle school students.
- 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 frequently using e-cigarettes among current users increased from 16.2% in 2018 to 18.0% in 2019.<sup>2,8</sup>
- Current use of e-cigarettes among high school students declined from 27.5% in 2019 to 19.6% in 2020.<sup>7</sup> In middle school students, current e-cigarette use declined from 10.5% in 2019 to 4.7% in 2020.
- In 2016, 20.5 million US middle and high school students (80%) were exposed to e-cigarette advertising.<sup>84</sup>
- In 2019, the prevalence of current e-cigarette use in adults, defined as use every day or on some days, was 4.5% according to data from the NHIS. The prevalence of current e-cigarette use was highest in individuals 18 to 24 years of age (9.3%) and among those reporting severe generalized anxiety disorder (10.1%).<sup>9</sup>
- According to data from BRFSS 2016 to 2018, current use of e-cigarettes in adults ≥18 years of age was higher in sexual and gender minority individuals.<sup>85,86</sup> Data from 2017 and 2018 data sets show that the prevalence of current e-cigarette use among sexual and gender minority adults was 13.0% (95% CI, 12.0%–14.2%) versus 4.8% (95% CI, 4.6%–4.9%) among heterosexuals.<sup>85</sup> In 2016, 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%).<sup>86</sup>
- Limited data exist on the prevalence of other electronic nicotine delivery devices besides e-cigarettes. According to nationally representative data from the PATH study, in 2014 to 2015, 7.7% of youth 12 to 17 years of age reported ever e-hookah use.<sup>87</sup> Among adults >18 years of age, 4.6% reported ever e-hookah use, and 26.8% of them reported current use.
- E-cigarettes contain lower levels of most tobacco-related toxic constituents compared with traditional cigarettes,<sup>88</sup> including volatile organic compounds.<sup>89,90</sup> However, nicotine levels have been found to be consistent across long-term cigarette and long-term e-cigarette users.<sup>35,91</sup>
- E-cigarette use has a significant cross-sectional association with a less favorable perception of physical and mental health and with depression.<sup>92,93</sup>
- 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.<sup>94,95</sup>

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.<sup>96</sup>
- Effective August 8, 2016, the FDA's Deeming Rule prohibited sale of e-cigarettes to individuals <18 years of age.<sup>97</sup>
- 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).<sup>98</sup>
- According to data from the BRFSS 2016 and 2017, e-cigarette use among adults is associated with state-level regulations and policies regarding e-cigarettes: OR of 0.90 (95% CI, 0.83–0.98) for laws prohibiting e-cigarette use in indoor areas; OR of 0.90 (95% CI, 0.85–0.95) for laws requiring retailers to purchase a license to sell e-cigarettes; OR of 1.04 (95% CI, 0.99–1.09) for laws prohibiting self-service displays of e-cigarettes; OR of 0.86 (95% CI, 0.74–0.99) for laws prohibiting sales of tobacco products, including e-cigarettes, to people <21 years of age; and OR of 0.89 (95% CI, 0.83–0.96) for laws applying taxes to e-cigarettes.<sup>99</sup>

## 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%.<sup>18</sup>
  - 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.<sup>100</sup>

- 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.<sup>101</sup>
- A meta-analysis of 24 studies demonstrated that secondhand smoke can increase risks for preterm birth by 20%.<sup>102</sup>
- 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.<sup>103</sup>
- As of September 30, 2020, 15 states (California, Colorado, Delaware, Hawaii, Massachusetts, Minnesota, 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.<sup>48,104</sup>
- 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]).<sup>105</sup>
- The percentage of the US nonsmoking population with serum cotinine  $\geq 0.05$  ng/mL (which indicates exposure to secondhand smoke) declined from 52.5% in 1999 to 2000 to 24.7% in 2017 to 2018, with declines occurring for both children and adults. During 2017 to 2018, the percentage of nonsmokers with detectable serum cotinine was 38.2% for those 3 to 11 years of age, 33.2% for those 12 to 19 years of age, and 21.2% for those  $\geq 20$  years of age. The percentage was higher for NH Black individuals (48.0%) than for NH White individuals (22.0%) and Mexican American individuals (16.6%). People living below the poverty level (44.7%) had higher rates of secondhand smoke exposure than their counterparts (21.3% of those living above the poverty level; NHANES).<sup>106,107</sup>

## 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 attributable to premature death



accounted for \$151 billion (estimated from 2005–2009); and lost productivity resulting from secondhand smoke accounted for \$5.6 billion (in 2006).<sup>16</sup>

- 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).<sup>108</sup>
- 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.<sup>109</sup> In 2018, total US e-cigarette advertising expenditures (including print, radio, television, internet, and outdoors) were estimated to be \$110 million, which increased remarkably from \$48 million in 2017.<sup>110</sup>
- 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.<sup>111</sup>
- Cigarette prices in the United States increased steeply between the early 1970s and 2018, in large part because of excise taxes on tobacco products. The increase in cigarette prices appeared to be larger than general inflation: 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 was \$2.82.<sup>112</sup>
- 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.<sup>112</sup>
- Despite the morbidity and mortality resulting from tobacco use, Dieleman et al<sup>113</sup> 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 3-5)

- The GBD 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020. Oceania, East and Central Asia, and Central and Eastern Europe had the highest age-standardized mortality rates attributable to tobacco (Chart 3-5).
- Tobacco caused 8.09 (95% UI, 3.18–12.76) million deaths in 2020, with 6.27 (95% UI, 2.24–9.88)

million among males and 1.82 (95% UI, 0.83–2.95) million among females (Table 3-1).<sup>114</sup>

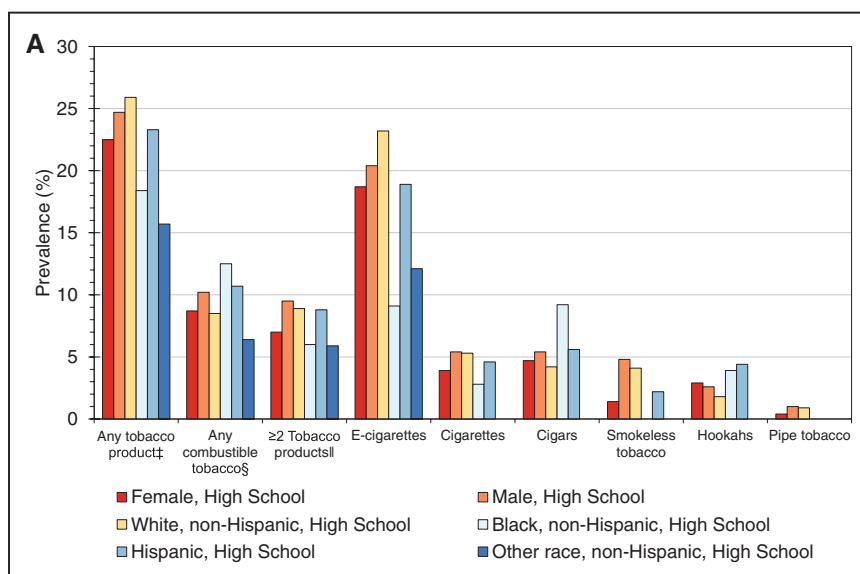
- GBD investigators estimated that in 2019 tobacco was the second leading risk of mortality (high SBP was number 1), and tobacco ranked third in DALYs globally.<sup>115</sup>
- In 2015, there were a total of 933.1 million (95% UI, 831.3–1054.3 million) smokers globally, of whom 82.3% were male. The annualized rate of change in smoking prevalence between 1990 to 2015 was –1.7% in females and –1.3% in males.<sup>116</sup>
- Worldwide, ≈80% of tobacco users live in low- and middle-income countries.<sup>117</sup>
- 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.<sup>118</sup> 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.<sup>86,119</sup> 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.<sup>120</sup>
- 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.<sup>121</sup>

**Table 3-1. Deaths Caused by Tobacco Worldwide by Sex, 2020**

	Both sexes (95% UI)	Males (95% UI)	Females (95% UI)
Total No. of deaths (millions), 2020	8.09 (3.18 to 12.76)	6.27 (2.24 to 9.88)	1.82 (0.83 to 2.95)
Percent change in total number, 1990–2020	31.44 (15.71 to 47.29)	36.43 (20.45 to 52.74)	16.73 (–1.23 to 41.09)
Percent change in total number, 2010–2020	10.51 (2.64 to 18.88)	11.34 (1.90 to 21.43)	7.72 (–0.56 to 15.81)
Mortality rate per 100 000, age standardized, 2020	98.79 (38.72 to 156.87)	169.11 (60.84 to 267.05)	40.88 (18.59 to 66.00)
Percent change in rate, age standardized, 1990–2020	–39.50 (–44.76 to –33.91)	–39.23 (–44.54 to –33.43)	–45.98 (–52.04 to –37.93)
Percent change in rate, age standardized, 2010–2020	–16.95 (–22.65 to –11.06)	–16.75 (–23.46 to –9.73)	–19.54 (–25.39 to –13.62)
PAF, all ages, 2020	14.26 (5.60 to 22.39)	20.29 (7.06 to 31.50)	7.05 (3.26 to 11.55)
Percent change in PAF, all ages, 1990–2020	4.90 (–6.04 to 16.13)	8.14 (–1.17 to 17.01)	–6.07 (–19.50 to 13.49)
Percent change in PAF, all ages, 2010–2020	1.71 (–3.01 to 6.80)	3.32 (–1.08 to 8.19)	–1.83 (–7.04 to 3.52)

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

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021, University of Washington. More information is available on the Global Burden of Disease Study website.<sup>114</sup>

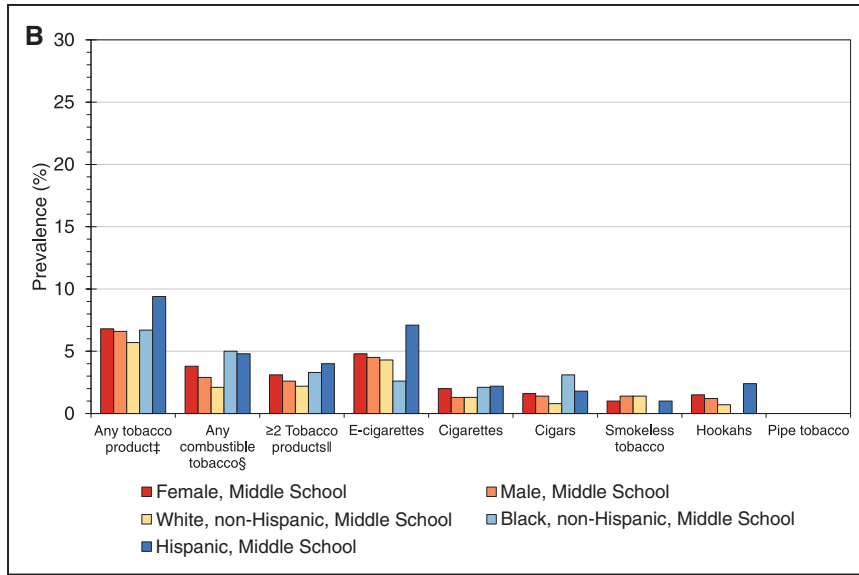


**Chart 3-1. Prevalence (percent) of tobacco use in the United States in the past 30 days by product,\* school level, sex, and race and ethnicity† (NYTS, 2020).**

**A**, High school students. **B**, Middle school students.

E-cigarette indicates electronic cigarette; and NYTS, National Youth Tobacco 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?” 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. (Continued)



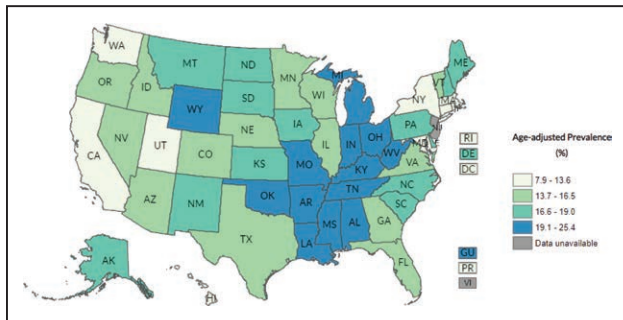
**Chart 3-1 Continued.** Past 30-day use of hookahs was determined by asking “During the past 30 days, on how many days did you smoke tobacco in a hookah or waterpipe?” Past 30-day use of pipe tobacco (not hookahs) was determined by asking “In the past 30 days, which of the following products have you used on at least 1 day?” Past 30-day use of heated tobacco products was determined by asking “During the past 30 days, on how many days did you use heated tobacco products?” Because of missing data on the past 30-day use questions, denominators for each tobacco product might be different.

‡In 2020, any tobacco product use was defined as use of any tobacco product (e-cigarettes, cigarettes, cigars, smokeless tobacco, hookahs, pipe tobacco, bidis [small brown cigarettes wrapped in a leaf], or heated tobacco products) on ≥1 day during the past 30 days.

§Any combustible tobacco product use was defined as use of cigarettes, cigars, hookahs, pipe tobacco, or bidis on ≥1 day during the past 30 days.

||In 2020, multiple tobacco product use was defined as use of ≥2 tobacco products (e-cigarettes, cigarettes, cigars, smokeless tobacco, hookahs, pipe tobacco, bidis, or heated tobacco products) on ≥1 day during the past 30 days.

Source: Data derived from Gentzke et al.<sup>7</sup>

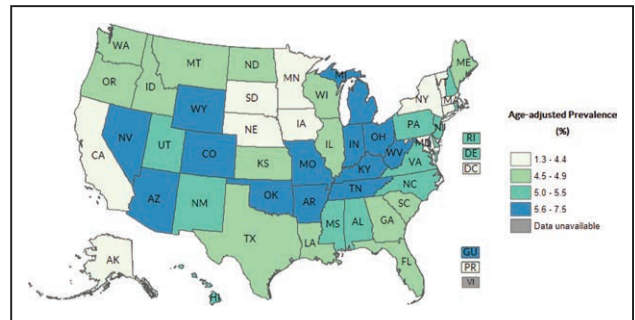


**Chart 3-2. Age-adjusted prevalence (percent) of current cigarette smoking for US adults by state (BRFSS, 2019).**

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.<sup>10</sup>

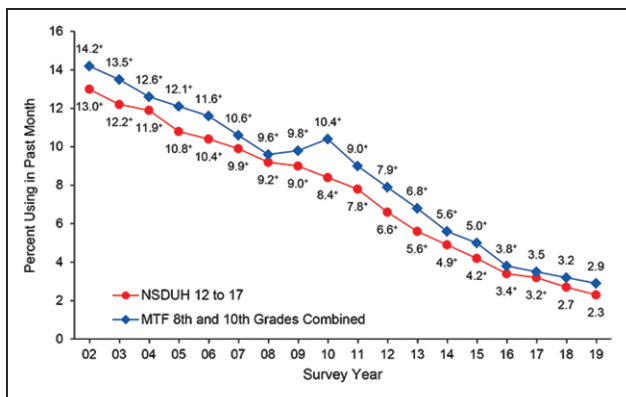


**Chart 3-3. Prevalence (age-adjusted) of current electronic cigarette use, United States (BRFSS, 2017).**

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.

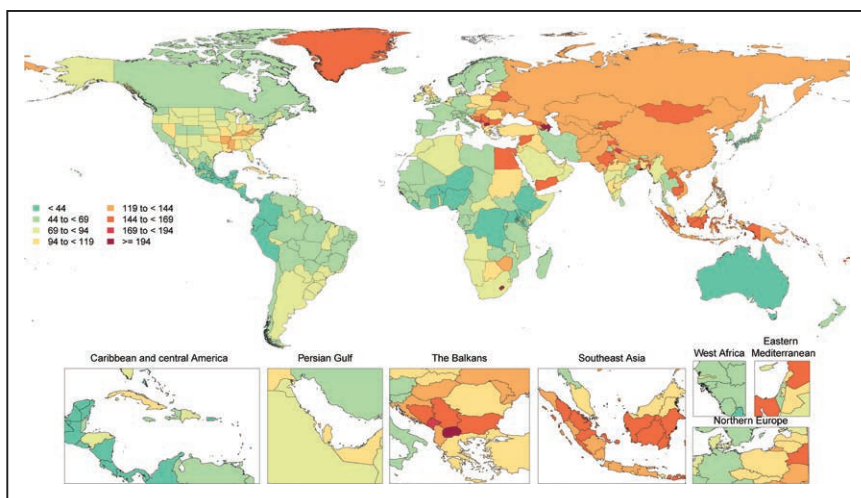
Source: BRFSS prevalence and trends data.<sup>10</sup>



**Chart 3-4. Past-month cigarette use among US youths in NSDUH and MTF: 2002 to 2019.**

MTF indicates Monitoring the Future; and NSDUH, National Survey on Drug Use and Health.

Source: Reprinted from NSDUH.<sup>12,14</sup>



**Chart 3-5. Age-standardized global mortality rates attributable to tobacco per 100 000, both sexes, 2020.**

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021, University of Washington. More information is available on the GBD website.<sup>114</sup>

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## 4. PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR

See *Charts 4-1 through 4-9*

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PA is defined as any body movement produced by skeletal muscles that results in energy expenditure. In 1992, the AHA first published a position statement declaring lack of PA as a risk factor for the development of CHD.<sup>1</sup> As the research accumulated, lack of PA was established as a major risk factor for CVD (eg, CHD, stroke, PAD, HF).<sup>2</sup>

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).<sup>3</sup> In 2019, on the basis of survey interviews, only 23.2% of high school students reported achieving at least 60 minutes of daily PA,<sup>4</sup> which is likely an overestimation of those actually meeting the guidelines.<sup>5</sup> The 2018 Physical Activity Guidelines for Americans<sup>3</sup> recommend that adults accumulate at least 150min/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. The 2019 CVD Primary Prevention Clinical Practice Guidelines<sup>6</sup> support the aerobic recommendations. For many people, examples of absolutely defined 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). Achieving the guideline recommendations for PA is 1 of the AHA's 7 components of ideal CVH for both children and adults.<sup>7</sup>

More recently, the 2020 WHO guidelines supported moderate to vigorous PA across all age groups and abilities,<sup>8</sup> including those living with a disability.<sup>9</sup> Even for those who cannot meet recommended levels of PA, being as physically active as abilities and conditions allow is still beneficial; some PA is better than none.<sup>3</sup> Small

increases in moderate-intensity PA or replacing sedentary behavior with light-intensity PA can provide health benefits.<sup>3,8-10</sup> Cardiorespiratory fitness is the ability to perform whole-body, large-muscle exercise at moderate to vigorous levels of intensity for extended time periods.<sup>3</sup> PA and cardiorespiratory fitness provide distinct metrics in assessment of CVD risk.<sup>11</sup>

Sedentary behavior is defined as “any waking behavior characterized by an energy expenditure  $\leq 1.5$  MET while in a sitting, reclining, or lying posture.”<sup>12</sup> Sedentary behavior is a distinct construct from PA and is characterized by activities such as driving/riding in a vehicle, using a screen (eg, watching television, playing video games, using a computer), or reading. The WHO guidelines<sup>8</sup> recommend reducing sedentary behaviors across all age groups and abilities, but precise guidance is not yet possible given the current state of the science.

### Measuring PA and Sedentary Behavior

Several dimensions (eg, mode or type, frequency, duration, and intensity) and domains (eg, occupational, domestic, transportation, and leisure time) characterize PA. There are additional considerations of where PA occurs such as in homes, worksites, schools, and communities. The federal guidelines<sup>3</sup> specify the suggested frequency, duration, and intensity of PA and focus on aerobic and strengthening modalities.

Measurement of PA can be defined by 2 broad assessment methods: (1) self-reported methods that use questionnaires and diaries/logs and (2) device-based methods that use wearables (eg, pedometers, accelerometers). Studies that have compared the findings between methods have shown that there is discordance between self-reported and measured PA, with respondents often overstating their PA compared with device-based measures.<sup>5</sup> Sedentary behavior also has several dimensions (eg, type, frequency, duration) and domains (eg, driving/riding in a vehicle, using a screen, reading) that can also be assessed with both self-reported and device-based methods.

### Prevalence

#### Youth

(See *Chart 4-2*)

#### Physical Activity

- Using parental report, from 2018 to 2019, the nationwide prevalence of youth who were active for  $\geq 60$  minutes every day of the week was higher for youth 6 to 11 years of age (28.3%) compared with youth 12 to 17 years of age (16.5%; Chart 4-2).<sup>13</sup>
- Using nationwide self-reported PA (YRBSS, 2019)<sup>4</sup>:
  - The nationwide prevalence of high school students who engaged in  $\geq 60$  minutes of PA on at

The 2022 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 2022. 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.



least 5 days of the week was 44.1% and was lower with each successive grade (from ninth [49.1%] to 12th [40.0%] grades). The prevalence was higher in boys (52.8%) than in girls (35.3%). The nationwide prevalence of high school students who engaged in  $\geq 60$  minutes of PA on all 7 days of the week was 23.2%, with similar patterns by grade and sex.

- Among high school students, 17.0% reported that they did not participate in  $\geq 60$  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 (19.6% versus 14.4%).
- With the use of accelerometry (NHANES, 2003–2006),<sup>14</sup> youth 6 to 19 years of age had a median of 53 min/d of moderate to vigorous PA.
- With regard to measured cardiorespiratory fitness (NHANES, 2012),<sup>15</sup> for adolescents 12 to 15 years of age, boys at each age were more likely to have adequate levels of cardiorespiratory fitness than girls.
- With regard to self-reported muscle-strengthening activities (YRBSS, 2019),<sup>4</sup> the proportion of high school students who participated in muscle-strengthening activities (such as push-ups, sit-ups, or weight lifting) on  $\geq 3$  d/wk was 49.5% nationwide and was lower in 12th grade (45.9%) compared with 9th grade (52.4%). More high school boys (59.0%) than girls (39.7%) reported having participated in muscle-strengthening activities on  $\geq 3$  d/wk.
- From a nonrepresentative sample of US parents of youth 5 to 13 years of age, there is an indication that PA declined from before COVID-19 to early COVID-19 in 2020.<sup>16</sup> The longer-term impacts of the pandemic on PA and sedentary behavior patterns are not known.

### Physical Education Classes and Organized Sports

- Only 25.9% of students attended physical education classes in school daily (28.9% of boys and 22.8% of girls; YRBSS, 2019).<sup>4</sup>
- Daily physical education class participation was lower with successively higher grades from the 9th grade (34.7%) through the 12th grade (19.7%; YRBSS, 2019).<sup>4</sup>
- Just more than half (57.4%) of high school students played on at least 1 school or community sports team in the previous year (54.6% of girls and 60.2% of boys); this number was lower in 12th grade (49.8%) compared with 9th grade (61.9%; YRBSS, 2019).<sup>4</sup>

### Sedentary Behavior

#### (See Charts 4-3 and 4-4)

- Research suggests that screen time (watching television or using a computer) is associated with less

PA among children.<sup>17</sup> In addition, television viewing is associated with poor nutritional choices, overeating, and weight gain (Chapter 5, Nutrition).

- Nationwide, 46.1% of high school students used a computer, tablet, or smartphone for activities other than school work (eg, video games, texting, social media) for  $\geq 3$  h/d on an average school day (YRBSS, 2019; Chart 4-3).<sup>4</sup> The prevalence differed by race and ethnicity and was high among both boys (47.5%) and girls (44.6%; YRBSS, 2019).<sup>4</sup>
- Among high school students, the prevalence of watching television  $\geq 3$  h/d was 19.8% (YRBSS, 2019; Chart 4-4).<sup>4</sup> The prevalence varied by race and ethnicity and was higher among boys than girls. (31.6%).<sup>4</sup>

### Adults

#### (See Charts 4-5 through 4-7)

#### Physical Activity

- According to NHIS (2018), for self-reported leisure-time aerobic PA:
  - The age-adjusted proportion who reported meeting the 2018 aerobic PA guidelines for Americans ( $\geq 150$  minutes of moderate PA,  $\geq 75$  minutes of vigorous PA, or an equivalent combination each week) through leisure-time activities was 54.2% (Chart 4-5). 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 and ethnic group, males had higher PA than females.<sup>18</sup>
  - The age-adjusted prevalence of meeting the aerobic PA guidelines varied by geography, ranging from the lowest in Puerto Rico (30.4%) and Kentucky (35.9%) to the highest in Montana (62.4%) and Vermont (61.2%; Chart 4-6).<sup>19</sup>
- According to NHANES (2003–2006), adults from urban areas reported more transportation activity, but adults from rural areas reported spending more time in household PA and total PA than individuals from urban areas.<sup>20</sup>
- According to NHIS (2015), the prevalence of any walking for transportation in the United States varied by geographic location, ranging from 17.8% for adults living in the East South Central region to 43.5% for adults living in New England.<sup>21</sup>
- From NHIS (2018) data, 25.4% of adults did not engage in leisure-time PA (no sessions of leisure-time PA of  $\geq 10$  minutes in duration).<sup>22</sup> Trends in physical inactivity over time (1998–2018) are shown in Chart 4-7.
- According to accelerometer-assessed PA (NHANES, 2005–2006),<sup>23</sup> 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 (NHANES, 2003–2006) also revealed that rural-dwelling adults were generally more active than urban-dwelling adults (mean, 325 bout min/d versus 314 bout min/d).<sup>20</sup> Self-reported data from the same sample indicated higher total (438 min/wk versus 371 min/wk) and household PA (202 min/wk versus 124 min/wk), similar leisure PA (207 min/wk versus 206 min/wk), and lower transportation PA (30 min/wk versus 41 min/wk) among rural- compared with urban-dwelling adults.
- In a nonrepresentative sample of adults from 14 countries, a cross-sectional study indicated that self-reported PA declined from before to after COVID-19 restrictions in 2020.<sup>24</sup> The decline was greater for occupational activity compared with leisure activity, for more compared with less active adults, and for younger compared with older adults.
- Activity tracker companies also documented declines in PA among their users during the COVID-19 pandemic. Comparing the week of March 22, 2020, with the same week in 2019 showed that Fitbit-measured steps declined worldwide (eg, declined 24% Argentina, 4% Australia, 15% Brazil, 14% Canada, 16% China, 13% Mexico, 14% Norway, 7% South Africa, 38% Spain, 9% United Kingdom, 12% United States), with the greatest decline occurring in Europe.<sup>25</sup> Users of Garmin activity trackers also documented a decline in average daily steps during the month of March 2020 both globally and for the United States, as well as a shift to indoor fitness-oriented activities.<sup>26</sup> The total number of steps decreased by 7.3% from 2019 to 2020 for Garmin users.<sup>27</sup> It is important to note that those who own and wear activity trackers are not representative of the general population.<sup>28,29</sup>

### Sedentary Behavior

- According to NHANES (2015–2016), 25.7% reported sitting >8 h/d; the time spent sitting was successively higher with older age.<sup>30</sup>
- A Nielsen report indicated that in January 2020 US adults spent on average 12 hours 21 minutes connected to media (eg, television, radio, smartphone, tablet, internet on computer), higher than in January 2018 (11 hours 6 minutes) and January 2019 (11 hours 27 minutes).<sup>31</sup> These habits affect time available for PA and contribute to sedentary behavior.

## Secular Trends

### Youth

#### PA Trends Using YRBS Data

- Among high school students nationwide, the prevalence of being physically active for ≥60 minutes for at least 5 d/wk decreased from 49.5% in 2011 to 44.1% in 2019.<sup>32</sup> Similarly, the prevalence of being physically active for ≥60 minutes on all 7 days in a week decreased from 28.7% in 2011 to 23.2% in 2019.<sup>32</sup>
- Nationwide, the prevalence 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 2019 (52.2%).<sup>32</sup> However, the prevalence of attending physical education classes on all 5 days of the week decreased from 1991 (41.6%) to 2019 (25.9%).
- The prevalence of high school students playing ≥1 team sports in the past year did not substantively change between 1999 (55.1%) and 2019 (57.4%).<sup>32</sup>

#### Sedentary Behavior Trends Using YRBS Data

- Among high school students nationwide, the prevalence of playing video or computer games or using a computer ≥3 hours/d increased from 22.1% in 2003 to 46.1% in 2019.<sup>32</sup> However, watching television for ≥3 h/d decreased from 42.8% in 1999 to 19.8% in 2019.

### Adults

#### (See Chart 4-7)

#### PA Trends Using NHIS Data

- The prevalence of physical inactivity among adults ≥18 years of age, overall and by sex, decreased from 1998 to 2018 (Chart 4-7).
- 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.<sup>33</sup> The percentage of US adults who reported meeting the aerobic guidelines increased from 43.5% in 2008 to 54.2% in 2018.<sup>33</sup>
  - 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% between 2005 and 2015.<sup>34</sup>

#### Sedentary Behavior Trends Using NHANES Data

- 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).<sup>35</sup>

## Social Determinants of Health

### (See Chart 4-8)

- The proportion of adults  $\geq 25$  years of age who met the 2018 guidelines for aerobic PA was higher with successively higher educational attainment category (Chart 4-8). This pattern was similar for meeting recommendations for both aerobic and strengthening activities.
- In 26 high- and 34 middle-income countries between 2001 and 2016, the levels of insufficient PA were greater when there were greater income inequalities (defined as the difference between those with the highest and lowest incomes).<sup>36</sup>

## Genetics and Family History

- Genetic factors have been shown to contribute to the propensity to exercise; however, more work is needed to identify genetic factors that contribute to PA.<sup>37,38</sup>
- Genome-wide association analysis in  $>377\,000$  individuals identified multiple variants associated with habitual PA, including *CADM2* and *APOE*.<sup>37</sup>
- A GWAS of 91 105 individuals with device-measured PA identified 14 significant loci.<sup>39</sup>
- Multiethnic analysis of  $>20\,000$  individuals identified several loci associated with leisure-time PA in individuals of European and African ancestry.<sup>40</sup> Specifically, 4 previous loci (*GABRG3*, *CYP19A1*, *PAPSS2* and *CASR*) were replicated. Among African Americans, 2 variants were identified (rs116550874 and rs3792874) and among European Americans, 1 variant was identified (rs28524846) as being associated with leisure-time PA.
- Genetic variants have been identified, but few have been replicated by other studies.<sup>41</sup>

## Promotion of PA

The US Surgeon General supports Step It Up! A Call to Action to Promote Walking and Walkable Communities in recognition of the importance of PA.<sup>42</sup> There are opportunities for positive changes in communities, schools, and worksites to support walking.

### Communities

- Community-level interventions are effective in promoting PA.<sup>43</sup> Communities can encourage walking with street design that includes sidewalks, improved street lighting, and landscaping design that reduces traffic speed to improve pedestrian safety.<sup>44</sup> Nationwide, in 2017, the most prominent barriers to bicycling included heavy traffic and lack of separated paths or trails.<sup>45</sup> In a qualitative study

across 10 US cities, other barriers to bicycling were identified.<sup>46</sup>

- Park prescriptions, which prescribe PA in local parks, may increase park use, time spent in parks, and recreational PA.<sup>47</sup>
- The COVID-19 pandemic affected walking and bicycling for transportation and leisure through environmental and policy changes designed to limit or accommodate shifting users.<sup>48</sup> The short- and long-term impacts of the environmental and policy changes on representative patterns of walking and bicycling are not yet known.

### Schools

- Schools can provide opportunities for PA through physical education, recess, before- and after-school activity programs, and PA breaks, as well as offering by a place for PA for the community.<sup>49</sup>

### Worksites

- Worksites can offer access to onsite exercise facilities or employer-subsidized offsite 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.<sup>50,51</sup>

## 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.<sup>52</sup>
- A meta-analysis of 23 studies revealed an association between participating in more transportation-related PA and lower all-cause mortality, CVD, and diabetes.<sup>53</sup>
- 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.<sup>54</sup> Data on participants in NHANES enrolled from 1999 to 2006 indicated that participation in moderate to vigorous walking, bicycling, or running was most beneficial for reducing all-cause and CVD mortality.<sup>55</sup>
- 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.<sup>56</sup> However, a lower risk of 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. There are several limitations to the literature that demonstrate these seemingly paradoxical results and likely other confounding factors such as fitness, SES, preexisting CVD, type of occupation, and other domains of PA that may modify this relationship.<sup>57</sup>

- A harmonized 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 (HR, 1.27 [95% CI, 1.22–1.32]). For active individuals (top quartile for PA), sitting time was not associated with all-cause mortality (HR, 1.04 [95% CI, 0.98–1.10]), but active people who watched television ≥5 h/d did have higher mortality risk (HR, 1.15 [95% CI, 1.05–1.27]).<sup>58</sup>
- An umbrella review of 24 systematic reviews of older adults concluded that those who are physically active are at a reduced risk of CVD mortality (25%–40% risk reduction), all-cause mortality (22%–35%), breast cancer (12%–17%), prostate cancer (9%–10%), and depression (17%–31%) while experiencing better quality of life, healthier aging trajectories, and improved cognitive functioning.<sup>59</sup> Another review indicated that sedentary behavior, specifically transportation-related sitting time, was associated with a lower risk of CVD and less favorable cardiovascular risk factors, whereas less consistent associations were found when the exposure focused on occupational sitting.<sup>60</sup>
- 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.<sup>61</sup>

### Device-Measured PA, Sedentary Behavior, and Mortality

- In a review of 15 cohort studies, adults in the highest category of total, light, and moderate to vigorous PA had 67%, 40%, and 56% lower risk for mortality compared with adults in the lowest categories, respectively.<sup>62</sup>
- Among individuals 70 years of age who wore an accelerometer for 1 week, both light PA and moderate PA were associated with a lower risk and sedentary behavior was associated with an increased risk of all-cause mortality, stroke, and MI.<sup>63</sup>

- Among participants 40 to 79 years of age in the population-based European Prospective Investigation Into Cancer and Nutrition–Norfolk Study, higher levels of accelerometer-assessed total and moderate to vigorous PA were associated with a lower incident CVD risk; models indicated an initial steep decrease in the HR followed by a flattening of the curve.<sup>64</sup>
- Among females ≥63 years of age who wore an accelerometer for 1 week, those who spent more time standing (quartile 4 versus 1 HR, 0.63 [95% CI, 0.49–0.81]) and more time standing with ambulation (quartile 4 versus 1 HR, 0.50 [95% CI, 0.35–0.71]) had a lower risk of all-cause mortality.<sup>65</sup>
- In a harmonization meta-analysis of 8 prospective studies of adults measured with accelerometry, over a median of 5.8 years of follow-up, the highest 3 quartiles of light (HR, 0.38–0.60 across quartiles) and moderate to vigorous (HR, 0.52–0.64 across quartiles) PA compared with the lowest quartile (least active) were associated with a lower risk of all-cause mortality.<sup>66</sup> 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). In a follow-up analysis of 9 prospective studies, 30 to 40 min/d of moderate to vigorous PA attenuated the adverse association between sedentary behavior and mortality.<sup>67</sup>
- 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.<sup>10,68</sup> Results from a systematic review revealed that for every 1000 steps taken at baseline, risk reductions ranged from 6% to 36% for all-cause mortality and 5% to 21% for CVD.<sup>69</sup> 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.<sup>10,68</sup>

### Cardiorespiratory Fitness and Mortality

- 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<sup>-1</sup>·kg<sup>-1</sup> increase, respectively, in cardiorespiratory fitness estimated from a submaximal bicycle test.<sup>70</sup> The risk reduction with higher cardiorespiratory fitness was observed for both males and females across ages.

### PA and Cardiovascular/Metabolic Risk Factors

#### Youth

- In a study of 36 956 Brazilian adolescents, higher self-reported moderate to vigorous PA levels (≥600 min/wk compared with 0 min/wk; adjusted proportional OR, 0.80 [95% CI, 0.6–0.95]) and lower

amounts of screen time ( $\geq 6$  h/d compared with  $\leq 2$  h/d; OR, 1.23 [95% CI, 1.10–1.37]) were associated with lower cardiometabolic risk.<sup>71</sup>

- Among the NHANES 2003 to 2006 cohort of youths 6 to 17 years of age assigned to 4 latent classes with the use of accelerometry-assessed PA, those in the highest latent class PA had lower SBP ( $-4.1$  mmHg [95% CI,  $-7.7$  to  $-0.6$ ]), lower glucose levels ( $-4.3$  mg/dL [95% CI,  $-7.8$  to  $-0.7$ ]), and lower insulin levels ( $-6.8$   $\mu$ U/mL [95% CI,  $-8.7$  to  $-5.0$ ]) than youths in the lowest latent class PA group.<sup>72</sup>
- An umbrella review of 21 systematic reviews found that greater amounts and higher intensities of PA and limiting sedentary behavior were associated with improved health outcomes (eg, cardiometabolic health, cardiorespiratory fitness, adiposity, and cognition) among youth 5 to 17 years of age.<sup>73</sup> However, the evidence base available was insufficient to fully describe the dose-response relationship or whether the association varied by type or domain of PA or sedentary behavior.

### Adults

- A meta-analysis of 37 RCTs of walking interventions in apparently healthy adults indicated favorable effects on cardiovascular risk factors, including body fat, BMI, SBP, DBP, fasting glucose, and maximal cardiorespiratory fitness.<sup>74</sup>
- Multisession behavioral counseling can improve PA among those with elevated lipid levels or BP and reduce LDL, BP, adiposity, and cardiovascular events.<sup>75</sup> The US Preventive Services Task Force recommends “offering or referring adults with CVD risk factors to behavioral counseling interventions to promote a healthy diet and PA” (Grade B).<sup>76</sup>
- In a meta-analysis of 11 studies investigating the role of exercise among individuals with MetS, aerobic exercise significantly improved DBP ( $-1.6$  mmHg;  $P=0.01$ ), WC ( $-3.4$  cm;  $P=0.01$ ), fasting glucose ( $-0.15$  mmol/L;  $P=0.03$ ), and HDL-C ( $0.05$  mmol/L;  $P=0.02$ ).<sup>77</sup>
- 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]).<sup>78</sup>
- In an umbrella review of 17 meta-analyses and 1 systematic review, there was a strong inverse dose-response relationship between PA and incident hypertension, and PA reduced the risk of CVD progression among hypertensive adults.<sup>79</sup>
- 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).<sup>68</sup>

### Cardiovascular Events Among Adults

- 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-intensity PA (150–750 min/wk) and high-intensity PA ( $>750$  min/wk) 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.<sup>80</sup>
- 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.<sup>81</sup>
- 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–step/d increase).<sup>82</sup>
- 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]).<sup>82</sup>
- 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.<sup>83</sup>
- 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.<sup>84</sup> In addition, those watching less television had longer life expectancy free of CHD, stroke, and HF of close to 1 year.
- According to data from the NHANES-III survey, adults with poor PA (OR, 1.30 [95% CI, 1.10–1.54]) and intermediate PA (OR, 1.19 [95% CI, 1.02–1.38]) had an increased odds of subclinical myocardial injury (based on the ECG) compared with those with ideal PA.<sup>85</sup>
- A meta-analysis summarizing 10 studies found that the pooled fully adjusted risk of venous thromboembolism was 0.87 (95% CI, 0.79–0.95) when the



most physically active group was compared with the least physically active group.<sup>86</sup>

- 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]).<sup>87</sup>
- 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.<sup>88</sup>

## Secondary Prevention

- In 2020, the WHO began a review that concluded that services and programs are needed to increase PA and limit sedentary behavior among adults living with chronic conditions, including diabetes and hypertension.<sup>89</sup>
- In a prospective cohort study of 15 486 participants with stable CAD from 39 countries, higher levels of PA were associated with a lower risk of mortality such that doubling the exercise volume was associated with a 10% lower risk of all-cause mortality.<sup>90</sup>
- 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.<sup>91</sup>
- 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]).<sup>92</sup>
- A study of females in the WHI observational study after MI demonstrated that compared with those who maintained low PA levels, participants 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]) had lower risks of mortality.<sup>93</sup>
- Among males after an MI, those who maintained high PA had a 39% lower risk of all-cause mortality, and those who walked for at least 30 min/d had a 29% lower risk of all-cause mortality.<sup>94</sup>
- Exercise and resistance training are recommended for adults after stroke.<sup>95</sup> In a review pooling 499 patients with stroke, exercise programs adhering to

these guidelines indicated improved walking speed and endurance, but no differences for PA or other mobility outcomes, compared with usual care.<sup>96</sup> An RCT found that higher doses of walking during inpatient rehabilitation 1 to 4 weeks after stroke provided greater walking endurance and gait speed and improved quality of life compared with usual care physical therapy.<sup>97</sup>

- 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.<sup>98</sup>

## Costs

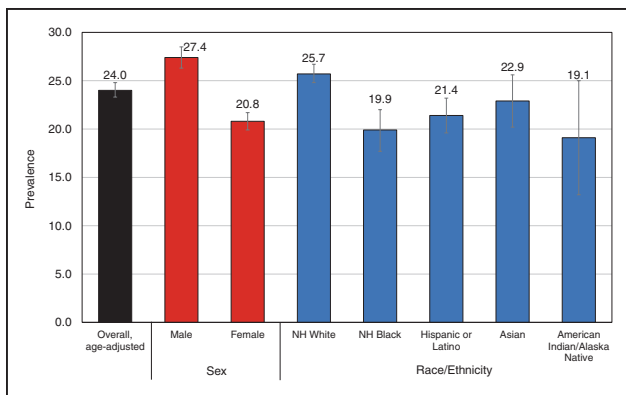
- The economic consequences of physical inactivity are substantial. A global analysis of 142 countries (93.2% of the world's population) concluded that physical inactivity cost health care systems \$53.8 billion in 2013, including \$9.7 billion paid by individual households.<sup>99</sup>
- Increasing population levels of PA could increase productivity, particularly through presenteeism, and lead to substantial economic gains.<sup>100</sup>

## Global Burden

### (See Chart 4-9)

- 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 the number of males globally.<sup>101</sup>
- The GBD 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020.
  - In 2020, age-standardized mortality rates attributable to low PA were highest in North Africa and the Middle East and southern sub-Saharan Africa (Chart 4-9).
  - Low PA caused an estimated 0.66 (95% UI, 0.29–1.05) million deaths in 2020, an increase of 137.69% (95% UI, 115.53%–169.46%) since 1990. (Data courtesy of the GBD study.)
- 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.<sup>80</sup>



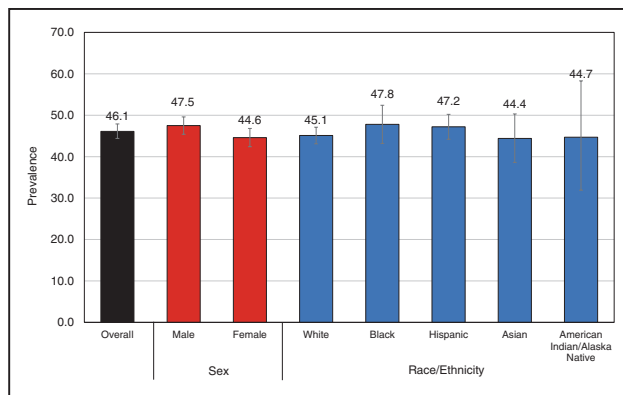


**Chart 4-1. Prevalence of meeting both the aerobic and muscle-strengthening guidelines among US adults ≥18 years of age, overall and by sex and race and ethnicity, 2018.**

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). Error bars represent 95% CIs.

NH indicates non-Hispanic; and PA, physical activity.

Source: Data derived from Healthy People 2020<sup>22</sup> using National Health Interview Survey, 2018.<sup>18</sup>

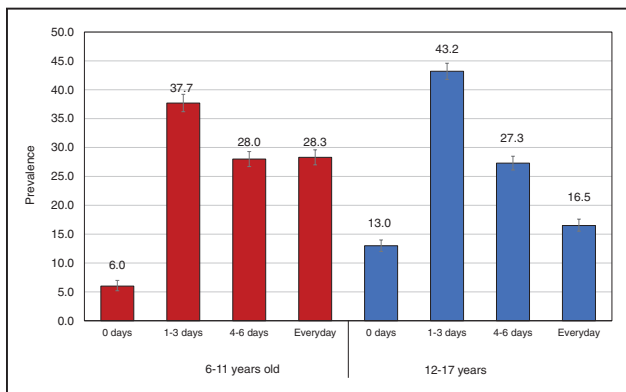


**Chart 4-3. Percentage of US students in grades 9 through 12 who played video or computer games or used a computer\* for ≥3 hours on an average school day, overall and by sex and race and ethnicity, 2019.**

Error bars represent 95% CIs.

\*Counts time spent playing games, watching videos, texting, or using social media on their smartphone, computer, Xbox, PlayStation, iPad, or other tablet for something that was not schoolwork.

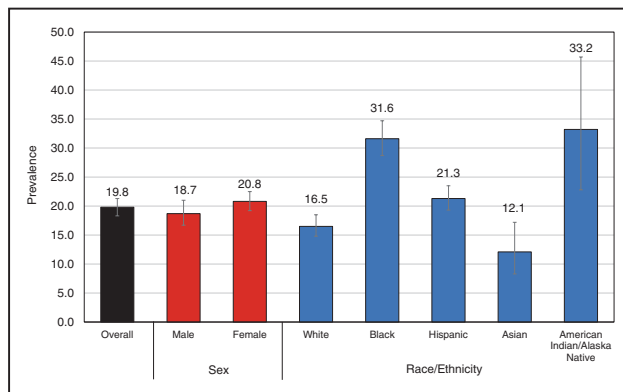
Source: Data derived from Youth Risk Behavior Surveillance System.<sup>4</sup>



**Chart 4-2. Prevalence of US youth 6 to 11 and 12 to 17 years who were physically active for at least 60 minutes, by number of days a week, 2018 to 2019.**

Error bars represent 95% CI.

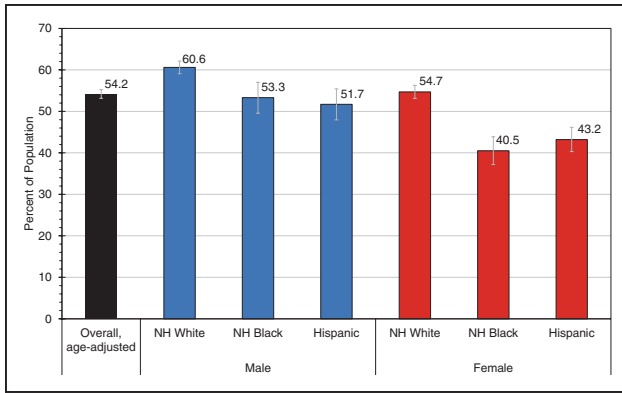
Source: Data derived from National Survey of Children's Health.<sup>13</sup>



**Chart 4-4. Percentage of US students in grades 9 through 12 who watched television for ≥3 hours on an average school day, overall and by sex and race and ethnicity, 2019.**

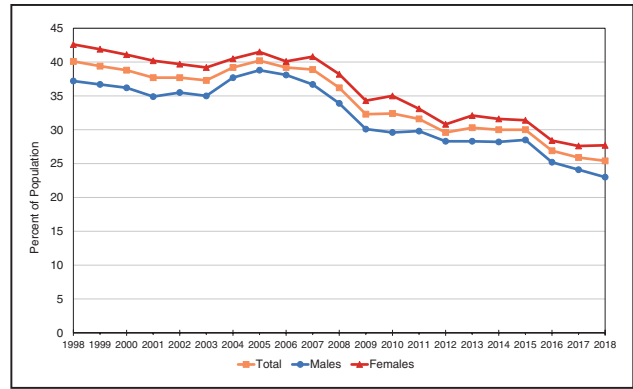
Error bars represent 95% CIs.

Source: Data derived from Youth Risk Behavior Surveillance System.<sup>4</sup>



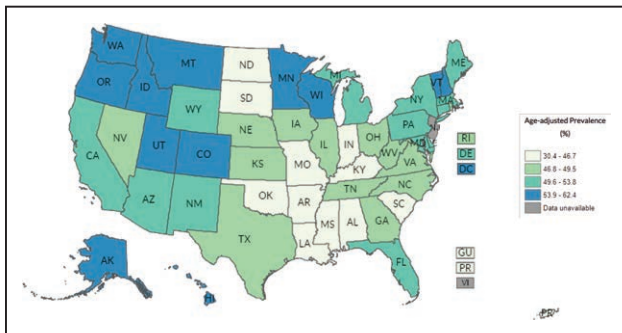
**Chart 4-5. Prevalence of meeting the aerobic PA guidelines among US adults ≥18 years of age, overall and by sex and race and ethnicity, 2018.**

Percentages are age adjusted. The aerobic guidelines of the 2018 Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time PA for ≥150 min/wk, vigorous activity for ≥75 min/wk, or an equivalent combination. Error bars represent 95% CIs. NH indicates non-Hispanic; and PA, physical activity. Source: Data derived from National Health Interview Survey.<sup>18</sup>



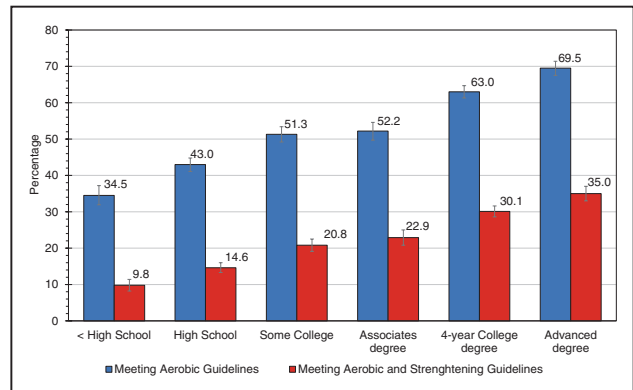
**Chart 4-7. Trends in the prevalence of physical inactivity among US adults ≥18 years of age, overall and by sex, 1998 to 2018.**

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<sup>22</sup> using National Health Interview Survey.<sup>18</sup>



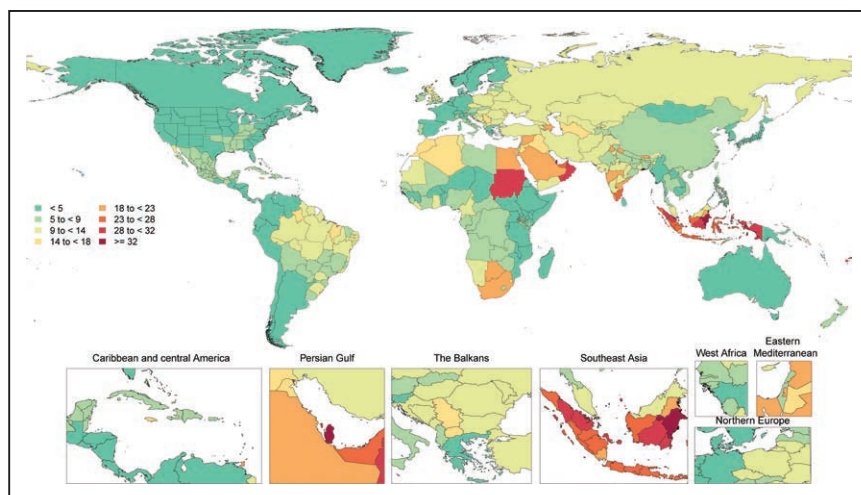
**Chart 4-6. Age-adjusted prevalence of meeting the aerobic PA guidelines among US adults ≥18 years of age, by state, 2019.**

The aerobic guidelines of the 2018 Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time PA for ≥150 min/wk, vigorous activity for ≥75 min/wk, or an equivalent combination. Error bars represent 95% CIs. PA indicates physical activity. Source: Reprinted from Centers for Disease Control and Prevention, Behavioral Risk Factor Surveillance System.<sup>19</sup>



**Chart 4-8. Prevalence of meeting the aerobic PA guidelines among US adults ≥25 years of age, by educational attainment, 2018.**

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 PA for ≥150 min/wk, vigorous activity for ≥75min/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). Error bars represent 95% CIs. PA indicates physical activity. Source: Data derived from Healthy People 2020<sup>22</sup> using National Health Interview Survey.<sup>18</sup>



**Chart 4-9. Age-standardized global mortality rates attributable to low PA per 100,000, both sexes, 2020.**

PA indicates physical activity.  
Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021, University of Washington. More information is available on the Global Burden of Disease Study website.<sup>103</sup>

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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 to further stimulate efforts to monitor and improve dietary habits in relation to CVH.

### Prevalence and Trends in the AHA Healthy Diet Metrics

(See Tables 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 CVH of all Americans by 20%, while reducing deaths from CVDs and stroke by 20%.”<sup>1</sup> 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.<sup>1</sup>

The AHA scoring system for ideal, intermediate, and poor diet patterns uses a binary-based scoring system that awards 1 point for meeting the ideal target for each metric and 0 points otherwise.<sup>2</sup> 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 2017 to 2018 in the United States for adults. In adults, the prevalence of a poor diet decreased from 56.0% to 47.7% for the primary score and 43.7% to 36.6% for the

secondary score (Table 5-2). Changes in score were attributable largely to increased consumption of whole grains, nuts/seeds/legumes, and saturated fat and decreased consumption of total fruits and vegetables, SSBs, processed meat, and sodium. No significant changes were observed for consumption of fish and shellfish.

Similar changes in AHA healthy diet scores between 2003 to 2004 and 2017 to 2018 were seen in under-represented racial and ethnic 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 55.5% for NH Black individuals, from 66.0% to 48.8% for Mexican American individuals, and from 54.0% to 47.4% for NH White individuals (Chart 5-1). The proportion with a poor diet (<40% adherence) decreased from 50.7% to 41.4% in adults with an income-to-poverty ratio  $\geq 3.0$  but only from 67.7% to 63.6% in adults with an 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 2017 to 2018 NHANES is detailed below by sex and race and ethnicity (Table 5-3):

- Consumption of whole grains was low with sex and racial variations and ranged from 0.6 (Mexican American males) to 0.9 (NH White males) servings per day. For each of these groups, <10% of adults met guidelines of  $\geq 3$  servings per day.
- Whole fruit consumption similarly showed a sex and racial difference and ranged from 1.1 (NH Black males) to 1.7 (Mexican American females) servings per day. For each of those groups except Mexican American females, <10% of adults met guidelines of  $\geq 2$  cups/d. When 100% fruit juices were included, the number of servings increased, and the proportions of adults consuming  $\geq 2$  cups/d increased.
- Nonstarchy vegetable consumption ranged from 1.5 (NH Black males) to 2.3 (NH White females) servings per day. The proportion of adults meeting guidelines of  $\geq 2.5$  cups/d was <10%.
- Consumption of fish and shellfish ranged from 1.0 (NH White individuals) to 1.9 (NH Black females) servings per week. The proportions of adults meeting guidelines of  $\geq 2$  servings per week were  $\approx 18\%$  of NH White adults,  $\approx 28\%$  of NH Black adults, and  $\approx 19\%$  of Mexican American adults.
- Weekly consumption of nuts and seeds was  $\approx 6$  servings among NH White adults,  $\approx 3$  servings among NH Black adults, and  $\approx 4$  servings among Mexican American adults. Approximately 1 in 3

The 2022 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 2022. 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.

White adults, 1 in 5 NH Black adults, and 1 in 4 Mexican American adults met guidelines of  $\geq 4$  servings per week.

- Consumption of processed meats was lowest among Mexican American females (1.0 servings per week) and highest among NH White males ( $\approx 2.5$  servings per week). Between 59% (NH White males) and 87% (Mexican American females) of adults consumed  $\leq 2$  servings per week.
- Consumption of SSBs was lowest among NH White females (6.4 servings per week) and highest among NH Black individuals and Mexican American males ( $\approx 10$  servings per week). The proportions of adults meeting guidelines of  $< 36$  oz/wk were  $\approx 61\%$  for NH White adults, 48% for Mexican American adults, and 41% for NH Black adults.
- Consumption of sweets and bakery desserts ranged from 4.4 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 11.8% for NH White males to 20.4% for NH Black females. Between 16.6% of NH Black females and 38.3% of Mexican American males consumed  $\leq 6.5\%$  of total energy intake from added sugars.
- Consumption of EPA and DHA ranged from 0.079 to 0.124 g/d in each sex and racial or ethnic subgroup. Fewer than 9% of US adults met the guideline of  $\geq 0.250$  g/d.
- Two-fifths to one-third 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+monounsaturated fatty acids)/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  $\geq 2.5$  ranged from 40.6% in NH Black females to 11.2% in NH White males.
- Only  $\approx 5\%$  of NH White adults,  $\approx 4\%$  of Black adults, and  $\approx 15\%$  of Mexican American adults consumed  $\geq 28$  g 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).<sup>3</sup> Top sources of sodium intake vary by race and 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.<sup>4</sup>

### 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<sup>5</sup>:

- 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 those of 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 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 had the highest intake of processed meat, followed by NH Black youth, Mexican American youth, NH Asian youth, and those of 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 had the highest intake of SSBs, followed by Mexican American youth, NH White youth, other Hispanic youth, NH Asian youth, and those of 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 and 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 those of other races, including multiracial youth, had 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 and 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 those of other races, including multiracial youth, had 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. 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.<sup>6</sup> 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 2016, the average HEI-2015 score of US adults improved from 55.7 to 57.7 (difference, 2.01 [95% CI, 0.86–3.16];  $P < 0.001$  for trend).<sup>7</sup> This was related to improvements in the macronutrient composition, including decreases in low-quality carbohydrates (primarily added sugar) and increases in high-quality carbohydrates (primarily whole grains), plant protein (primarily whole grains and nuts), and polyunsaturated fat. However, intake of low-quality carbohydrates and saturated fat remained high. The HEI-2015 score increased more in younger versus older adults and in those with a higher versus lower level of income.

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).<sup>5</sup> 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 improved 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 of 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 children 2 to 4 years of age from low-income households.<sup>8</sup> 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.<sup>9</sup> 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.<sup>10</sup> 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%).<sup>11</sup> 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 and ethnicity, and (at least cross-sectionally) neighborhood availability of supermarkets.<sup>12,13</sup>
- 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 CVH.<sup>14,15</sup>

- Disparities may be driven in part by an 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.<sup>16</sup> The percentage of the White population was inversely associated with density of fast food restaurants in low-income neighborhoods and with density of smaller grocery stores across all income levels.
- 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.<sup>17</sup>

### Genetics/Family History

- Genetic factors may contribute to food preferences and modulate the association between dietary components and adverse CVH outcomes.<sup>18–20</sup> 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.<sup>21</sup>
- The interactions between a GRS composed of 97 BMI-associated variants and 3 diet-quality scores were examined in a pooled analysis of 30904 participants from the Nurses' Health Study, the HPFS, 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).<sup>22</sup> 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.
- In a study of  $\approx 9000$  women from the WHI, a GRS for LDL-C, composed of 1760 LDL-associated variants, explained 3.7% (95% CI, 0.09%–11.9%) of the variance in 1-year LDL-C changes in a dietary fat intervention arm but was not associated with changes in the control arm.<sup>23</sup>



## 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.<sup>24</sup>
- Essential to any healthy diet, higher intakes of fruit and vegetables are associated with lower mortality. Specifically, data from 66 719 females from the Nurses' Health Study (1984–2014) and 42 016 males from the HPFS (1986–2014) showed that daily intake of 5 servings of fruit and vegetables (versus 2 servings per day) was associated with lower total mortality (HR, 0.87 [95% CI, 0.85–0.90]), CVD mortality (HR, 0.88 [95% CI, 0.83–0.94]), cancer mortality (HR, 0.90 [95% CI, 0.86–0.95]), and respiratory disease mortality (HR, 0.65 [95% CI, 0.59–0.72]).<sup>25</sup>
- NHANES III (1988–1994) data from 3733 overweight/obese (BMI  $\geq 25$  kg/m<sup>2</sup>) adults (20–90 years of age) were analyzed to assess the relationship between the DII score and mortality. Results show that the DII scores of metabolically unhealthy obese/overweight individuals were associated with increased mortality risk (HR<sub>tertile 3 versus tertile 1</sub>, 1.44 [95% CI, 1.11–1.86];  $P_{\text{trend}} = 0.008$ ; HR<sub>1SD increase</sub>, 1.08 [95% CI, 0.99–1.18]) and, more specifically, CVD-related mortality (HR<sub>T3 versus T1</sub>, 3.29 [95% CI, 2.01–5.37];  $P_{\text{trend}} < 0.001$ ; HR<sub>1SD increase</sub>, 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 score in relation to mortality. Significant associations were found in differences between the highest and lowest quartiles of the DII score and mortality in both SUN (HR, 1.85 [95% CI, 1.15–2.98];  $P_{\text{trend}} = 0.004$ )<sup>26</sup> and PREDIMED (HR, 1.42 [95% CI, 1.00–2.02];  $P_{\text{trend}} = 0.009$ ). A subsequent meta-analysis of 12 studies examined the association between the DII score and mortality and found the DII score to be significantly associated with a 23% increase in mortality (95% CI, 16%–32%) in the highest versus lowest quartiles of the DII score.<sup>26,27</sup>
- 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 apolipoprotein B, 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.<sup>28</sup>
- 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.<sup>29</sup> 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 (HR, 1.30 [95% CI, 1.12–1.51]), and low sugar consumption (<5% energy intake) was also associated with higher mortality risk (HR, 1.23 [95% CI, 1.11–1.35]) in the MDCS study.<sup>30</sup>
- 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 among females with the highest (versus lowest) glycemic index (RR, 1.17 [95% CI, 1.02–1.35]).<sup>31</sup> Using data from 137 851 participants between 35 and 70 years of age living in high-, middle-, and low-income countries across 5 continents with a median follow-up of 9.5 years, the international PURE study reported that a high glycemic index was associated with an increased risk of a major cardiovascular event or death among participants with (HR, 1.51 [95% CI, 1.25–1.82]) and without (HR, 1.21 [95% CI, 1.11–1.34]) preexisting CVD at baseline.<sup>32</sup>
- 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 of 45 009 Italian participants 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.<sup>33–35</sup> In addition, several meta-analyses of prospective cohort studies have consistently reported that higher plant protein intake is inversely associated with total and CVD mortality, lending support for dietary recommendations to replace foods high in animal protein with plant protein sources.<sup>36–38</sup>

- 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, and 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];  $P = 0.001$ ).<sup>39</sup>
- Moderate egg consumption and all-cause and cause-specific<sup>40</sup> 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];  $P = 0.036$ ).<sup>40</sup>

- 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). Higher choline consumption was found to be 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 total (RR, 1.23 [95% CI, 1.09–1.38]), stroke (RR, 1.30 [95% CI, 1.02–1.66]), and CVD (RR, 1.33 [95% CI, 1.19–1.48]) mortality (all comparisons  $P < 0.001$ ).<sup>41</sup> 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];  $P = 2.9$ ) and CVD mortality risk (RR, 1.28 [95% CI, 1.17–1.39];  $P = 9.6$ ).<sup>41</sup>

## 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.<sup>42</sup> The PREDIMED trial demonstrated an  $\approx 30\%$  relative 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,<sup>42</sup> without changes in body weight.<sup>43</sup> 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<sub>12</sub> were lower during the vegetarian diet, whereas triglycerides were lower during the Mediterranean diet, without substantial differences between oxidative stress markers and inflammatory cytokines.<sup>44</sup>
- 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.<sup>45</sup>
- 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.<sup>46</sup>
  - 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]).<sup>47</sup>
  - 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.<sup>47</sup>
  - 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 mmHg in adults with baseline SBP <130, 130 to 139, 140 to 149, and ≥150 mmHg, respectively.<sup>48</sup> 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 mmHg [95% CI, –7.0 to –3.4]), DBP (–2.60 mmHg [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]), HbA1c (–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]).<sup>49</sup> 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]).<sup>49</sup> 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.<sup>50</sup>
  - Compared with a higher-carbohydrate DASH diet, a DASH-type diet with higher protein lowered BP by 1.4 mmHg, 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 mmHg, increased HDL-C by 1.1 mg/dL, and lowered triglycerides by 10 mg/dL.<sup>51</sup> The DASH-type diet higher in unsaturated fat also improved glucose-insulin homeostasis compared with the higher-carbohydrate DASH diet.
  - A secondary analysis of the AHS-2 among NH White participants showed that vegetarian dietary patterns (vegan, lacto-ovo vegetarian, and pescatarian) at baseline were associated with lower prevalence of hypertension at 1 to 3 years of follow-up compared with the nonvegetarian patterns: PR 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 pescatarian. This association remained after adjustment for BMI among the lacto-ovo-vegetarians.<sup>52</sup>
  - 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]).<sup>53</sup>
  - In an RCT of 48835 postmenopausal females, a low-fat dietary pattern (lower fat and higher carbohydrates, 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.<sup>54</sup>
  - 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.<sup>55</sup>
  - An umbrella review of 16 meta-analyses of 116 primary prospective cohort studies with 4.8 million participants reported moderate-quality evidence for the inverse association of healthy dietary patterns with the risk of type 2 diabetes (RR, 0.81 [95% CI, 0.76–0.86]) and for a positive association between unhealthy dietary patterns and the risk of type 2 diabetes (RR, 1.44 [95% CI, 1.33–1.56]) and MetS (RR, 1.29 [95% CI, 1.09–1.52]).<sup>56</sup>
  - A meta-analysis of 7 RCTs with 425 participants for an average duration of 8.6 weeks found that compared with breakfast consumption, breakfast skipping led to modest weight loss (WMD, –0.54 kg [95% CI, –1.05 to –0.03]) but a modest increase in LDL-C (WMD, 9.24 mg/dL [95% CI, 2.18–16.30]).<sup>57</sup> Another meta-analysis of 23 RCTs with 1397 participants reported that fasting and energy-restricting diets resulted in significant reductions in SBP (WMD, –1.88 mmHg [95% CI, –2.50 to –1.25]) and DBP (WMD, –1.32 mmHg [95% CI, –1.81 to –0.84]), and the SBP-lowering effects were stronger with fasting (WMD, –3.26 mmHg) than energy restriction (WMD, –1.09 mmHg).<sup>58</sup>



### 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]), TC (−0.15 mmol/L [95% CI, −0.22 to −0.07]), and SBP (−1.27 mmHg [95% CI, −2.50 to −0.04]) and tended to lower HbA1c (−0.54% [95% CI, −1.28% to 0.20%]).<sup>59</sup> In similar meta-analyses of RCTs for whole grains and glycemic index, higher whole grain intake significantly reduced only body weight (−0.62 kg [95% CI, −1.19 to −0.05]), 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]).<sup>59</sup> 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]). In a meta-analysis of 40 prospective cohort studies in the United States, Asia, and Europe, total dietary fiber (HR, 0.92 [95% CI, 0.88–0.96]) and cereal fiber (HR, 0.83 [95% CI, 0.77–0.90]) were shown to be associated with decreased risk of developing type 2 diabetes among adults with overweight or obesity in US-based studies. The same meta-analysis also reported increased risks of type 2 diabetes with higher glycemic index or glycemic load in US and Asian studies.<sup>60</sup>
- In a randomized trial of 609 participants without diabetes with a BMI of 28 to 40 kg/m<sup>2</sup> 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.<sup>21</sup> A meta-analysis of 12 randomized studies confirmed the benefit of consuming low-carbohydrate healthy diets for multiple CVD risk factors, including reductions in body weight, triglycerides, LDL-C, SBP, and DBP, as well as increases in HDL-C, although the effects are modest in general and the sustainability is uncertain.<sup>61</sup>
- A study of NHANES 1999 to 2010 data from 24 144 participants comparing those in the fourth versus first quartiles of consumption of dietary fats by type found an inverse association between total fat (HR, 0.90 [95% CI, 0.82–0.99]) and PUFA (0.81 [95% CI, 0.78–0.84]) but an increased association between SFA (1.08 [95% CI, 1.04–1.11]), and all-cause mortality. In the same study, a meta-analysis of 29 prospective cohorts (N=1 164 029) was also conducted and corroborated the findings for the inverse association between total fat and PUFA and all-cause mortality. In addition, the meta-analysis showed an inverse association between monounsaturated fatty acid (HR, 0.94 [95% CI, 0.89–0.99]) intake and all-cause mortality and between monounsaturated fatty acid (0.80 [95% CI, 0.67–0.96]) and PUFA (0.84 [95% CI, 0.80–0.90]) intake and stroke mortality. A positive association between SFA (HR, 1.10 [95% CI, 1.01–1.21]) intake and CHD mortality was observed.<sup>62</sup> However, another meta-analysis reported a protective association between dietary SFA intake and risk for stroke (RR, 0.87 [95% CI, 0.78–0.96]), and there was a linear relation in that every 10-g/d increase in SFA intake was associated with a 6% lower RR of stroke (RR, 0.94 [95% CI, 0.89–0.98]).<sup>63</sup> A recent review underscores the controversy surrounding SFA intake as a risk or protective factor for CVD and total mortality and recommends against arbitrary population-wide upper limits on SFA intake without regard to the types of SFA, the food sources, the overall micronutrient distributions, and the health outcomes of interest.<sup>64</sup> 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<sup>2</sup>, 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  $\alpha$ -diversity assessed by the Shannon index (*P*=0.03) and increased abundance of *Blautia* (*P*=0.007) and *Faecalibacterium* (*P*=0.04).<sup>65</sup>
- 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.<sup>66</sup> 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<sup>10</sup> 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]).<sup>67</sup>
- 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.<sup>68</sup>

- 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.<sup>69</sup> In the same study, adults with  $\geq 50$  mg/dL lipoprotein(a) had 2 times higher CVD risk than those with  $< 50$  mg/dL lipoprotein(a) (HR, 2.18 [95% CI, 1.11–4.28]), driven mainly by the lipoprotein(a) effect in males.<sup>70</sup>

### 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.<sup>71</sup> In contrast, the risk of these conditions was positively associated with consumption of egg, red meat, processed meat, and SSBs.
- In a dose-response meta-analysis of prospective cohort studies in adults, each 250-mL/d increase in SSB and ASB intake was associated with an increased risk in obesity (RR, 1.12 [95% CI, 1.05–1.19] for SSB; 1.21 [95% CI, 1.09–1.35] for ASB), type 2 diabetes (1.19 [95% CI, 1.13–1.25] for SSB; 1.15 [95% CI, 1.05–1.26] for ASB), hypertension (1.10 [95% CI, 1.06–1.14] for SSB; 1.08 [95% CI, 1.06–1.10] for ASB), and total mortality (1.04 [95% CI, 1.01–1.07] for SSB; 1.06 [95% CI, 1.02–1.10] for ASB).<sup>72</sup> A network meta-analysis of isocaloric substitution interventions in 38 RCTs involving 1383 participants suggested beneficial effects of replacing sucrose and fructose with starch for LDL-C and replacing fructose with glucose for insulin resistance and uric acid; however, the evidence was judged to be of low to moderate certainty and warrants replication.<sup>73</sup> In a prospective study of 512891 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]).<sup>74</sup>
- 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]).<sup>75</sup> 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]).<sup>76</sup>
- 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]).<sup>77</sup> The association was stronger in Asian cohorts than Western cohorts. Another meta-analysis reported similar results on the beneficial association of higher fish intake with CHD incidence (RR, 0.91 [95% CI, 0.84–0.97]) and mortality (0.85 [95% CI, 0.77–0.94]).<sup>78</sup> In the REGARDS study, individuals who consumed  $\geq 2$  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]).<sup>79</sup>
- 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]).<sup>80</sup> In an RCT (N=113 healthy adults), LDL-C and apolipoprotein B 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 ( $\approx 14\%$  total energy) significantly increased LDL-C, apolipoprotein B, and large LDL particles compared with low SFA content ( $\approx 7\%$  total energy).<sup>81</sup>
- In a study of 169310 female nurses and 41526 male health professionals, consumption of 1 serving of nuts  $\geq 5$  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.<sup>82</sup> In a meta-analysis of 61 trials (N=2582), tree nut consumption lowered TC by 4.7 mg/dL, LDL-C by 4.8 mg/dL, apolipoprotein B by 3.7 mg/dL, and triglycerides by 2.2 mg/dL. No heterogeneity by nut type was observed.<sup>83</sup> 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]).<sup>84</sup>
- An umbrella review of 41 meta-analyses with 45 unique health outcomes concluded that milk consumption was more beneficial than harmful; for example, in dose-response analyses, an increment of 200 mL ( $\approx 1$  cup) milk intake per day was associated with a lower risk of common cardiometabolic disease, such as CVD, stroke, hypertension, type 2 diabetes, MetS, and obesity.<sup>85</sup> A meta-analysis of 10 cohort studies also showed that fermented dairy foods intake was associated with reduced CVD risk (OR, 0.83 [95% CI 0.76–0.91]), in particular cheese (0.87 [95% CI, 0.80–0.94]) and yogurt (0.78 [95% CI, 0.67–0.89]).<sup>86</sup>



- 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 participants with moderate hypercholesterolemia. The beneficial influence on SBP, DBP, heart rate, and body weight was also observed in healthy participants.<sup>87</sup>
- 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.<sup>88</sup> 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.<sup>89</sup> 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.<sup>88</sup> 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.<sup>89</sup>

### **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-mmHg (95% CI, –10.4 to –5.0) lower SBP and a 3.0-mmHg (95% CI, –4.6 to –1.4) lower DBP among people with >131/78 mmHg SBP/DBP. The association was weak in people with ≤131/78 mmHg SBP/DBP: A 100-mmol/d reduction in sodium was associated with a 1.46-mmHg (95% CI, –2.7 to –0.20) lower SBP and a 0.07-mmHg (95% CI, –1.5 to 1.4) lower DBP.<sup>90</sup> The effects of sodium reduction on BP appear to be stronger in individuals who are older, hypertensive, and Black.<sup>91,92</sup>
- 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]).<sup>93</sup>

- 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.<sup>94–98</sup> 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.<sup>98</sup>
- In a meta-analysis of 133 RCTs with 12 197 participants, interventions with reduced sodium versus usual sodium resulted in a mean reduction of 130 mmol (95% CI, 115–145) in 24-hour urinary sodium, 4.26 mmHg (95% CI, 3.62–4.89) in SBP, and 2.07 mmHg (95% CI, 1.67–2.48) in DBP. The results also showed a dose-response relationship between each 50-mmol reduction in 24-hour sodium excretion and a 1.10-mmHg (95% CI, 0.66–1.54) reduction in SBP and a 0.33-mmHg (95% CI, 0.04–0.63 mmHg) reduction in DBP. BP-lowering effects of sodium reductions were stronger in older people, populations that are not White, and those with higher baseline SBP levels.<sup>99</sup>
- 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 mmHg/100 mg [95% CI, 0.36–2.12]) and DBP (0.83 mmHg/100 mg [95% CI, 0.22–1.44]). An increase in urinary phosphorus excretion was significantly associated with an increase in DBP (0.14 mmHg/100 mg [95% CI, 0.01–0.28]).<sup>100</sup>
- 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]).<sup>101</sup>

### **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).<sup>102</sup>
- A 2017 AHA science advisory 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).<sup>103</sup>
  - A meta-analysis of 77 917 participants in 10 RCTs with  $\geq 500$  participants treated for  $\geq 1$  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]).<sup>104</sup> 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.<sup>105</sup>
  - 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.<sup>106</sup>
  - Results from a meta-analysis of 62 RCTs with 3772 participants showed that flaxseed supplementation improved TC (WMD,  $-5.389$  mg/dL [95% CI,  $-9.483$  to  $-1.295$  mg/dL]), triglycerides ( $-9.422$  mg/dL [95% CI,  $-15.514$  to  $-3.330$  mg/dL]), and LDL-C ( $-4.206$  mg/dL [95% CI,  $-7.260$  to  $-1.151$  mg/dL]) concentrations.<sup>107</sup>
  - In an RCT of 25 871 adults (males  $\geq 50$  years of age and females  $\geq 55$  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.<sup>108</sup> 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 nonphosphorylated undercarboxylated matrix Gla protein). 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.<sup>109</sup> A similar study, a post hoc analysis of the EVITA trial, assessing daily vitamin D<sub>3</sub> supplementation of 4000 IU, also found no improvement in cardiac function among patients with advanced HF. However, subgroup analyses among those  $\geq 50$  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.<sup>110</sup>
  - 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<sup>111</sup> (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  $\approx 25\%$  of the sample was lost to follow-up.<sup>112</sup>
  - The VITAL-HF, an ancillary study of the VITAL RCT, examined whether vitamin D<sub>3</sub> (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];  $P=0.048$ ).<sup>113</sup>

- 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<sub>3</sub>/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 synergistic effect of calcium and vitamin D and hormone therapy on LDL-C was observed ( $P=0.03$ ).<sup>114</sup>
- A meta-analysis of 14 RCTs with 1088 participants 4 to 19 years of age concluded that the evidence does not support vitamin D supplementation for improving cardiometabolic health in children and adolescents.<sup>115</sup> Another review article similarly reported that vitamin D supplementation had no beneficial effects on SBP and DBP in children and adolescents.<sup>116</sup>
- Meta-analyses of RCTs examining the effects of multivitamins, vitamin D, calcium, vitamin C, B-complex, antioxidants, and vitamin B<sub>3</sub> (niacin) have demonstrated no salutary cardiovascular benefits.<sup>117</sup>
- 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.<sup>118</sup>
- 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]), and 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]).<sup>119</sup>

- 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.<sup>120</sup>

## Cost

The US Department of Agriculture reported that the Consumer Price Index for all food increased by 3.5% from March 2020 to March 2021.<sup>121</sup> Prices for foods eaten at home increased by 3.3% over the same period, whereas prices for foods eaten away from home increased by 3.7%.<sup>121</sup> 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.<sup>122</sup>

## 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.<sup>123</sup>
- 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.<sup>124</sup> 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 eating pattern (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–\$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–\$25.4 billion). The biggest contributors to these costs savings were HD (\$5.4 billion), type 2 diabetes (\$4.6 billion), AD (\$2.6 billion), stroke (\$1.0 billion), and, to a lesser degree, site-specific cancer (<\$1 billion).<sup>125</sup>
- 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 US adults with low income. 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 incremental cost-effectiveness ratios of <\$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.<sup>126</sup>

### 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).<sup>127</sup> Model estimates were based

on sodium intake, BP, and CVD data from 183 countries. Country-specific cost data were used to estimate the cost-effectiveness ratio, 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 cost-effectiveness ratio was \$204 (international dollars) per DALY (95% CI, 149–322) saved. The estimated cost-effectiveness ratio was highly favorable in high-, middle-, and low-income countries. A US study examined the 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 incremental cost-effectiveness ratio of \$62 000 (95% UI, 1000–171 000) per each QALY gained. 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 incremental cost-effectiveness ratio of \$486 000 (95% UI, 148 000–1 094 000) for each QALY gained. 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.<sup>128</sup>

- 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 of its effectiveness in lowering SSB consumption in several countries to date.<sup>129</sup> 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%) 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).<sup>130</sup> Similar evidence was found in the Philippines, where a 13%/L SSB tax was



associated with fewer deaths resulting from diabetes (−5913), IHD (−10339), and stroke (−7950) across 20 years and 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.<sup>131</sup>

### 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.<sup>132</sup> 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 the 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).<sup>133</sup> In Berkeley, CA, a 1-cent per ounce SSB excise tax was implemented in January 2015.<sup>134</sup> 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.<sup>135</sup> 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.<sup>136</sup> 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,<sup>137</sup> along with concurrent decreases in BP (3.0/1.4 mmHg) 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 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020. The age-standardized mortality rate attributable to dietary risks was 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.<sup>139</sup> 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 and 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 CVH**

	AHA target	Consumption range for alternative healthy diet score*	Alternative scoring range*
Primary dietary metrics†			
Fruits and vegetables	≥4.5 cups/d‡	0–≥4.5 cups/d‡	0–10
Fish and shellfish	2 or more 3.5-oz servings/wk (≥200 g/wk)	0–≥7 oz/wk	0–10
Sodium	≤1500 mg/d	≤1500–>4500 mg/d	10–0
SSBs	≤36 fl oz/wk	≤36–>210 fl oz/wk	10–0
Whole grains	3 or more 1-oz-equivalent servings/d	0–≥3 oz/d	0–10
Secondary dietary metrics†			
Nuts, seeds, and legumes	≥4 servings/wk (nuts/seeds, 1 oz; legumes, ½ cup)	0–≥4 servings/d	0–10
Processed meats	2 or fewer 1.75-oz servings/wk (≤100 g/wk)	≤3.5–>17.5 oz/wk	10–0
Saturated fat	≤7% energy	≤7–>15 (percent energy)	10–0
AHA Diet Score (primary)	Ideal: 4 or 5 dietary targets (≥80%) Intermediate: 2 or 3 dietary targets (40% to 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% to 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; CVH, cardiovascular health; 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 0 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.<sup>2</sup> 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% to 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,<sup>1</sup> Lloyd-Jones et al,<sup>2</sup> and Rehm et al.<sup>140</sup>

**Table 5-2. Trends in Key Dietary Components Among US Adults, NHANES 2003 to 2004 to NHANES 2017 to 2018**

AHA score	Survey-weighted mean/percentages (95% CI)*								
	2003–2004	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	2017–2018	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)	20.8 (19.8–21.9)	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)	4.6 (4.3–4.9)	0.01
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)	2.6 (2.4–2.9)	<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)	2.5 (2.2–2.8)	0.32
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)	7.1 (6.7–7.5)	<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)	3.9 (3.8–4.1)	0.002
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)	37.0 (35.7–38.3)	<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)	4.9 (4.6–5.2)	<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)	6.9 (6.7–7.1)	0.007
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)	4.3 (4.1–4.5)	<0.001
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)	47.7 (42.6–52.9)	0.002
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)	51.1 (45.9–56.2)	0.004
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)	1.2 (0.8–1.9)	0.007
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)	36.6 (32.8–40.6)	<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)	61.6 (57.5–65.6)	<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)	1.8 (1.2–2.6)	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, Icahn School of Medicine at Mount Sinai, using NHANES.<sup>141</sup>

**Table 5-3. Population Mean Consumption\* of Food Groups and Nutrients of Interest, by Sex and Race and Ethnicity Among US Adults ≥20 Years of Age, NHANES 2017 to 2018**

	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
<b>Foods</b>												
Whole grains, servings/d	0.9±0.8	7.1	0.7±1.1	3.1	0.6±0.9	2.5	0.8±0.6	3.4	0.7±1.1	3.6	0.7±0.9	2.5
Whole fruit, servings/d	1.3±1.2	8.8	1.1±2.4	5.9	1.7±2.2	7.1	1.3±1.0	7.6	1.1±1.9	6.2	1.7±1.9	13.2
Total fruit, servings/d	1.7±1.4	13.5	1.7±2.9	11.9	2.2±2.4	12.1	1.5±1.2	10.0	1.8±2.5	13.7	2.2±2.3	19.3
Nonstarchy vegetables, servings/d	2.0±1.1	5.8	1.5±1.8	2.1	2.1±1.7	5.6	2.3±1.2	9.3	1.9±2.3	8.4	2.3±1.8	9.5
Starchy vegetables,† servings/d	0.9±0.7	NA	0.9±1.2	NA	0.7±0.9	NA	0.9±0.7	NA	0.9±1.2	NA	0.7±0.9	NA
Legumes, servings/wk	1.2±1.8	21.4	1.2±3.9	18.2	3.4±6.1	40.6	1.2±1.6	21.9	0.99±3.3	17.0	2.8±5.1	42.1
Fish and shellfish, servings/wk	1.0±1.8	15.0	1.5±4.2	21.6	1.5±3.8	19.3	1.1±1.5	21.2	1.9±3.8	33.7	1.2±3.2	18.0
Nuts and seeds, servings/wk	5.8±6.7	36.0	4.0±11.1	21.9	3.6±8.2	22.5	6.1±6.0	37.9	3.5±9.8	21.0	3.4±6.5	33.2
Unprocessed red meats, servings/wk	3.6±2.5	NA	2.9±4.1	NA	4.2±4.3	NA	2.6±1.9	NA	1.7±3.0	NA	2.6±3.3	NA
Processed meat, servings/wk	2.4±1.8	58.8	2.0±3.2	66.6	2.1±2.8	68.0	1.7±1.4	68.6	1.8±3.1	68.3	1.0±1.9	87.1
SSBs, servings/wk	7.3±7.3	55.6	9.8±12.4	38.6	9.9±10.7	37.9	6.4±6.7	66.7	8.6±13.6	44.1	6.5±12.8	57.3
Sweets and bakery desserts, servings/wk	4.2±4.0	51.9	3.3±6.4	65.2	4.5±6.8	58.6	3.8±3.2	53.7	4.0±8.0	58.9	4.4±6.1	53.1
Refined grain, servings/d	5.1±1.5	7.9	5.1±2.8	7.1	6.6±2.9	1.3	5.1±1.6	10.4	5.1±2.7	9.2	6.5±3.0	7.2
<b>Nutrients</b>												
Total calories, kcal/d	2415±541	NA	2284±1220	NA	2450±967	NA	1797±398	NA	1810±839	NA	1772±671	NA
EPA/DHA, mg/d	0.079±0.107	6.5	0.09±0.213	9.0	0.082±0.140	10.0	0.083±0.114	7.6	0.124±0.334	12.6	0.093±0.209	7.3
α-Linolenic acid, g/d	1.75±0.64	47.8	1.71±0.97	48.7	1.66±0.72	41.7	1.84±0.62	84.0	2.0±1.0	90.1	1.79±0.77	86.5
n-6 PUFAs, % energy	8.0±2.99	NA	9.88±10.2	NA	7.74±5.75	NA	11.5±5.04	NA	13.1±11.1	NA	10.7±5.77	NA
Saturated fat, % energy	12.4±2.2	24.3	11.3±4.0	32.0	11.1±3.3	34.6	12.3±2.1	21.9	11.3±4.2	38.6	11.1±3.3	39.7
Ratio of (PUFAs+MUFAs)/SFAs	1.8±0.5	11.2	2.3±2.6	29.4	1.9±1.2	12.9	2.2±0.6	26.9	2.6±1.7	40.6	2.4±1.2	37.5
Dietary cholesterol, mg/d	299±137	61.7	320±275	55.6	315±195	55.1	304±130	62.9	313±216	54.9	350±244	52.1
Carbohydrate, % energy	44.4±6.1	NA	46.0±12.8	NA	46.7±9.2	NA	46.3±6.2	NA	47.4±11.5	NA	49.0±9.9	NA
Dietary fiber, g/d	15.1±4.4	4.1	13.7±8.3	3.8	18.5±8.9	14.6	16.7±4.3	6.1	15.2±8.3	5.1	19.7±8.4	16.0
Sodium, g/d	3.4±1.3	6.5	3.4±3.98	11.3	3.4±0.94	6.9	3.4±0.65	7.8	3.5±0.91	5.7	3.5±0.95	7.2
Added sugar, % energy	11.8±25.0	37.9	17.8±43.2	23.5	13.0±21.3	38.3	17.8±9.6	19.7	20.4±33.6	16.6	18.0±32.7	28.4

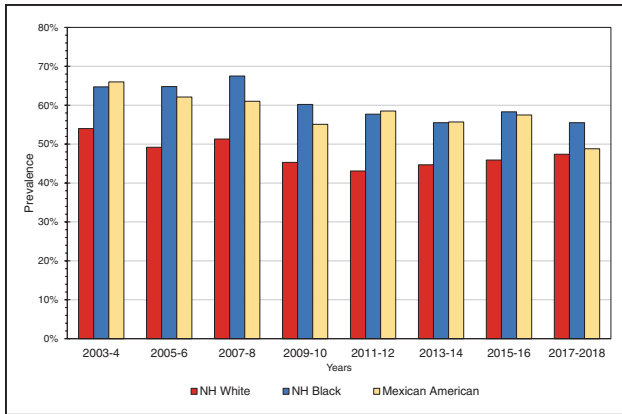
Values for average consumption are mean±SD. Data are from NHANES 2017 to 2018, derived from two 24-hour dietary recalls per person, with population SD adjusted for within-person vs between-person variation. All values are energy adjusted by individual regressions or percent energy, and for comparability, 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.

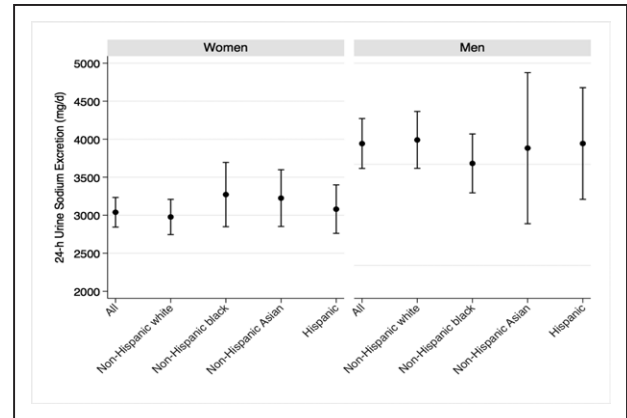
\*All intakes and guidelines adjusted to a 2000-kcal/d diet. Servings are defined as follows: whole grains, 1-oz equivalents; fruits and vegetables, 1/2-cup equivalents; legumes, 1/2 cup; fish/shellfish, 3.5 oz or 100 g; nuts and seeds, 1 oz; unprocessed red or processed meat, 3.5 oz or 100 g; SSBs, 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 (approximately one-fourth of discretionary calories); sweets and bakery desserts, 2.5 or fewer 50-g servings/wk (approximately one-fourth of discretionary calories); EPA/DHA, ≥0.250 g/d<sup>90</sup>; α-linolenic 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.

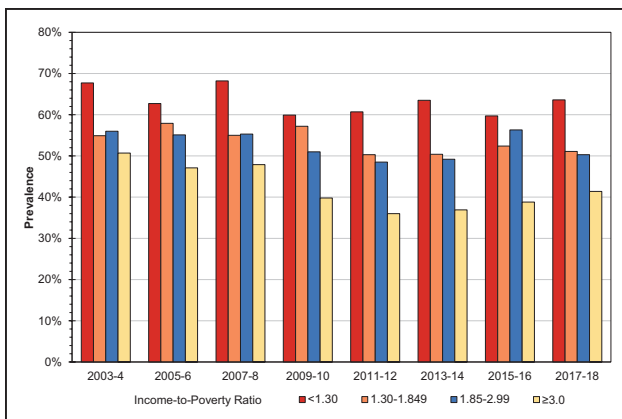
Source: Unpublished analyses courtesy of Dr Junxiu Liu, Icahn School of Medicine at Mount Sinai, using NHANES.<sup>141</sup>



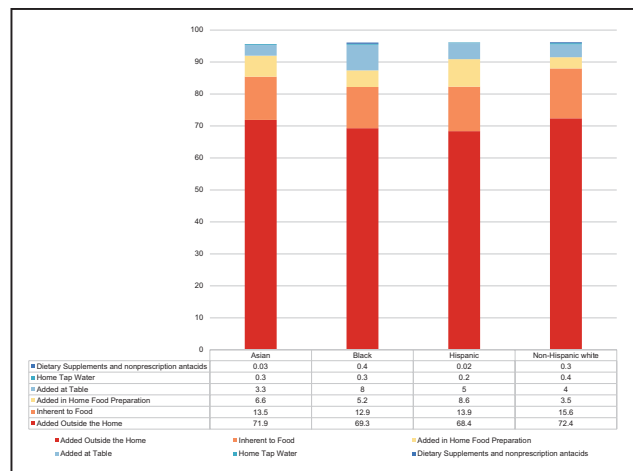
**Chart 5-1. Trends in prevalence of poor AHA healthy diet score, by race and ethnicity, United States, 2003 to 2018.** Components of AHA healthy diet score are defined in Table 5-1. Poor diet was defined as <40% adherence on the basis of the primary AHA continuous diet score. AHA indicates American Heart Association; and NH, non-Hispanic. Source: Unpublished analyses courtesy of Dr Junxiu Liu, Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, using National Health and Nutrition Examination Survey data.<sup>141</sup>



**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<sup>142</sup> using NHANES.<sup>141</sup>



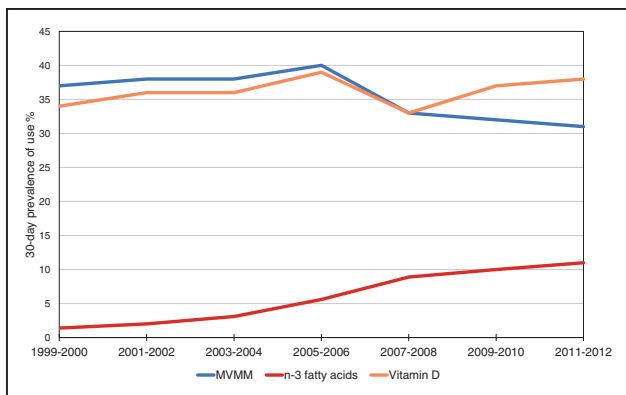
**Chart 5-2. Trends in prevalence of poor AHA healthy diet score in the United States, by ratio of family income to poverty level, 2003 to 2018.** Components of AHA healthy diet score are defined in Table 5-1. Poor diet was defined as <40% adherence on the basis of the primary AHA continuous diet score. AHA indicates American Heart Association. Source: Unpublished analyses courtesy of Dr Junxiu Liu, Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, using National Health and Nutrition Examination Survey data.<sup>141</sup>



**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 and ethnic groups (Asian, Black, Hispanic, non-Hispanic White individuals). Source: Reprinted from Harnack et al.<sup>3</sup> Copyright © 2017 American Heart Association, Inc.

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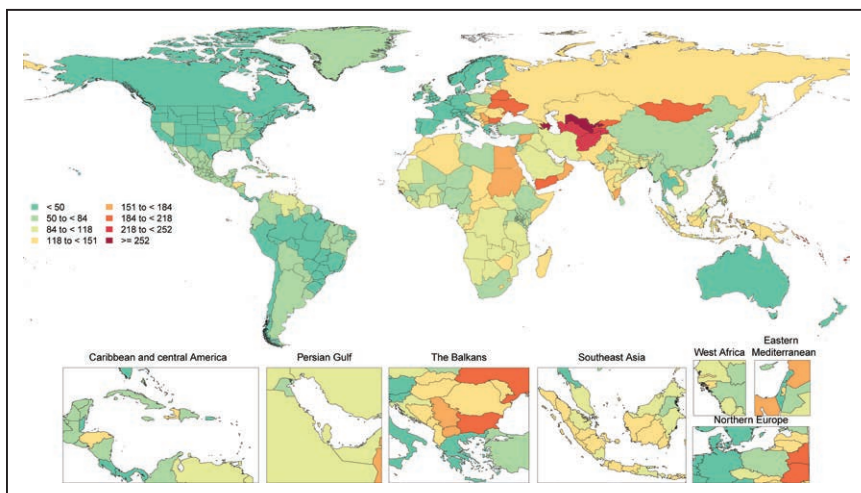




**Chart 5-5. Trends in use of MVMM, vitamin D, and n-3 fatty acid supplements among adults in the United States (NHANES, 1999–2012).**

MVMM indicates multivitamin/mineral; and NHANES, National Health and Nutrition Examination Survey.

Source: Data derived from Kantor et al.<sup>11</sup>



**Chart 5-6. Age-standardized global mortality rates attributable to dietary risks per 100 000, both sexes, 2020.**

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>143</sup>

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## 6. OVERWEIGHT AND OBESITY

See Tables 6-1 and 6-2 and Charts 6-1 through 6-10

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Overweight and obesity are major risk factors for CVD, including CHD, stroke, AF, and congestive HF.<sup>1,2</sup> In addition, overweight and obesity increase the risk of hypertension, dyslipidemia, and type 2 diabetes.<sup>1,2</sup> 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 (Table 6-1). 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<sup>2</sup> in adults (≥20 years of age) as 1 of the 7 components of ideal CVH.<sup>3</sup> 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).

### Classification of Overweight and Obesity

- For adults, the NHLBI weight categories are as follows: overweight (BMI, 25.0–29.9 kg/m<sup>2</sup>) and obese class I (BMI, 30.0–35.0 kg/m<sup>2</sup>), class II (BMI, 35.0–39.9 kg/m<sup>2</sup>), and class III (BMI ≥40.0 kg/m<sup>2</sup>). 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 and ethnicity; they appear to overestimate risk in Black people and underestimate risk in Asian people.<sup>4</sup> For this reason, lower BMI cutoffs have been recommended to identify increased health risks for Asian and South Asian populations.<sup>5</sup>
- For youth, sex-specific BMI-for-age 2000 CDC growth charts for the United States are used,<sup>6</sup> and overweight is defined as 85th to <95th percentile and obesity as ≥95th percentile. A 2013 AHA scientific statement recommended a definition of severe obesity for children ≥2 years of age and adolescents of BMI ≥120% of the 95th percentile for age and sex or an absolute BMI ≥35 kg/m<sup>2</sup>, whichever is lower.<sup>7</sup> NHANES typically uses a definition of severe obesity for children ≥2 years of age and adolescents of BMI ≥120% of the 95th percentile for age and sex.<sup>8</sup>

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<sup>9</sup>; however, different cutoffs have been recommended for various racial and ethnic groups, for example, ≥90 cm for Asian males and ≥80 cm for Asian females<sup>4,10</sup> and >97 cm for Hispanic/Latino women.<sup>11</sup> WC measurement is recommended for those with BMI of 25 to 34.9 kg/m<sup>2</sup> to provide additional information on CVD risk.<sup>12</sup>

### Prevalence

#### Youth

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

- 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 2017 to 2018, with higher prevalence in older age groups (Chart 6-1).<sup>13,14</sup>
- According to 2015 to 2018 data from NHANES, prevalence of obesity was lower for NH Asian boys and girls than youth in other racial and ethnic groups (Table 6-1).<sup>14</sup> Similar prevalences were found with the use of NHANES data from 2017 to 2018 (Chart 6-2).<sup>13</sup>
- Prevalence of childhood obesity varies by SES.
  - According to 2011 to 2014 NHANES data, for children 2 to 19 years of age, 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.<sup>15</sup>
  - 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%]).<sup>15</sup>
- According to NHANES 1999 to 2014, 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.<sup>16</sup>
- According to self-reported height and weight data from the YRBSS 2019, 15.5% of US high school students had obesity and 16.1% were overweight.

The 2022 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 2022. 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.

Obesity was more common in males (18.9%) than females (11.9%) and in Black students (21.1%) and Hispanic students (19.2%) than in White students (13.1%).<sup>17</sup>

### Adults

#### (See Table 6-1 and Charts 6-3 through 6-7)

- According to NHANES 2015 to 2018, among US adults  $\geq 20$  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 severe obesity (BMI  $\geq 40$  kg/m<sup>2</sup>) was 6.2% in males and 10.5% in females.
- In both males and females according to NHANES 2015 to 2018, 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).
- According to NHANES 2017 to 2018, the age-adjusted prevalence of obesity was 44.8% among middle-aged (40–59 years of age) adults, 42.8% among older ( $\geq 60$  years of age) adults, and 40.0% among younger (20–39 years of age) adults. No significant differences by age groups or between males and females were observed (Chart 6-3).<sup>18</sup>
- Among females, according to 2001 to 2014 NHANES, obesity prevalence was inversely associated with income and educational attainment among females. For example, females with a household income  $\leq 130\%$  of the federal poverty level had a prevalence of obesity of 45.2%, those with household income of 130% to 350% of the federal poverty level had a prevalence of 42.9%, and those with household income  $>350\%$  of the federal poverty level had a prevalence of 29.7%. Among males, the relationship is not as clear. Males with a household income  $\leq 130\%$  of the federal poverty level had a prevalence of obesity of 31.5%; those with household income of 130% to 350% of the federal poverty level had a prevalence of 38.5%; and those with household income  $>350\%$  of the federal poverty level had a prevalence of 32.6%.<sup>19</sup>
- In NHANES 2013 through 2016, the age-adjusted prevalence of obesity and severe obesity was generally higher among individuals living in areas with higher levels of urbanization. For example, females living in nonmetropolitan statistical areas had a prevalence of obesity of 47.2% compared with 38.1% among females living in large metropolitan statistical areas.<sup>20</sup>
- Self-reported BMI weight and height data are available through BRFSS.<sup>21,22</sup>
  - In BRFSS 2019, adults without a high school degree or equivalent had a prevalence of obesity

of 36.2%, high school graduates had a prevalence of 34.3%, adults with some college had a prevalence of 32.8%, and college graduates had a prevalence of 25.0%.

- In BRFSS 2017 through 2019, NH Black adults had a prevalence of obesity of 39.8%, Hispanic adults had a prevalence of 33.8%, and NH White adults had a prevalence of 29.9%
- Prevalence of obesity varies by region and state. In BRFSS 2019, all states and territories had a prevalence of obesity of at least 20%. The prevalence of obesity was higher in the Midwest (33.9%) and South (33.3%) and lower in the Northeast (29.0%) and West (27.4%; Charts 6-4 through 6-7).

## Secular Trends

### Youth

- According to NHANES data, overall prevalence of obesity and severe obesity in youth 2 to 19 years of age increased from 13.9% to 19.3% and 2.6% to 6.1% between 1999 to 2000 and 2017 to 2018. Over the same period, prevalence of obesity and severe obesity increased from 14.0% to 20.5% and from 3.7% to 6.9% for males and from 13.8% to 18.0% and from 3.6% to 5.2% for females.<sup>13</sup>
- Among children 2 to 5 years of age, prevalence of obesity was 10.3% in 1999 to 2000 and 13.4% in 2017 to 2018, 9.5% and 14.7% for males, and 11.2% and 12.2% for females.<sup>13</sup> Among children 6 to 11 years of age, the prevalence of obesity was 15.1% in 1999 to 2000 and 20.3% in 2017 to 2018, 15.8% and 21.3% for males, and 14.3% and 19.2% for females. Among adolescents 12 to 19 years of age, the prevalence of obesity was 14.8% in 1999 to 2000 and 21.2% in 2017 to 2018, 14.8% and 22.5% for males, and 14.8% and 19.9% for females.
- The change in the prevalence of obesity between 1999 and 2018 was not significant for youth  $<6$  years of age but was for adolescents.<sup>8</sup>
- From 1999 through 2000 to 2017 through 2018, the prevalence of obesity for US children 2 to 19 years of age increased from 11.0% to 16.1% for NH White children, from 18.8% to 24.2% for NH Black children, and from 20.2% to 26.9% for Mexican American children.<sup>13</sup> For NH Asian children, data have been available since 2011 to 2012, and prevalence of obesity remained stable for NH Asian children from 8.6% in 2011 to 2012 to 8.7% in 2017 to 2018.
- According to the YRBSS, among US high school students, prevalence of obesity increased from 10.6% in 1999 to 15.5% in 2019.<sup>17</sup>

## Adults

### (See Charts 6-8 and 6-9)

- From NHANES data, from 1999 to 2000 through 2017 to 2018, the age-standardized prevalence of obesity and severe obesity (BMI  $\geq 40$  kg/m<sup>2</sup>) increased significantly from 30.5% to 42.4% and from 4.7% to 9.2%, respectively (Chart 6-8).<sup>18</sup>
- From NHANES data, from 1999 to 2000 through 2017 to 2018, prevalence of obesity among males increased from 27.5% (95% CI, 24.3%–30.8%) to 43.0% (95% CI, 37.6–48.6%), and severe obesity increased from 3.1% (95% CI, 1.9%–4.7%) to 6.9% (95% CI, 5.1%–9.1%). Prevalence of obesity among females increased from 33.4% (95% CI, 29.8%–37.1%) to 41.9% (95% CI, 37.8%–46.1%) and severe obesity from 6.2% (95% CI, 5.0%–7.7%) to 11.5% (95% CI, 8.9%–14.5%).<sup>8</sup>
- Significant increases in the prevalence of obesity were seen between 1999 to 2000 and 2017 to 2018 in all age-race and ethnicity groups except for NH Black males, in whom the prevalence increased from 1999 through 2006 (Chart 6-9).<sup>8</sup>
- Comparing NHANES 1999 and 2016 shows an increase in mean weight, WC, and BMI in adults. No changes in height were seen in most demographic subgroups, and height decreased in some subgroups.<sup>23</sup>

## Family History and Genetics

- Overweight and obesity have considerable genetic components, with heritability estimates ranging from  $\approx 30\%$  to  $75\%$ .<sup>24,25</sup> Estimates suggest that as much as 21% of variation in BMI can be explained by genetic variation in commonly occurring SNPs.<sup>26</sup> This suggests a role for DNA methylation variants in explaining the genetic contributions to obesity.<sup>27</sup>
- Monogenic or mendelian causes of obesity include variants with strong effects in genes that control appetite and energy balance (eg, *LEP*, *MC4R*, *POMC*) and obesity that occurs in the context of genetic syndromes (eg, Prader-Willi syndrome).<sup>28</sup>
- GWASs in diverse populations have implicated multiple loci for obesity, defined mostly by BMI, WC, or waist-hip ratio. The *FTO* locus is the most well-established obesity locus, first reported in 2007<sup>29,30</sup> and replicated in many studies with diverse populations and age groups since then.<sup>31–35</sup> The mechanisms underlying the association remain incompletely elucidated but could be related to mitochondrial thermogenesis<sup>5</sup> or food intake.<sup>36</sup>
- Other GWASs have reported numerous additional loci,<sup>37</sup> 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.

- A GWAS of BMI in  $>330\,000$  individuals identified 97 loci, accounting for  $\approx 2.7\%$  of BMI variation, with genes related to synaptic function, glutamate signaling, insulin secretion, energy metabolism, lipid biology, and adipogenesis.<sup>26</sup>
- A meta-analysis of GWASs of childhood BMI in  $>46\,000$  children from 33 studies identified 15 genetic loci associated with childhood BMI; although most of these are loci found from adult BMI GWASs, 3 novel loci were identified, suggesting that the genetics of BMI are common in children and adults. Of note, a risk score combining all 15 loci explained only 2% of the variance in childhood BMI.<sup>38</sup>
- Variants associated with lean mass also have been reported.<sup>39,40</sup> 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.<sup>41</sup>
- Aggregating individual genetic variants associated with BMI into a GRS comprising 2.1 million common variants demonstrates the potential clinical utility of GRS over individual variants. In a study of 300 000 individuals, a BMI GRS was associated with a 13-kg gradient in weight and a 25-fold gradient in risk of severe obesity across GRS deciles.<sup>42</sup> However, genetics are not deterministic for obesity; in fact, 17% of individuals in the top decile of the BMI GRS had a normal BMI.
- It is important to note that a high GRS was associated with increased risk of 6 cardiometabolic diseases (28% increased risk of CAD, 72% increased risk of diabetes, 38% increased risk of hypertension, 34% increased risk of congestive HF, 23% increased risk of ischemic stroke, and 41% increased risk of VTE).<sup>42</sup>
- A mendelian randomization study has shown that a high BMI GRS is associated with shorter life span in the UK Biobank (HR of per 1-SD BMI GRS for increase in mortality, 1.07 [95% CI, 1.05–1.09]).<sup>43</sup>
- A large GWAS of obesity in  $>240\,000$  individuals of predominantly European ancestry revealed an interaction with smoking, which highlights the need to consider gene-environment interactions in genetic studies of obesity.<sup>44</sup> Furthermore, a study of gene-environment interactions in the UK Biobank study found that gene-environment interactions increased the proportion of BMI variance explained by a GRS from 5.2% to 7.1%.<sup>45</sup>
- Rare variants have also been found to be associated with nonsyndromic obesity; in a study of 2737 individuals with severe obesity, rare variants in 3 novel genes (*PHIP*, *DGKI*, *ZMYM4*) were identified.<sup>46</sup>
- Genetic variants also are associated with weight loss response to dietary intervention.<sup>47</sup>

- 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.<sup>48</sup>
- Beyond genetics, other molecular technologies have identified BMI and obesity biomarkers that have elucidated novel biology. For example, metabolomic profiling has uncovered that branched chain amino acids and related catabolic byproducts are dysregulated in patients with obesity.<sup>49</sup> Branched chain amino acid biomarkers are also associated with response to weight loss interventions<sup>50</sup> and cardiometabolic diseases.<sup>51</sup>
- The microbiome has also been shown to be associated with BMI, with several microbial taxa associated with BMI.<sup>52</sup>

## 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.<sup>53</sup>
- 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.<sup>54</sup> Obesity reduction policies and programs implemented by country are also available online.<sup>55</sup>

## Awareness, Treatment, and Control

- The randomized Look AHEAD trial showed that among adults with type 2 diabetes who had overweight or obesity, an intensive lifestyle intervention produced a greater percentage of weight loss at 4 years than diabetes support education.<sup>56,57</sup> After 8 years of intervention, the percentage of weight loss  $\geq 5\%$  and  $\geq 10\%$  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).<sup>57</sup>
- 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.<sup>58</sup>
- A systematic review conducted for the US Preventive Services Task Force in 2018 found that

behavior-based weight loss interventions with or without weight loss medications led to increased weight loss compared with usual care.<sup>59</sup> These interventions also decreased the risk of incident diabetes.

- 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.<sup>60,61</sup>
  - Between 2008 and 2020, 12 published RCTs compared bariatric surgery with medical therapy for treatment of type 2 diabetes. All but 1 study showed better outcomes for the bariatric surgery groups.<sup>61</sup> Studies have also shown improvements in dyslipidemia and hypertension.<sup>61</sup>
  - A meta-analysis of population-based observational studies found improved outcomes among individuals undergoing bariatric surgery compared with nonsurgical control subjects, including reduced all-cause mortality (OR, 0.62 [95% CI, 0.55–0.69]; 11 studies), reduced cardiovascular mortality (OR, 0.50 [95% CI, 0.35–0.71]; 3 studies), reduced diabetes incidence (OR, 0.39 [95% CI, 0.18–0.83]; 6 studies), reduced hypertension incidence (OR, 0.36 [95% CI, 0.32–0.40]; 5 studies), and reduced IHD (OR, 0.46 [95% CI, 0.29–0.73]; 5 studies).<sup>62</sup>
  - Among participants in the Swedish Obese Subjects study, over a median follow-up of 20 years, participants with obesity who underwent bariatric surgery had an adjusted median life expectancy of 3.0 years (95% CI, 1.8–4.2 years) longer than participants with obesity who received usual care. In addition, both cardiovascular mortality and cancer mortality were lower (HR, 0.70 [95% CI, 0.57–0.85] and 0.77 [95% CI, 0.61–0.96], respectively).<sup>63</sup>
  - In a population-based study in Ontario, Canada, individuals undergoing bariatric surgery had a mortality rate of 1.4% over a median follow-up of 4.9 years compared with 2.5% among age-, sex-, BMI-, and diabetes-matched control subjects, with an aHR of 0.68 (95% CI, 0.57–0.81). Relative effects were similar between males and females, with a greater absolute reduction among males. Cardiovascular mortality and cancer mortality were also lower (HR, 0.53 [95% CI, 0.34–0.84] and 0.54 [95% CI, 0.36–0.80], respectively).<sup>64</sup>
  - In a retrospective observational matched cohort study of  $\approx 31\,000$  patients undergoing bariatric surgery and nearly 88 000 matched nonsurgical patients, at 5 years of follow-up, patients undergoing Roux-en-Y gastric bypass had a mean percent total weight loss of 21.7%; those undergoing sleeve gastrectomy, 16.0%; and nonsurgical patients, 2.2%.<sup>65</sup>



- A study using data from NIS 2012 through 2016 found lower odds of MACEs comparing individuals with obesity who had an identifiable history of bariatric surgery to those without bariatric surgery (OR, 0.62 [95% CI, 0.60–0.65]).<sup>66</sup>
- A study from the Scandinavian Obesity Register found improvement in both cardiovascular outcomes and renal outcomes. Among individuals with obesity and type 2 diabetes who underwent gastric bypass surgery compared with matched control subjects, with a mean follow-up of 4.5 years, the risk of a composite of severe renal disease or halved eGFR was 0.56 (95% CI, 0.44–0.71).<sup>67</sup>
- Long-term follow-up of the Longitudinal Assessment of Bariatric Surgery study, a multicenter observational cohort study of 2348 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.<sup>68</sup> In a retrospective cohort study of individuals with a median follow-up of 3.9 years, the 2287 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 11 435 matched patients who did not undergo bariatric surgery.<sup>69</sup>
- 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]).<sup>70</sup>

## Mortality

- 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<sup>2</sup> among healthy never smokers.<sup>71</sup>
- 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 increased cardiovascular morbidity and mortality.<sup>72</sup>
- 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, 0.79 [95% CI, 0.76–0.83], 0.81 [95% CI, 0.76–0.86], and 0.83 [95% CI,

0.74–0.94], respectively) relative to normal-weight individuals, as well as greater mortality risk in those who were underweight (OR, 1.51 [95% CI, 1.41–1.62]), with these results persisting after adjustment for residual confounding and reverse causation.<sup>73</sup>

- 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 (85% higher, 117% higher, 136% higher, and 124% higher, respectively, compared with those in the lowest quintile of body weight fluctuation).<sup>74</sup>

## 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.<sup>53</sup>
- Children and adolescents who are overweight and have obesity are at increased risk for future adverse health effects<sup>75</sup> such as increased prevalence of traditional cardiovascular risk factors, including hypertension, hyperlipidemia, and diabetes.<sup>76,77</sup> Among 8579 youths in NHANES, higher BMI was associated with higher SBP and DBP, lower HDL-C, and higher triglyceride and HbA1c levels.<sup>78</sup>
- 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 with which childhood BMI predicted 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 having overweight or obesity.<sup>77</sup>
- A 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.<sup>79</sup>

## Adults

- Obesity is associated with increased lifetime risk of CVD and increased prevalence of type 2 diabetes, hypertension, dyslipidemia, and AF.<sup>1,2,72</sup>
- In the Cardiovascular Disease Lifetime Pooling Project, among middle-aged adults, compared with individuals with normal weight, males with overweight or obesity had higher lifetime risk of incident CVD (competing HRs, 1.21 [95% CI, 1.14–12.8] and 1.67 [95% CI, 1.55–1.79], respectively).<sup>72</sup> Similarly, females with obesity or overweight had higher lifetime risk of incident CVD (competing HRs, 1.32 [95% CI, 1.24–1.40] and 1.85 [95% CI, 1.72–1.99], respectively).
- In the SPRINT trial, there was a J-shaped association between BMI and all-cause mortality and risk of stroke.<sup>80</sup> 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]).<sup>81</sup>
- Cardiovascular risks are even higher with class III obesity than with class I or II obesity.<sup>82</sup> 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 and ethnicity with adjustment for differences in BMI and CVD risk factors.<sup>82</sup>
- A meta-analysis of 25 studies with 2 405 381 participants found a summary RR for risk of AF of 1.28 (95% CI, 1.20–1.38) for each 5-unit increase in BMI.<sup>83</sup>
- Among 1956 individuals in the FANTASIA registry with AF receiving anticoagulation, BMI was not independently associated with MACEs, stroke, major bleeding, cardiovascular mortality, or all-cause mortality.<sup>84</sup>
- 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).<sup>85</sup> Among females in the Swedish Medical Birth Register with 1982 to 2014 used as a baseline, BMI was associated with subsequent cardiomyopathy. The lowest risk of cardiomyopathy

was found for those with a BMI of 21 kg/m<sup>2</sup>. For DCM, individuals with BMI of 25 to 27.5 kg/m<sup>2</sup> had an HR of 1.55 (95% CI, 1.14–2.11) compared with individuals with a BMI of 20 to 22.5 kg/m<sup>2</sup>.<sup>86</sup>

- Among older adults in MESA, approximately half of the participants with MHO developed MetS over a median of 12.2 years of follow-up. Individuals with MHO who developed MetS had increased odds of CVD (OR, 1.60 [95% CI, 1.14–2.25]) compared with those with stable MHO or healthy normal weight.<sup>87</sup>
- 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]).<sup>88</sup>

## COVID-19

- A meta-analysis showed that preexisting cardio-metabolic conditions, including obesity and obesity-related chronic diseases such as hypertension, diabetes, and CVD, were 2 to 3 times more prevalent among severe COVID-19 cases than nonsevere cases.<sup>89</sup>
- A study from a Chinese hospital of individuals hospitalized with COVID-19 found an aOR of severe COVID-19 of 3.40 (95% CI, 1.40–2.86) for individuals with obesity compared with individuals with normal weight.<sup>90</sup>
- A study based in 3 Chinese hospitals found that the likelihood of severe COVID-19 was directly related to BMI. Individuals with obesity had an aOR of severe COVID-19 of 3.00 (95% CI, 1.22–7.38) compared with individuals without obesity. The aOR for each 1-unit increase in BMI was 1.13 (95% CI, 1.01–1.28).<sup>91</sup>
- Two studies based in New York hospitals found that 42% to 46% of individuals admitted with COVID-19 had obesity.<sup>92,93</sup> Another New York study of people with COVID-19 infection found that risk of hospitalization was associated with BMI. Compared with individuals with a BMI <25 kg/m<sup>2</sup>, the aOR for admission for BMI 25.0 to 29.9 kg/m<sup>2</sup> was 1.30 (95% CI, 1.07–1.57), for BMI 30 to 39.9 kg/m<sup>2</sup> was 1.80 (95% CI, 1.47–2.20), and for BMI >40 kg/m<sup>2</sup> was 2.45 (95% CI, 1.78–3.36).<sup>94</sup>
- Data from Massachusetts General Hospital found among individuals hospitalized with COVID-19, obesity was associated with greater odds of ICU admission (OR, 2.16 [95% CI, 1.20–3.88]) and mechanical ventilation (OR, 2.13 [95% CI, 1.14–4.00]).<sup>95</sup>
- Data from the AHA's COVID-19 Cardiovascular Disease Registry found that among individuals hospitalized with COVID-19, obesity was

overrepresented. Higher risks of in-hospital death or mechanical intervention were found for individuals with class I, II, and III obesity compared with individuals with normal weight (aOR, 1.28 [95% CI, 1.09–1.51], 1.57 [95% CI, 1.29–1.91], and 1.80 [95% CI, 1.47–2.20], respectively).<sup>96</sup>

- A study conducted in the United States using NHANES and data on US COVID-19 hospitalizations reported that 30.2% of COVID-19 hospitalizations were attributable to total obesity (BMI  $\geq$ 30 kg/m<sup>2</sup>) with large differences by race and ethnicity. Among individuals 18 to 49 years of age, the percentages of COVID-19 hospitalizations that could be attributable to total obesity were 28.8% for NH White individuals, 33.9% for NH Black individuals, 31.6% for Hispanic individuals, and 22.4% for Asian individuals and others.<sup>97</sup>

## Health Care Use and Cost

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

- In the United States in 2014, direct costs for medical treatment for health conditions causally related to obesity were \$427.8 billion.<sup>98</sup> The direct and indirect costs associated with obesity were \$1.42 trillion, equivalent to 8.2% of the US gross domestic product in 2014.
- In an instrumental variable analysis based on a pooled cross-sectional analysis of MEPS 2001 through 2016, compared with adults with normal weight, adults with obesity had \$2505 or 100% higher annual medical care costs. Costs increased by class of obesity. Individuals with class 1 obesity had 68.4% higher annual medical costs, and individuals with class 3 obesity had 233.6% higher annual medical costs. In 2016, it was estimated that the increased medical cost attributable to obesity among adults in the United States was \$260.6 billion.<sup>99</sup>
- It is estimated that \$9.7 billion in health care costs in 2016 was attributable to morbid obesity.<sup>100</sup>
- Another study estimated that mean annual per capita health care expenses associated with obesity were \$1160 for males and \$1525 for females.<sup>101</sup>
- It is estimated that obesity raises the annual medical care costs of adults with obesity by an average of \$3429 (in 2013 US dollars) and that the total health care spending of noninstitutionalized adults attributable to treated obesity-related illnesses increased from 20.6% in 2005 to 28.2% in 2013.<sup>102</sup>
- From 2010 through 2015, compared with adults who are normal weight, adults with obesity had higher annual rates of hospitalization (9.3% compared with 6.0%) and were more likely to have  $\geq$ 3 physician visits annually.<sup>103</sup>
- A study recommended the use of \$19000 (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.<sup>104</sup>

- With the use of an instrumental variable analysis and MEPS from 2001 and 2015, it was estimated that obesity in youth increased annual medical care cost by \$907 in 2015 US dollars or by 92% compared to youth without obesity.<sup>105</sup> Adolescents with obesity are more likely to be taking prescription medications compared with adolescents without obesity.<sup>106</sup>
- Studies have investigated the cost-effectiveness of bariatric surgery. A study of veterans undergoing bariatric surgery found that total health care expenditures were initially higher among individuals receiving bariatric surgery compared with nonsurgical control subjects, with costs of the 2 groups converging after 10 years of follow-up.<sup>107</sup>

## Global Burden

### (See Chart 6-10)

- The GBD 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020.
  - Age-standardized mortality rates attributable to high BMI were lowest in high-income Asia Pacific and highest in Oceania, Central Asia, the Middle East and North Africa, southern sub-Saharan Africa, and locations in Central and Eastern Europe, Central sub-Saharan Africa, and Central Latin America (Chart 6-10).
  - High BMI was attributed to 2.40 (95% UI, 1.37–3.52) million deaths in 2020, a change of 131.46% (95% UI, 100.77%–157.62%) compared with 1990 (Table 6-2).
- 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% to 10.8% 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<sup>2</sup> in males and from 22.1 to 24.4 kg/m<sup>2</sup> in females.<sup>109</sup> 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% in males in Tonga and females in Kuwait, Kiribati, the Federated States of Micronesia, Libya, Qatar, Tonga, and Samoa.<sup>109</sup>

**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 severe 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	84754	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 are defined as body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup>. Obesity in adults is defined as BMI  $\geq 30$  kg/m<sup>2</sup>. Severe obesity is defined as BMI  $\geq 40$  kg/m<sup>2</sup>. Prevalence estimates for adults were age adjusted with the direct method to standardize estimates to the projected 2000 US census population with categories of 20 to 39, 40 to 59, and  $\geq 60$  years of age. In children, overweight and obesity are based on BMI-for-age values  $\geq 85$ th percentile of the 2000 Centers for Disease Control and Prevention (CDC) growth charts. In children, obesity is based on BMI-for-age values  $\geq 95$ th percentile of the CDC growth charts.<sup>2</sup> 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.<sup>14</sup>

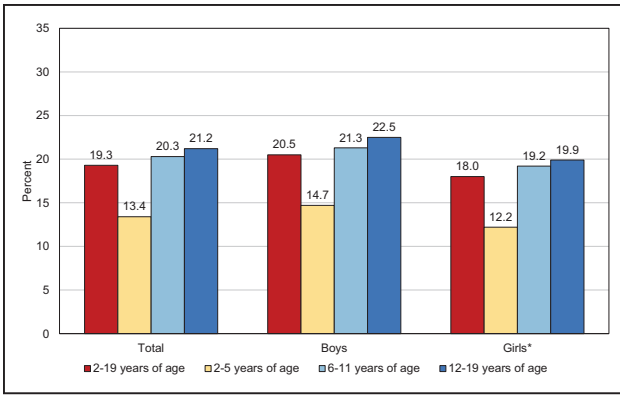
**Table 6-2. Deaths Caused by High BMI Worldwide, by Sex, 2020**

	Deaths		
	Both sexes (95% UI)	Male (95% UI)	Female (95% UI)
Total No. of deaths (millions), 2020	2.40 (1.37 to 3.52)	1.15 (0.66 to 1.70)	1.24 (0.70 to 1.85)
Percent change in total number, 1990–2020	131.46 (100.77 to 157.62)	152.70 (127.69 to 177.76)	114.76 (73.46 to 149.35)
Percent change in total number, 2010–2020	37.57 (29.89 to 45.12)	40.75 (32.28 to 49.54)	34.75 (24.31 to 43.75)
Mortality rate per 100 000, age standardized, 2020	28.93 (16.46 to 42.69)	29.98 (16.93 to 43.87)	27.81 (15.78 to 41.33)
Percent change in rate, age standardized, 1990–2020	4.21 (−4.08 to 13.32)	12.70 (3.26 to 22.97)	−1.57 (−12.88 to 9.93)
Percent change in rate, age standardized, 2010–2020	3.43 (−1.24 to 8.81)	6.15 (0.19 to 12.75)	1.43 (−4.50 to 7.30)
PAF, all ages, 2020, %	4.23 (2.42 to 6.21)	3.73 (2.20 to 5.52)	4.82 (2.72 to 7.14)
Percent change in PAF, all ages, 1990–2020	84.84 (61.12 to 104.53)	100.42 (80.88 to 119.06)	72.89 (40.04 to 98.24)
Percent change in PAF, all ages, 2010–2020	26.68 (20.56 to 31.56)	30.68 (25.15 to 36.02)	22.86 (14.69 to 29.08)

BMI indicates body mass index; PAF, population attributable fraction; and UI, uncertainty interval.

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021, University of Washington.



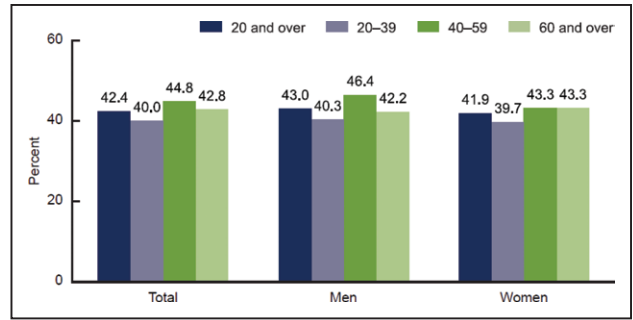


**Chart 6-1. Prevalence of obesity among US youth 2 to 19 years of age, by sex and age, 2017 to 2018.**

Obesity is BMI at or above the 95th percentile from the sex-specific BMI-for-age 2000 CDC Growth Charts. BMI indicates body mass index; and CDC, Centers for Disease Control and Prevention.

\*Excludes pregnant females.

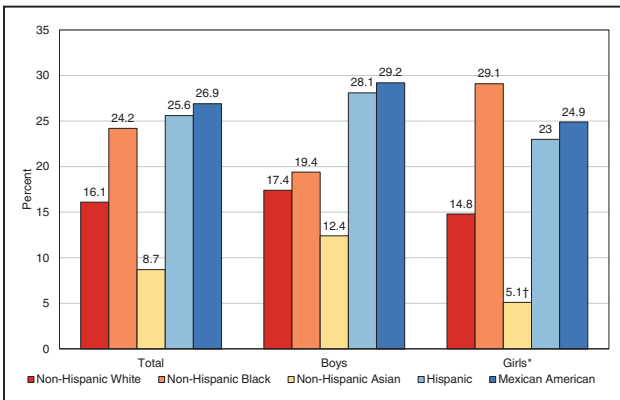
Source: Data derived from Fryar et al<sup>13</sup> using data from National Health and Nutrition Examination Survey.<sup>14</sup>



**Chart 6-3. 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<sup>18</sup> using data from National Health and Nutrition Examination Survey.<sup>14</sup>



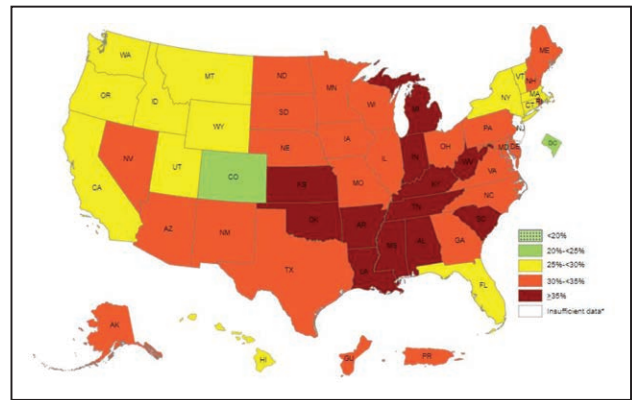
**Chart 6-2. Prevalence of obesity among US youth 2 to 19 years of age, by sex and race and ethnicity, 2017 to 2018.**

Obesity is BMI at or above the 95th percentile from the sex-specific BMI-for-age 2000 CDC Growth Charts. BMI indicates body mass index; and CDC, Centers for Disease Control and Prevention.

\*Excludes pregnant females.

†Estimate has a CI width between 5 and 30 and a relative CI width >130% and does not meet National Center for Health Statistics standards of reliability.

Source: Data derived from Fryar et al<sup>13</sup> using data from National Health and Nutrition Examination Survey.<sup>14</sup>

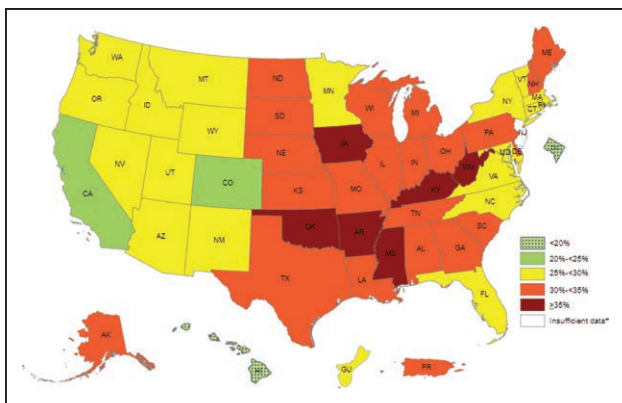


**Chart 6-4. Age-adjusted prevalence of self-reported obesity among adults, by US state and territory, 2019.**

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; and SE, standard error.

\*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.<sup>21,22</sup>

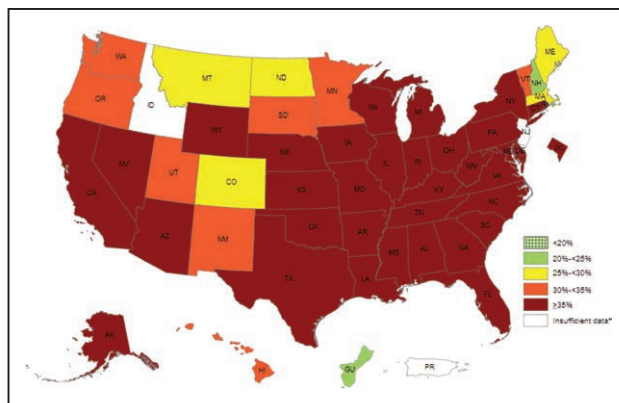


**Chart 6-5. Prevalence of self-reported obesity among non-Hispanic White adults, by US state and territory, 2017 to 2019.**

SE indicates standard error.

\*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.<sup>21,22</sup>

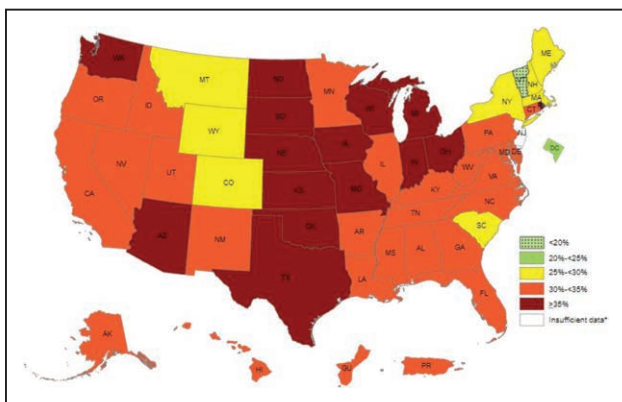


**Chart 6-7. Prevalence of self-reported obesity among non-Hispanic Black adults, by US state and territory, 2017 to 2019.**

SE indicates standard error.

\*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.<sup>21,22</sup>

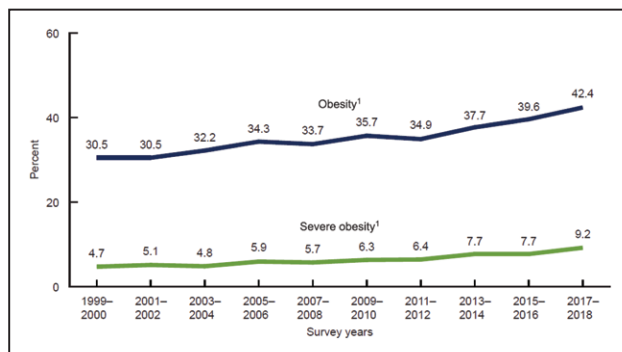


**Chart 6-6. Prevalence of self-reported obesity among Hispanic adults, by US state and territory, 2017 to 2019.**

SE indicates standard error.

\*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.<sup>21,22</sup>

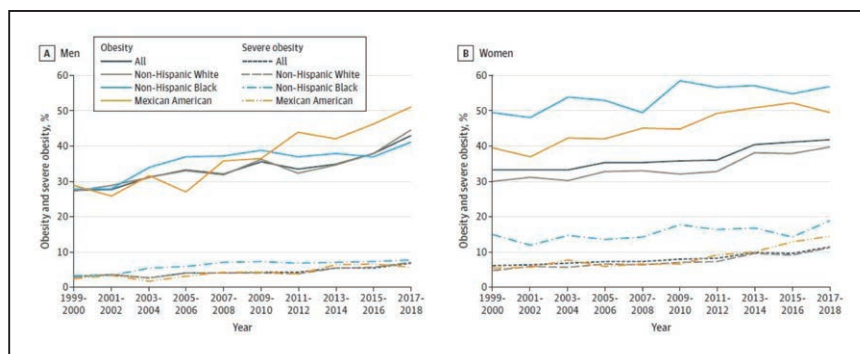


**Chart 6-8. Trends in age-adjusted obesity prevalence among US adults ≥20 years of age, 1999 to 2000 through 2017 to 2018.**

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.

<sup>1</sup>Significant linear trend.

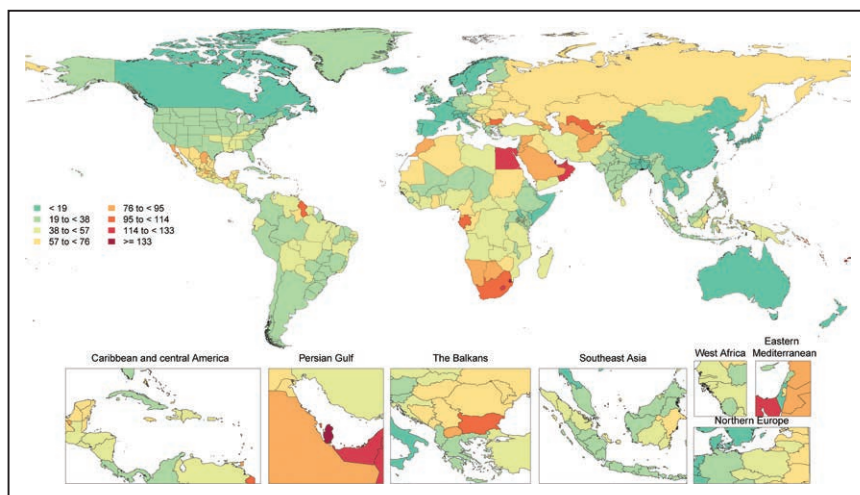
Source: Reprinted from Hales et al<sup>18</sup> using National Health and Nutrition Examination Survey, 1999 to 2018.<sup>14</sup>



**Chart 6-9. Trends in age-adjusted obesity prevalence among US adults  $\geq 20$  years of age, by race, ethnicity, and sex, 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  $\geq 60$  years. **A**, Men. **B**, Women.

Source: Reprinted with permission from Ogden et al<sup>8</sup> using National Health and Nutrition Examination Survey, 1999 to 2018.<sup>14</sup>



**Chart 6-10. Age-standardized global mortality rates attributable to high body mass index per 100 000, both sexes, 2020.**

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>110</sup>

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## 7. HIGH BLOOD CHOLESTEROL AND OTHER LIPIDS

See Tables 7-1 and 7-2 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 TC levels in the blood are 1 of 7 metrics the AHA has used to define CVH in children and adults. The AHA, ACC, and several other societies released the 2018 Cholesterol Clinical Practice Guideline and the 2019 CVD Primary Prevention Clinical Practice Guidelines, which focus on the use of LDL-C—lowering therapy to reduce ASCVD risk.<sup>1,2</sup>

### 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 and ethnic breakdown in NHANES 2015 to 2018<sup>3</sup> was as follows (unpublished NHLBI tabulation using NHANES<sup>3</sup>):
  - 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,<sup>3</sup> 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 and ethnic breakdown was as follows (unpublished NHLBI tabulation using NHANES<sup>3</sup>):
  - 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

The 2022 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 2022. 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.

- 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  $\geq$ 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).<sup>4</sup> The remainder of youth had borderline levels (TC, 170–199 mg/dL).

#### Adults ( $\geq$ 20 Years of Age)

(See Table 7-1 and Charts 7-2 through 7-4)

- Among adults  $\geq$ 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 with NH White adults and Mexican American adults (Chart 7-2). The racial and ethnic breakdown by sex in 2015 to 2018 was as follows (unpublished NHLBI tabulation using NHANES<sup>3</sup>):
  - 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  $\geq$ 200 mg/dL and  $\geq$ 240 mg/dL among US adults  $\geq$ 20 years of age in 2015 to 2018 (unpublished NHLBI tabulation using NHANES<sup>3</sup>) are shown overall and by sex and race and ethnicity in Table 7-1 and Charts 7-3 and 7-4. In 2015 to 2018, the percentages of adults with high TC ( $\geq$ 240 or  $\geq$ 200 mg/dL) were lower for NH Black adults than for NH White and Asian and Hispanic adults.
- 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 and ethnicity subgroup as of 2015 to 2018 NHANES (Chart 7-2).<sup>5</sup> Conversely, the Healthy People 2020 target of  $\leq$ 13.5% for the proportion of adults with high TC  $\geq$ 240 mg/dL has been achieved as of the combined period of 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).<sup>6</sup>

## 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 2015 to 2018 was 87.6 mg/dL (males, 87.6 mg/dL; females, 87.5 mg/dL). The racial and ethnic breakdown was as follows (unpublished NHLBI tabulation using NHANES<sup>3</sup>):
  - For NH White adolescents, 88.0 mg/dL for males and 86.4 mg/dL for females
  - For NH Black adolescents, 84.9 mg/dL for males and 94.4 mg/dL for females
  - For Hispanic adolescents, 85.9 mg/dL for males and 83.1 mg/dL for females
  - For NH Asian adolescents, 82.3 mg/dL for males and 95.4 mg/dL for females; however, these values are based on data from small sample sizes (50 NH Asian males and 53 NH Asian females)
- LDL-C levels  $\geq 130$  mg/dL occurred in 6.1% of male adolescents and 3.0% of female adolescents during 2015 to 2018 (unpublished NHLBI tabulation using NHANES<sup>3</sup>).
- Conversely, LDL-C levels  $< 110$  mg/dL were present in 84.1% (95% CI, 79.8%–88.4%) of all adolescents in 2013 to 2014 (Chart 7-1B).<sup>4</sup>

#### Adults

(See Table 7-1)

- In 2015 to 2018 (unpublished NHLBI tabulation using NHANES<sup>3</sup>), the mean level of LDL-C for American adults  $\geq 20$  years of age was 112.1 mg/dL. The racial and ethnic breakdown was as follows:
  - Among NH White adults, 111.1 mg/dL for males and 111.9 mg/dL for females
  - Among NH Black adults, 111.7 mg/dL for males and 109.7 mg/dL for females
  - Among Hispanic adults, 115.1 mg/dL for males and 110.8 mg/dL for females
  - Among NH Asian adults, 115.2 mg/dL for males and 110.4 mg/dL for females
- In 2015 to 2018, the age-adjusted prevalence of high LDL-C ( $\geq 130$  mg/dL) was 27.8% (unpublished NHLBI tabulation using NHANES<sup>3</sup> [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 and ethnic breakdown was as follows (unpublished NHLBI tabulation using NHANES<sup>3</sup>):

- 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<sup>3</sup>).
- 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 and ethnic breakdown was as follows (NHANES 2015–2018,<sup>3</sup> 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<sup>3</sup>).
- Conversely, HDL-C levels  $> 45$  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).<sup>4</sup>

#### Adults

(See Table 7-1)

- In 2015 to 2018 (unpublished NHLBI tabulation using NHANES<sup>3</sup>), the mean level of HDL-C for American adults  $\geq 20$  years of age was 54.4 mg/dL. The racial and 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 and 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 2015 to 2018 was 70.0 mg/dL. For males, it was 72.0 mg/dL, and for females, it was 67.9 mg/dL. The racial and ethnic breakdown was as follows (unpublished NHLBI tabulation using NHANES<sup>3</sup>):
  - Among NH White adolescents, 72.7 mg/dL for males and 70.6 mg/dL for females
  - Among NH Black adolescents, 59.5 mg/dL for males and 49.7 mg/dL for females
  - Among Hispanic adolescents, 76.2 mg/dL for males and 72.1 mg/dL for females
  - Among NH Asian adolescents, 56.9 mg/dL for males and 86.7 mg/dL for females
- High levels of triglycerides ( $\geq 130$  mg/dL) occurred in 9.7% of male adolescents and 6.6% of female adolescents during 2015 to 2018 (unpublished NHLBI tabulation using NHANES 2015–2018).<sup>3</sup>
- 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).<sup>4</sup>

### Adults

- Among American adults  $\geq 20$  years of age, the geometric mean triglyceride level in 2015 to 2018 was 93.2 mg/dL (unpublished NHLBI tabulation using NHANES<sup>3</sup>). The geometric mean triglyceride levels were 100.6 mg/dL for males and 86.8 mg/dL for females. The racial and ethnic breakdown was as follows:
  - Among NH White adults, 100.6 mg/dL for males and 88.3 mg/dL for females
  - Among NH Black adults, 78.0 mg/dL for males and 66.5 mg/dL for females
  - Among Hispanic adults, 111.7 mg/dL for males and 97.1 mg/dL for females
  - Among NH Asian adults, 112.2 mg/dL for males and 84.4 mg/dL for females
- In 2015 to 2018, 21.1% of adults had high triglyceride levels ( $\geq 150$  mg/dL; unpublished NHLBI tabulation using NHANES<sup>3</sup>).

## Secular Trends in TC and Lipid Subfractions

### Youth

(See Charts 7-1 and 7-2)

- 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 apolipoprotein B 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 apolipoprotein B 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).<sup>4</sup>

### Adults ( $\geq 20$ Years of Age)

- The prevalence of high TC ( $\geq 240$  mg/dL) has decreased over time, from 18.3% of adults in 1999 to 2000 to 10.5% in 2017 to 2018.<sup>7</sup>
  - From 1999 to 2018, mean serum TC for adults  $\geq 20$  years of age decreased across all subgroups of race and 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.<sup>8</sup>
  - 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).<sup>9</sup>
- 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 ( $\geq 130$  mg/dL) decreased from 42.9% during 1999 to 2000 to 26.2% during 2017 to 2018 (unpublished NHLBI tabulation using NHANES<sup>3</sup>).
- The prevalence of low HDL-C ( $< 40$  mg/dL) declined from 22.2% in 2007 to 2008 to 16.0% in 2017 to 2018.<sup>7</sup>
- Mean HDL-C levels were stable between 2001 to 2004 and 2013 to 2016 among both males (from 47–48 mg/dL) and females (from 58–60 mg/dL), with no significant differences by sex in changes over time ( $P$  for interaction by sex=0.872).<sup>9</sup>
- Geometric mean levels of triglycerides declined from 123 mg/dL in 1999 to 2000 to 97 mg/dL in 2013 to 2014.<sup>10</sup>
- Among males, age-adjusted levels of apolipoprotein B 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 apolipoprotein B declined from 94 mg/dL in 2005 to 2006 to 91 mg/dL in 2015 to 2016.<sup>11</sup>

## Family History and Genetics

- There are several known monogenic or mendelian causes of high TC and other lipid fractions, the most common of which is FH, which affects  $\approx 1$  in 311 individuals in the general population and  $\approx 1$  in 17 individuals with ASCVD.<sup>12</sup>
- High TC with or without a clinical FH phenotype is heritable even in families who do not harbor one of these monogenic forms of disease.
  - GWASs in hundreds of thousands 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  $>200$ .<sup>13–17</sup>
  - 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,<sup>18</sup> and mendelian randomization studies confirm causal associations between LDL-C, triglycerides, non-HDL-C, apolipoprotein B, and CAD and coronary events but do not support a causal role for apolipoprotein A1 or HDL-C.<sup>19–24</sup>

## Familial Hypercholesterolemia

- FH is an autosomal codominant genetic disorder that has been associated with pathogenic variants in *LDLR*, *APOB*, *LDLRAP1*, and *PCSK9*, which affect uptake and clearance of LDL-C.<sup>25,26</sup>
- 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  $\geq 190$  mg/dL) was 6.6% (SE, 0.2%) among adults.<sup>27</sup> According to data from NHANES 1999 to 2012, the estimated US prevalence of LDL-C  $\geq 190$  mg/dL was 0.42% (95% CI, 0.15%–0.70%) among adolescents.<sup>28</sup>
- 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.<sup>29</sup>
- Individuals with the FH phenotype (LDL-C  $\geq 190$  mg/dL) experience an acceleration in CHD risk by 10 to 20 years in males and 20 to 30 years in

females.<sup>30</sup> However, individuals with LDL-C  $\geq 190$  mg/dL and a confirmed pathogenic variant for FH representing lifelong elevation of LDL-C levels have substantially higher odds for CAD than those with LDL-C  $\geq 190$  mg/dL without pathogenic variants.<sup>25</sup>

- Compared with individuals with LDL-C  $< 130$  mg/dL and no pathogenic variant, those with both LDL-C  $\geq 190$  mg/dL and a pathogenic variant for FH 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 pathogenic variant, individuals with LDL-C  $\geq 190$  mg/dL and no pathogenic variant for FH 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).<sup>31</sup>
- Among 48 741 individuals 40 to 69 years of age with genotyping array and exome sequencing data from the UK Biobank, a pathogenic variant associated with FH was identified in 0.6%.<sup>32</sup> Among participants with a pathogenic variant associated with FH compared with those without a pathogenic variant associated with FH, risk of premature ASCVD ( $\leq 55$  years of age) was higher (HR, 3.17 [95% CI, 1.96–5.12]).
- Among 2404 adult patients (mean, 45.5 years of age [SD, 15.4 years]) with FH in a multicenter, nationwide, cohort study, SAFEHEART, independent predictors of ASCVD over a mean follow-up of 5.5 years (SD, 3.2 years) included traditional clinical predictors of ASCVD (age [30–59 years versus  $< 30$  years: 2.92; 95% CI, 1.14–7.52;  $\geq 60$  years versus  $< 30$  years: 4.27; 95% CI, 1.60–11.48], male sex [2.01; 95% CI, 1.33–3.04], HBP [1.99; 95% CI, 1.26–3.15], overweight [2.40; 95% CI, 1.36–4.23] or obesity [2.67; 95% CI, 1.47–4.85], smoking [1.62; 95% CI, 1.08–2.44], and lipoprotein[a] level  $> 50$  mg/dL [1.52; [95% CI, 1.05–2.21]).<sup>33</sup>
- 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).<sup>34</sup>

- 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%]).<sup>27</sup> 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%).<sup>35</sup>
- Among 493 children with diagnosed FH in the CASCADE FH Registry, the mean age at diagnosis was 9.4 years (SD, 4.0 years), the mean highest pretreatment LDL-C was 238 mg/dL (SD, 61 mg/dL), 1 or ≥2 additional CVD risk factors were present in 35.1% and 8.7%, respectively, and 64% of participants used lipid-lowering therapy (56% used a statin) with a mean age at initiation of 11.1 years (SD, 3.2 years). Among 315 participants ≥10 years of age with either pretreatment LDL-C ≥190 mg/dL or pretreatment LDL-C ≥160 mg/dL plus family history of premature CVD, 76.5% were using lipid-lowering therapy (statin in 71.6%, nutraceutical in 7.3%). Only 27.6% of children overall and 39% of children receiving lipid-lowering therapy achieved the recommended LDL-C of either ≥50% decrease from baseline or <130 mg/dL.<sup>36</sup> These figures are similar to the medians reported for 8 European countries, although there is substantial variation between countries.<sup>37</sup>
- 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.<sup>38</sup> A systematic review of 10 studies of cascade testing for FH identified that the average yield was 44.8% and the mean number of new cases per index case was 1.65.<sup>39</sup>
- A 2020 modeling study found that child-parent cascade screening, consisting of universal screening of children at 1 year of age during immunizations followed by cascade screening of relatives, was more effective than either cascade or child-parent screening in isolation at shortening the time to identify 25%, 50%, and 75% of FH cases in the population; the estimates for the United States were 6, 16, and 30 years of age, respectively, to reach these proportions.<sup>40</sup>
- In a report of 24 pediatric patients with biallelic (homozygous or compound heterozygous) FH in Germany, mean age at diagnosis was 6.3 years (SD, 3.4 years) and mean LDL-C at diagnosis was 752 mg/dL (SD, 193 mg/dL); 21 patients were

diagnosed on the basis of clinical lipid deposits (xanthomas/xanthelasmas), and 3 were diagnosed after screening based on family history of biallelic FH. Diet and medications alone reduced LDL-C by 32.2% (SD 18.0%) to a mean (SD) of 510 (201) mg/dL, whereas weekly or twice-weekly lipoprotein apheresis resulted in an additional reduction of 63.9% (SD, 15.5%) to a mean LDL-C of 184 mg/dL (SD, 83 mg/dL) between apheresis treatments. After apheresis was started at a mean age of 8.5 years (SD, 3.1 years), 67% of patients remained clinically stable (ie, no ASCVD events or interventions) over a mean follow-up of 17.2 years (SD, 5.6 years).<sup>41</sup>

### 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 apolipoprotein B 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.<sup>42</sup>

### 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.<sup>43</sup>
  - 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 2019, the median crude prevalence of adults reporting that they had their blood cholesterol checked within the past 5 years across all states was 86.6%, whereas 8.6% reported that they never had it checked, and 3.9% reported that it was not checked in the past 5 years. The highest age-adjusted percentages of adults who had their blood cholesterol checked in the past 5 years was in the District of Columbia (92.4%) and Puerto Rico

(92.3%), whereas the state with the lowest percentage was in South Dakota (77.1%).<sup>44</sup>

- 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.<sup>1,45</sup>
  - 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 children 9 to 11 years of age and those 17 to 21 years of age, respectively.<sup>46</sup>
  - 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  $\geq$ 190 mg/dL or LDL-C  $\geq$ 160 mg/dL plus family history) or any hyperlipidemia (LDL-C  $\geq$ 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  $\approx$ 8000 more children with severe hyperlipidemia and 126 000 more children with any hyperlipidemia.<sup>47</sup>
- In a cross-sectional analysis of primary care visits from the IQVIA National Disease and Therapeutic Index, a nationally representative audit of outpatient practices in the United States, a 36.9% decrease was noted in cholesterol level measurements in the second quarter of 2020 compared with the same time frame in 2018 to 2019.<sup>48</sup>
- During the COVID-19 pandemic, an integrated health care system in Boston, Mass General Brigham, documented a decline in weekly cholesterol testing rates of 39.2% in 2020 among 220 215 individuals  $\geq$ 40 years of age; the greatest reduction occurred between March and May 2020 (up to 92%).<sup>49</sup>

## Awareness

- According to BRFSS 2019 data, 33.1% of US adults report having been told that they have high cholesterol (although lipid levels are not available for comparison with actual prevalence of high cholesterol [ie, awareness] in this sample).<sup>44</sup> The percentage of adults reporting that they have been told they have high cholesterol was highest in Louisiana

(33.6%) and lowest in South Dakota (24.1%) and Wyoming (24.1%).

- 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).<sup>8</sup>
- According to NHANES 2005 to 2014 data, awareness among young adults 18 to 39 years of age with high ( $\geq$ 240 mg/dL) or borderline high (200–239 mg/dL) TC was 56.9% (SE, 2.4%) and 22.5% (SE, 1.4%), respectively.<sup>50</sup> Independent predictors of awareness included older age (OR, 2.35 [95% CI, 1.53–3.61] for 30–39 years 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 49 447 patients with LDL-C  $\geq$ 190 mg/dL in the ACC NCDR PINNACLE registry of cardiology practices between 2013 and 2016, the proportions documented as receiving medications were as follows: 58.5% statin, 31.9% high-intensity statin, 34.6% any lipid-lowering therapy associated with  $\geq$ 50% reduction in LDL-C level, 8.5% ezetimibe, and 8.5% PCSK9 inhibitor. Treatment rates were even lower 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.<sup>51</sup>
- 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.<sup>52</sup>
- The REGARDS<sup>53</sup> 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  $\geq$ 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).<sup>9</sup>



- Among 63 576 adult patients in the Veterans Affairs Health System between 2011 and 2014 with LDL-C  $\geq 190$  mg/dL but no diabetes or ASCVD, 52% received statin therapy and 9.7% received high-intensity statin therapy, with lower treatment rates among females (versus males) 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 ( $P < 0.001$ ).<sup>54</sup>
- Among US adults with diabetes, statin use increased from 48.3% to 60.2% between 2005 to 2006 and 2015 to 2016.<sup>8</sup>
- Among US adults with a 10-year predicted ASCVD risk  $\geq 7.5\%$ , the proportion taking a statin increased from 27.9% to 32.5% between 2005 to 2006 and 2015 to 2016.<sup>8</sup>

## Control

- The 2018 Cholesterol Clinical Practice Guidelines focus on lowering LDL-C to reduce ASCVD risk.<sup>1</sup>
  - 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.<sup>55</sup>
- The REGARDS<sup>53</sup> 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.<sup>56</sup>
  - 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.<sup>57</sup> In an analysis of time-weighted average exposures to LDL-C during young adulthood (18–39 years of age) versus later adulthood ( $\geq 40$  years of age)

among 36 030 participants from 6 US cohorts, CHD rates were significantly elevated among individuals who had young-adult LDL-C  $\geq 100$  mg/dL (versus  $< 100$  mg/dL), independently of later adult exposures (aHR, 1.64 [95% CI, 1.27–2.11]). Specifically, compared with LDL-C  $< 100$  mg/dL, aHRs were as follows: for LDL-C 100 to 129 mg/dL, 1.62 (95% CI, 1.25–2.10); for LDL-C 130 to 159 mg/dL, 1.89 (95% CI, 1.43–2.50); and for LDL-C  $\geq 160$  mg/dL, 2.03 (95% CI, 1.47–2.82;  $P$  for trend across LDL-C categories  $< 0.001$ ).<sup>57</sup>

- An analysis of 4958 asymptomatic, healthy participants from CARDIA demonstrated that the AUC for LDL-C exposure between 18 and 40 years of age (aHR, 1.05 per 100 mg/dL $\times$ years [95% CI, 1.02–1.09]) and the slope of the LDL-C accumulation (0.797 per mg/dL per year [95% CI, 0.57–0.89]) were significantly associated with incident CVD. The latter supports that LDL-C exposure accumulated earlier (versus later) in life conferred greater risk.<sup>58</sup>
- Among 28 024 participants in the WHS, in addition to significant associations of standard cholesterol measures such as TC (1.39 [95% CI, 1.12–1.73]), LDL-C (1.38 [95% CI, 1.10–1.74]), HDL-C (0.39 [95% CI, 0.27–0.55]), and apolipoprotein B (1.89 [95% CI, 1.52–2.35]) with premature CHD (onset  $< 55$  years of age), total LDL particles (1.75 [95% CI, 1.42–2.15]), novel lipoprotein fractions such as small LDL particles (2.25 [95% CI, 1.76–2.89]), and total triglyceride-rich lipoproteins (1.74 [95% CI, 1.44–2.10]) were significantly associated with premature CHD.<sup>59</sup>
- In a prospective case-cohort study ( $n=480$  cases and 496 controls) within the Women's Heart Study, higher levels of triglyceride-rich lipoprotein cholesterol and small-dense LDL-C, novel lipoprotein fraction measures beyond LDL-C, were significantly associated with higher risk of MI (aHR, 3.05 [95% CI, 1.46–6.39] and 3.71 [95% CI, 1.59–8.63] for the fourth compared with first quartile of each measure, respectively).<sup>60</sup>
- In a large study of Health Survey for England and Scottish Health Survey participants ( $N=37\ 059$ ), on the basis of 2250 deaths resulting from all causes during 326 016 person-years of follow-up<sup>61</sup>:
  - 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 ( $\geq 96.7$  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 apolipoprotein B 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 apolipoprotein B-containing lipoprotein particles (very-low-density lipoprotein and LDL particles, respectively).<sup>23</sup>

- 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).<sup>62</sup>
- In a meta-analysis of individual-level data from 29 069 patients in 7 statin trials, both baseline and on-statin lipoprotein(a) concentrations were linearly associated with risk for CVD events, defined as fatal or nonfatal CHD, stroke, or coronary or carotid revascularization. Lipoprotein(a) levels of  $\geq 30$  mg/dL at baseline or  $\geq 50$  mg/dL on statin treatment were associated with increased risks compared with levels  $< 15$  mg/dL, with aHRs 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  $\geq 50$  mg/dL, and 1.43 (95% CI, 1.15–1.76) for on-statin levels  $\geq 50$  mg/dL.<sup>63</sup>
- Among 2170 patients from the Penn Heart Failure Study, levels of apolipoprotein M (present in  $\approx 5\%$  of HDL and  $< 2\%$  of LDL particles) were associated with risk of death in patients with both HF<sub>rEF</sub> and HF<sub>pEF</sub> (HR, 0.56 [95% CI, 0.51–0.61, per 1-SD-lower apolipoprotein M]). This relationship was validated in 2 external cohorts (Washington University Heart Failure Registry and the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial) and was independent of HDL-C levels, and the effect was observed to be mediated in part through inflammatory pathways.<sup>64</sup>
- Among 1211 participants who tested positive for severe acute respiratory syndrome coronavirus 2 and 387 079 control participants (tested negative or not tested between March 16, 2020, and May 31, 2020) from the UK Biobank, mendelian randomization analyses demonstrated that genetic predisposition to higher LDL-C (measured at baseline in 2006–2010) was associated with greater risk of COVID-19 infection (HR, 1.37 [95% CI, 1.14–1.65] for the top versus bottom quintile).<sup>65</sup>

- In a study of 9005 UK Biobank participants who were tested for severe acute respiratory syndrome coronavirus 2 in 2020, higher HDL-C at baseline (2006–2010) was associated with a lower odds of testing positive (OR, 0.85 [95% CI, 0.79–0.91]).<sup>66</sup>

### 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.<sup>67</sup> Costs were split relatively evenly between younger and older adults (51.0% for 20–64 years of age, 48.4% for  $\geq 65$  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 the United States, only 47% of patients who were prescribed PCSK9 inhibitors had at least 1 prescription approved between July 2015 and August 2016.<sup>68</sup> 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 and Table 7-2)

- Among the GBD data, 41.9% (95% UI, 31.7%–52.9%) of age-standardized IHD deaths in 2017 were attributed to high LDL-C, which was in the top 3 contributors, after dietary risks and high SBP.<sup>69</sup>
- The GBD 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020.
  - In 2020, age-standardized mortality rates attributable to high LDL-C were highest in Eastern Europe and Central Asia (Chart 7-5).
  - There were 4.51 (95% UI, 2.65–6.24) million deaths attributable to high LDL cholesterol in 2020. The PAF was 7.96% (95% UI, 4.68%–11.02%; Table 7-2).

**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, 2015–2018	Prevalence of HDL-C <40 mg/dL, 2015–2018
Both sexes	93 900 000 (38.1)	28 000 000 (11.5)	68 100 000 (27.8)	41 900 000 (17.2)
Males	41 600 000 (35.3)	12 200 000 (10.5)	32 200 000 (27.4)	31 600 000 (26.6)
Females	52 300 000 (40.4)	15 800 000 (12.1)	35 900 000 (28.1)	10 300 000 (8.5)
NH White males	35.0	10.1	26.0	26.3
NH White females	41.8	13.1	28.6	7.4
NH Black males	31.0	9.2	29.3	17.0
NH Black females	33.4	10.5	24.3	7.9
Hispanic males	37.7	12.4	29.4	32.0
Hispanic females	37.3	9.2	26.3	12.3
NH Asian males	38.6	13.0	33.4	26.4
NH Asian females	38.6	10.3	26.9	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, and 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.

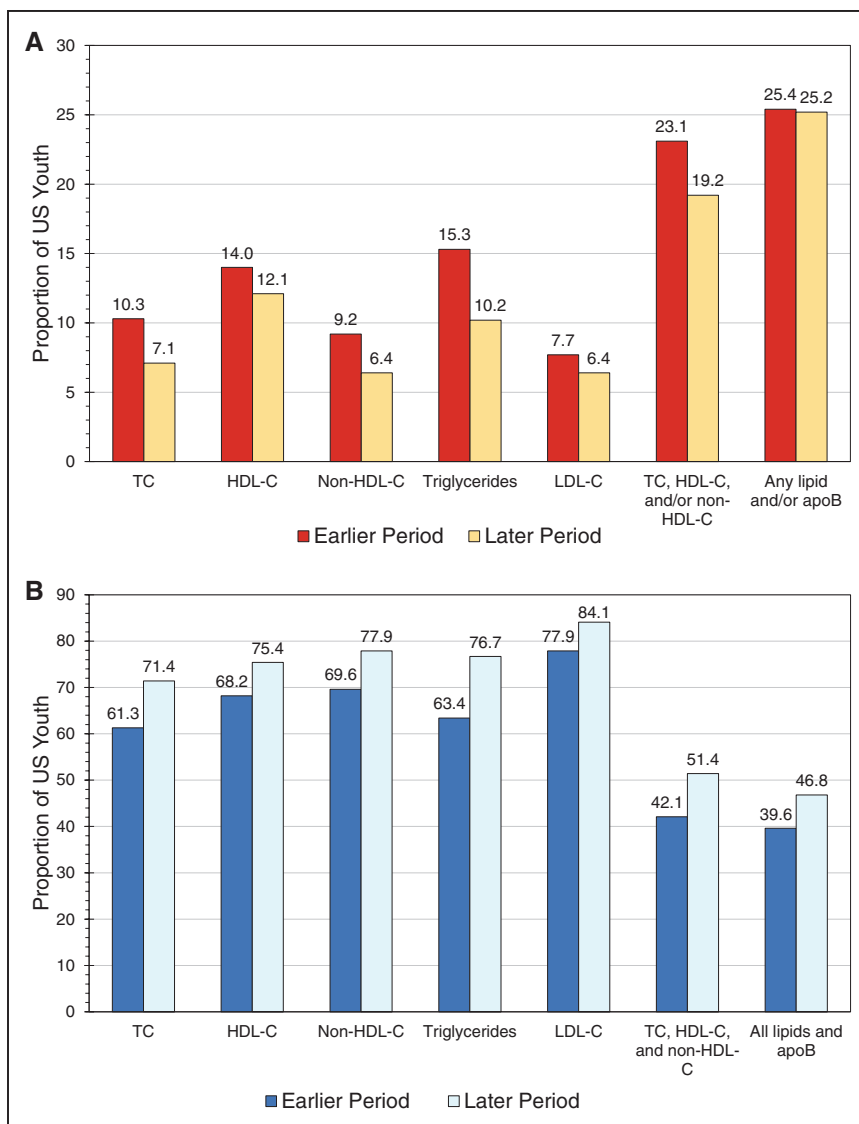
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Health and Nutrition Examination Survey,<sup>3</sup> applied to 2018 population estimates.

**Table 7-2. Deaths Caused by High LDL-C Worldwide, by Sex, 2020**

	Deaths		
	Both sexes (95% UI)	Male (95% UI)	Female (95% UI)
Total number of deaths (millions), 2020	4.51 (2.65 to 6.24)	2.33 (1.33 to 3.24)	2.18 (1.31 to 2.99)
Percent change in total number, 1990–2020	51.98 (42.94 to 60.23)	59.76 (47.78 to 71.87)	44.47 (32.67 to 55.16)
Percent change in total number, 2010–2020	18.69 (13.39 to 23.85)	19.59 (12.08 to 27.24)	17.75 (10.71 to 24.51)
Mortality rate per 100 000, age standardized, 2020	56.95 (33.63 to 78.78)	66.15 (38.09 to 91.84)	48.58 (29.29 to 66.72)
Percent change in rate, age standardized, 1990–2020	−36.86 (−40.57 to −33.49)	−34.39 (−38.99 to −29.98)	−39.57 (−44.40 to −35.13)
Percent change in rate, age standardized, 2010–2020	−12.69 (−16.33 to −8.98)	−11.67 (−16.85 to −6.50)	−13.58 (−18.75 to −8.76)
PAF (%), all ages, 2020	7.96 (4.68 to 11.02)	7.55 (4.34 to 10.44)	8.45 (5.06 to 11.61)
Percent change (%) in PAF, all ages, 1990–2020	21.33 (15.99 to 26.26)	26.66 (20.50 to 32.54)	16.27 (9.25 to 22.43)
Percent change (%) in PAF, all ages, 2010–2020	9.26 (6.67 to 11.79)	10.99 (7.99 to 14.02)	7.33 (3.70 to 10.66)

LDL-C indicates low-density lipoprotein cholesterol; PAF, population attributable fraction; and UI, uncertainty interval

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>71</sup>



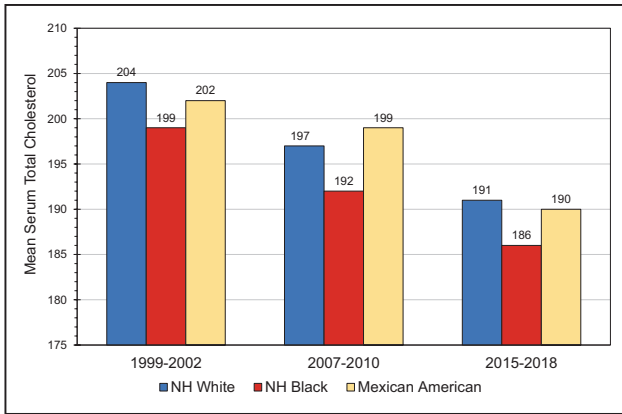
**Chart 7-1. Proportions of US youth with guideline-defined high (or for HDL-C, low) and acceptable lipid levels in the period 1999 to 2016, NHANES.**

**A**, High (or for HDL-C, low) lipid levels. **B**, Acceptable 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 high (or for HDL-C, low) 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 acceptable 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. High (or for HDL-C, low) and acceptable levels were defined according to the 2011 National Heart, Lung, and Blood Institute pediatric guideline<sup>45</sup> as follows: for TC,  $\geq 200$  and  $< 170$  mg/dL, respectively; for LDL-C,  $\geq 130$  and  $< 110$  mg/dL; for HDL-C,  $< 40$  and  $> 45$  mg/dL; for non-HDL-C,  $\geq 145$  and  $< 120$  mg/dL; for triglycerides,  $\geq 130$  and  $< 90$  mg/dL; and for apoB,  $\geq 110$  and  $< 90$  mg/dL.

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.

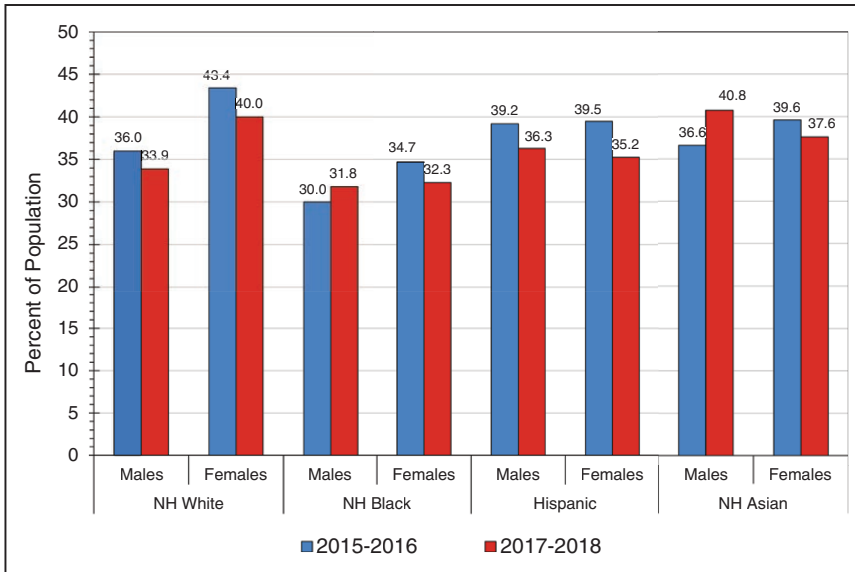
Source: Data derived from Perak et al.<sup>4</sup>





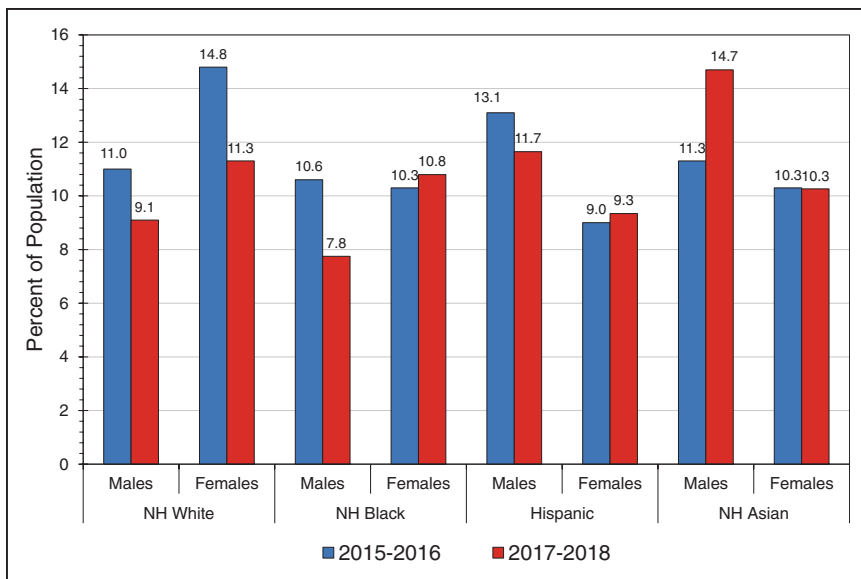
**Chart 7-2. Age-adjusted trends in mean serum TC among US adults ≥20 years of age, by race and survey year (NHANES, 1999–2002, 2007–2010, and 2015–2018).**

Values are in milligrams per deciliter. NH indicates non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and TC, total cholesterol.  
 \*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.<sup>3</sup>

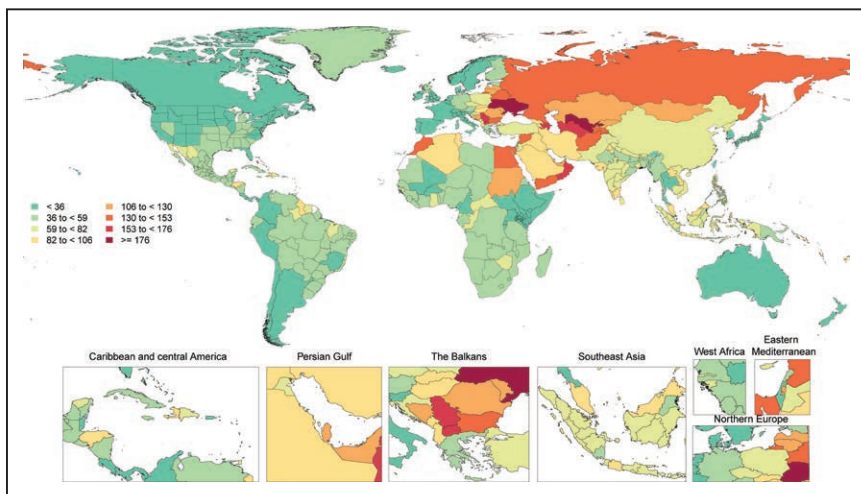


**Chart 7-3. Age-adjusted trends in the prevalence of serum TC ≥200 mg/dL in US adults ≥20 years of age, by race and ethnicity, sex, and survey year (NHANES, 2015–2016 and 2017–2018).**

NH indicates non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and TC, total cholesterol.  
 Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>3</sup>



**Chart 7-4. Age-adjusted trends in the prevalence of serum TC ≥240 mg/dL in US adults ≥20 years of age, by race and ethnicity, sex, and survey year (NHANES, 2015–2016 and 2017–2018).** NH indicates non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and TC, total cholesterol. Source: Unpublished National Health, Lung, and Blood Institute tabulation using NHANES.<sup>3</sup>



**Chart 7-5. Age-standardized global mortality rates attributable to high LDL-C per 100,000, both sexes, 2020.** LDL-C indicates low-density lipoprotein cholesterol. Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>71</sup>

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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 CHD, HF, and stroke.<sup>1–3</sup> The AHA has identified untreated BP <90th percentile (for children) and <120/<80 mmHg (for adults ≥20 years of age) as 1 of the 7 components of ideal CVH.<sup>4</sup> In 2017 to 2018, 89.2% of US children 12 to 19 years of age and 40.8% of US adults met these criteria (see Chapter 2, Cardiovascular Health, Chart 2-1).

### 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<sup>5</sup>:
  - SBP ≥130 mmHg, DBP ≥80 mmHg, 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 by 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
- 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).<sup>6</sup> 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,<sup>6</sup> 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,<sup>6</sup> 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<sup>6</sup> 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 and ethnicity and sex subgroups in Chart 8-2.
- 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%).<sup>7</sup>
- In a cohort of 3367 patients with established kidney disease, 40.4% had resistant hypertension, which was defined as having SBP ≥140 mmHg or DBP ≥90 mmHg on ≥3 antihypertensive medications or use of ≥4 antihypertensive medications and SBP <140 mmHg and DBP <90 mmHg.<sup>8</sup>
- 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 mmHg on at least 3 antihypertensive medications) was 16.9%, whereas the prevalence of white-coat resistant hypertension was 37.1%.<sup>9</sup> The prevalence of refractory hypertension (SBP/DBP ≥140/90 mmHg on ≥5 antihypertensive medications) was 1.4%, whereas the prevalence of white-coat refractory hypertension was 26.7%.<sup>9</sup>
- SPRINT demonstrated that an SBP goal of <120 mmHg resulted in fewer CVD events and a greater reduction in mortality than an SBP goal of <140 mmHg among people with SBP ≥130 mmHg and increased cardiovascular risk.<sup>10</sup> 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.<sup>11</sup>

The 2022 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 2022. 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.

### 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 mmHg (95% CI, 3.1–4.6) larger for each 10-year increase in age.<sup>12</sup>

- Among 5236 adults in the REGARDS study  $\geq 65$  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), with 2 versus 0 indicators was 1.49 (95% CI, 1.19–1.87), and with  $\geq 3$  versus 0 indicators 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.<sup>13</sup>

### Children and Adolescents

- In NHANES 2015 to 2016, 13.3% (SE, 1.3) of children and adolescents 8 to 17 years of age had elevated BP (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 elevated BP 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.<sup>14</sup>
- 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 elevated BP 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 elevated BP than NH White youth (10.7%).<sup>14</sup>
- In NHANES 2015 to 2016, the prevalence of hypertension was 11.6% among obese US adolescents (BMI  $\geq 120\%$  of 95th percentile of sex-specific BMI for age or BMI  $\geq 35$  kg/m<sup>2</sup>) compared with 2.7% among normal-weight/underweight children. The prevalence of elevated BP among obese versus normal/underweight youth was 16.2% compared with 8.7%.<sup>14</sup>
- 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.<sup>15</sup>

- Among 30565 children and adolescents (3–17 years of age) receiving health care between 2012 and 2015, 51.2% of those with a first BP reading  $\geq 95$ th 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  $< 95$ th percentile. Of those with a visit BP  $\geq 95$ th 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  $\geq 95$ th percentile at this visit.<sup>16</sup>

### Race and 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,<sup>6</sup> 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]).<sup>17</sup>
- Data from the 2018 NHIS showed that Black adults  $\geq 18$  years of age were more likely (32.2%) to have been told on  $\geq 2$  occasions that they had hypertension than American Indian/Alaska Native adults (27.2%), White adults (23.9%), Hispanic or Latino adults (23.7%), or Asian adults (21.9%).<sup>18</sup>
- 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.<sup>19</sup>
- Among 441 Black people in the JHS not taking antihypertensive medication, the prevalence of clinic hypertension (mean SBP  $\geq 140$  mmHg or mean DBP  $\geq 90$  mmHg) was 14.3%, the prevalence

of daytime hypertension (mean daytime SBP  $\geq 135$  mmHg or mean daytime DBP  $\geq 85$  mmHg) was 31.8%, and the prevalence of nighttime hypertension (mean nighttime SBP  $\geq 120$  mmHg or mean nighttime DBP  $\geq 70$  mmHg) 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.<sup>20</sup>

## 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  $\geq 130$  mmHg, DBP  $\geq 80$  mmHg, 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.<sup>21</sup>

## 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 according to 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.<sup>22</sup>
- Among 32 887 participants of the Kailuan study in Tangshan City, Hebei Province, China, with prehypertension (SBP 120–239 mmHg or DBP 80–89 mmHg 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  $\geq 140$  mmHg, DBP  $\geq 90$  mmHg, 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  $\geq 5$  ideal factors.<sup>23</sup>
- 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 mmHg (95% CI, 0.29–0.31 mmHg) 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.<sup>24</sup>

## Secular Trends

- In 51 761 participants from NHANES, according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure definition of hypertension (140/90 mmHg), the age-adjusted estimated prevalence of hypertension in US adults  $>18$  years of age (weighted to the US population) increased from 30.0% (95% CI, 27.1%–32.9%) in 1999 to 2000 to 32% (95% CI 29.3%–34.6%) in 2017 to 2018. However, with the use of the 2017 Hypertension Clinical Practice Guidelines (130/80 mmHg), the age-adjusted estimated prevalence of hypertension in US adults  $>18$  years of age was 48.6% (95% CI, 45.7%–51.5%) in 1999 to 2000 and 46.5% (95% CI, 44.0%–49.0%) in 2017 to 2018.<sup>25</sup>
- With the use of the 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 ( $P$  for trend  $<0.001$ ) and the prevalence of hypertension declined from 6.6% to 4.5% ( $P$  for trend = 0.005).<sup>14</sup>
- In NHANES, among underweight/normal-weight youth (8–17 years of age), there was a statistically significant decline in the prevalence of elevated BP/hypertension and hypertension between 2003 to 2004 and 2015 to 2016. There were no changes in the prevalence of elevated BP/hypertension or hypertension among overweight youth during this time period; among obese youth, there was a decline in the prevalence of elevated BP/hypertension ( $P$  for trend = 0.03) but not hypertension. Among underweight/normal-weight adolescents, the unadjusted prevalence of elevated BP/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 elevated BP/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 elevated BP/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.<sup>14</sup>

- In NHDS data compiled by the CDC, chronic hypertension in pregnancy (defined as SBP  $\geq$ 140 mm Hg or DBP  $\geq$ 90 mm Hg either before pregnancy or up to the first 20 weeks during pregnancy) increased >13-fold between 1970 and 2010. Black females had a persistent 2-fold higher rate of chronic hypertension compared with White females over the 40-year period.<sup>26</sup>

## 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).<sup>27</sup>
- 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).<sup>28</sup>
- Among 6897 Black and White individuals in the REGARDS cohort who were free from hypertension (SBP  $\geq$ 140 mm Hg, DBP  $\geq$ 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.<sup>29</sup>
- 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) higher SBP and 2.25-mm Hg (95% CI, 0.83–3.67) higher DBP. Each additional 1000 mg of potassium excretion was associated with 3.72-mm Hg (95% CI, 1.42–6.01) lower SBP.<sup>30</sup>
- 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).<sup>31</sup> This equated to an 8.2% increased RR 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).<sup>32</sup>
- In the JHS, intermediate and ideal levels versus poor level 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.<sup>33</sup>
- In a meta-analysis of 24 cohort studies (N=330 222), each 10 additional MET-h/wk 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-h/wk in total PA time was associated with an RR for hypertension of 0.93 (95% CI, 0.88–0.98).<sup>34</sup>
- 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).<sup>35</sup>
- 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.<sup>36</sup>
- 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.<sup>37</sup>
- 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]).<sup>38</sup>

## 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.<sup>39</sup>
- 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), even after adjustment for poverty and other relevant risk factors.<sup>40</sup>
- In 1845 Black participants from the JHS without hypertension at baseline, medium (HR, 1.49 [95% CI, 1.18–1.89]) and high (HR, 1.34 [95% CI, 1.07–1.68]) exposure versus low exposure to discrimination over the course of a lifetime was associated with a higher risk of incident hypertension after



adjustment for demographics and hypertension risk factors.<sup>41</sup>

- 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 (PR, 0.87 [95% CI, 0.74–1.00];  $P=0.041$ ) of treatment-resistant hypertension in multivariable-adjusted models.<sup>42</sup>
- 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 mmHg per 1-SD increase [95% CI, 0.25–2.83]) in both sexes and lower levels of DBP (1.24 mmHg [95% CI, 0.37–2.12]) among females only.<sup>43</sup>
- In a cohort of 3547 white collar workers from Quebec, in models adjusted for demographics and a range of other risk factors, the prevalence of masked hypertension was higher among individuals working 41 to 48 h/wk (PR, 1.51 [95% CI, 1.06–2.14]) and  $\geq 49$  h/wk (1.70 [95% CI, 1.09–2.64]) compared with those working  $\leq 40$  h/wk. Similarly, the prevalence of sustained hypertension was higher among those working 41 to 48 h/wk (PR, 1.33 [95% CI, 0.99–1.76]) and  $\geq 49$  h/wk (1.66 [95% CI, 1.15–2.50]) compared with those who worked  $\leq 40$  h/wk.<sup>44</sup>

### Risk Prediction

- A systematic review identified 48 hypertension risk prediction models reported in 26 studies (N=162358 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).<sup>45</sup>
- Using a total study sample of  $\approx 1.5$  million individuals in the Health Information Exchange data set of Maine, which covers  $\approx 95\%$  of Maine residents, the additive regression tree model software XGBoost achieved an AUC of 0.87 for predicting incident hypertension cases in 2015, based on the prospective cohort of 680810 participants from 2014.<sup>46</sup> 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 elevated BP (SBP 120–129 mmHg, DBP  $< 80$  mmHg) was 12.1% (95% CI, 11.0%–13.3%).<sup>47</sup>

- Among 17747 participants in NHANES 2007 to 2012 who were 8 to 80 years of age, the yearly net transition probabilities for ideal BP ( $< 90$ th percentile by age and sex for individuals 8–19 years of age; SBP  $< 120$  mmHg and DBP  $< 80$  mmHg for individuals 20–80 years of age) to prehypertension (90th–95th percentile or SBP  $\geq 120$  mmHg or DBP  $\geq 80$  mmHg for individuals 8–19 years of age; SBP 120–129 mmHg or DBP 80–89 mmHg 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.<sup>48</sup>

### 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  $> 1.3$  million individuals, have established  $> 300$  well-replicated hypertension loci, with several hundred additional suggestive loci.<sup>49–59</sup>
- GRSs for hypertension are also associated with increased risk of CVD and MI,<sup>49</sup> and mendelian randomization analysis suggests a causal role for higher BP in 14 cardiovascular conditions, including IHD (SBP, per 10 mmHg: OR, 1.33 [95% CI, 1.24–1.41]; DBP, per 5 mmHg: OR, 1.20 [95% CI, 1.14–1.27]) and stroke (SBP, per 10 mmHg: OR, 1.35 [95% CI, 1.24–1.48]; DBP, per 5 mmHg: OR, 1.20 [95% CI, 1.12–1.28]).<sup>60</sup>
- 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 hundred thousand people have to date revealed several loci of interest that interact with smoking<sup>61,62</sup> and sodium.<sup>63,64</sup>
- The clinical implications and utility of hypertension genes remain unclear, although some genetic variants have been shown to influence response to antihypertensive agents.<sup>65</sup>

### Prevention

- In NHANES 2011 to 2014 (N=10958), 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.<sup>66</sup>

- 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  $\geq 140$  mm Hg, DBP  $\geq 90$  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).<sup>67</sup>

## Awareness, Treatment, and Control

### (See Table 8-2 and Charts 8-3 through 8-5)

- On the basis of NHANES 2015 to 2018 data,<sup>6</sup> the extent of awareness, treatment, and control of HBP is provided by race and ethnicity in Chart 8-3, by age in Chart 8-4, and by race and ethnicity and sex in Chart 8-5. Awareness, treatment, and control of hypertension were higher at older ages (Chart 8-4). In all race and 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<sup>6</sup> found large increases in hypertension awareness, treatment, and control ( $\approx 10\%$ ) within each race and 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.<sup>68</sup>
- In an analysis of 18 262 adults  $\geq 18$  years of age with hypertension (defined as 140/90 mm Hg) in NHANES, the estimated age-adjusted proportion with controlled BP increased from 31.8% (95% CI, 26.9%–36.7%) in 1999 to 2000 to 48.5% (95% CI, 45.5%–51.5%) in 2007 to 2008, remained relatively stable at 53.8% (95% CI, 48.7%–59.0%) in 2013 to 2014, but declined to 43.7% (95% CI, 40.2%–47.2%) in 2017 to 2018.<sup>25</sup> Controlled BP was less prevalent among NH Black individuals (41.5%) compared with NH White individuals

(48.2%). In addition, compared with adults 18 to 44 years of age, controlled BP was more common in adults 45 to 64 years of age (36.7% and 49.7%, respectively).

- Among 3358 Black people taking antihypertensive medication in the JHS, 25.4% of participants reported not taking  $\geq 1$  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  $\geq 140$  mm Hg or DBP  $\geq 90$  mm Hg (PR, 1.26 [95% CI, 1.16–1.37]).<sup>69</sup>
- In an analysis of 1590 health care professionals who completed the DocStyles survey, a web-based survey of health care professionals, 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%).<sup>70</sup>
- 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%.<sup>71</sup>

## Mortality

### (See Table 8-1)

- According to data from the NVSS, in 2019,<sup>72</sup> 102 072 deaths were attributable primarily to HBP (Table 8-1). The 2019 age-adjusted death rate attributable primarily to HBP was 25.1 per 100 000. Age-adjusted death rates attributable to HBP (per 100 000) in 2019 were 25.7 for NH White males, 56.7 for NH Black males, 23.1 for Hispanic males, 17.4 for NH Asian/Pacific Islander males, 31.9 for NH American Indian/Alaska Native males, 20.6 for NH White females, 38.7 for NH Black females, 17.4 for Hispanic females, 14.5 for NH Asian/Pacific Islander females, and 22.4 for NH American Indian/Alaska Native females (unpublished NHLBI tabulation using CDC WONDER<sup>73</sup>).
- From 2009 to 2019, the death rate attributable to HBP increased 34.2%, and the actual number

of deaths attributable to HBP rose 65.3%. During this 10-year period, in NH White people, the HBP age-adjusted death rate increased 44.1%, whereas the actual number of deaths attributable to HBP increased 67.5%. In NH Black people, the HBP death rate increased 5.2%, whereas the actual number of deaths attributable to HBP increased 38.4%. In Hispanic people, the HBP death rate increased 22.6%, and the actual number of deaths attributable to HBP increased 103.8% (unpublished NHLBI tabulation using CDC WONDER<sup>73</sup>).

- When any mention of HBP was present, the overall age-adjusted death rate in 2019 was 126.7 per 100 000. Death rates were 143.1 for NH White males, 233.6 for NH Black males, 93.3 for NH Asian or Pacific Islander males, 168.5 for NH American Indian or Alaska Native males (underestimated because of underreporting), and 126.3 for Hispanic males. In females, rates were 104.3 for NH White females, 157.2 for NH Black females, 70.4 for NH Asian or Pacific Islander females, 115.3 for NH American Indian or Alaska Native females (underestimated because of underreporting), and 89.4 for Hispanic females (unpublished NHLBI tabulation using CDC WONDER<sup>73</sup>).
- The elimination of hypertension could reduce CVD mortality by 30.4% among males and 38.0% among females.<sup>74</sup> 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.<sup>74</sup>
- 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.<sup>75</sup>
- Among US adults meeting the eligibility criteria for SPRINT, SBP treatment to a treatment goal of <120 mmHg versus <140 mmHg has been projected to prevent ≈107 500 deaths per year (95% CI, 93 300–121 200).<sup>76</sup>
- 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.<sup>77</sup>
- 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.<sup>78</sup> 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 mmHg) 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.<sup>79</sup>

## Complications

- In a meta-analysis that included 95 772 US females and 30 555 US males, each 10-mmHg 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-mmHg higher SBP was 1.16 (95% CI, 1.10–1.23) among females and 1.17 (95% CI, 1.12–1.22) among males.<sup>80</sup>
- 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 mmHg or DBP 80–89 mmHg) per 1000 person-years and 8.04 (95% CI, 6.45–10.03) for those with stage 2 hypertension (≥140/90 mmHg or taking antihypertensive medication) per 1000 person-years over the median follow-up of ≈19 years.<sup>81</sup> 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 elevated BP or prehypertension (untreated SBP 130–139 mmHg or DBP 80–89 mmHg) 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.<sup>81</sup>
- 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%).<sup>82</sup>
- 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.<sup>83</sup>
- 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.<sup>1</sup> 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 was significantly lower, at 32% (95% CI, 11.9%–48.1%), among NH Black people ≥60 years of age.
- In 8022 individuals from SPRINT with hypertension but without AF at baseline, those in the intensive BP-lowering arm (target SBP <120 mmHg) had a 26% lower risk of developing AF over the 5.2 years of follow-up (28322 person-years) than those in the standard BP-lowering arm (target SBP <140 mmHg; HR, 0.74 [95% CI, 0.56–0.98];  $P=0.037$ ).<sup>84</sup>
  - Among 17312 participants with hypertension, non-dipping BP was associated with an HR for CVD of 1.40 (95% CI, 1.20–1.63).<sup>85</sup>
  - 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).<sup>86</sup> In 1034 participants from the JHS completing ambulatory BP monitoring, each 1-SD higher level of mean daytime SBP (13.5 mmHg) 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 mmHg, daytime DBP (HR, 1.25 [95% CI, 1.02–1.51]) per 9.3 mmHg, and nighttime DBP (HR, 1.30 [95% CI, 1.06–1.59]) per 9.5 mmHg.<sup>79</sup>
  - A meta-analysis (23 cohorts with 20445 participants) showed that white-coat hypertension is associated with an increased risk for CVD among untreated individuals (aHR, 1.38 [95% CI, 1.15–1.65]) but not among treated individuals (HR, 1.16 [95% CI, 0.91–1.49]).<sup>87</sup>
  - 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]).<sup>8</sup>
  - In an international case-control study ( $n=13447$  cases of stroke and  $n=13472$  controls), a history of hypertension or SBP/DBP ≥140/90 mmHg 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%.<sup>88</sup>

- 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).<sup>89</sup>
- In a prospective follow-up of the REGARDS, MESA, and JHS cohorts ( $N=31856$ ), 63.0% (95% CI, 54.9%–71.1%) of the 2584 incident CVD events occurred in participants with SBP <140 mmHg and DBP <90 mmHg.<sup>90</sup>
- Higher SBP explains ≈50% of the excess stroke risk among Black individuals compared with White individuals.<sup>92</sup>
- Among 3319 adults ≥65 years of age from the S.AGES cohort in France, higher SBP variability (assessed in 6-month intervals over the course of 3 years) was associated with poorer global cognition independently of baseline SBP (adjusted 1-SD increase of coefficient of variation:  $\beta=-0.12$  [SE, 0.06];  $P=0.04$ ).<sup>92</sup> Similar results were observed for DBP variability ( $\beta=-0.20$  [SE, 0.06];  $P<0.001$ ). Higher SBP variability was also associated with greater dementia risk (adjusted 1-SD increase of coefficient of variation: HR, 1.23 [95% CI, 1.01–1.50];  $P=0.04$ ).
- In a subsample of 191 participants from CARDIA, cumulative BP from baseline through year 30 was associated with slower walking speed, smaller step length, and worse cognitive function in the executive, memory, and global domains.<sup>93</sup> Associations between cumulative BP and both walking speed and step length were moderated by cerebral WMH burden.

## 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 2008 to 2018, the number of inpatient discharges from short-stay hospitals with HBP as the principal diagnosis increased from 282000 to 1331000. The number of discharges with any listing of HBP increased from 14851000 to 17917000 (Table 8-1).
- In 2018, there were 10000 principal diagnosis discharges for essential hypertension (HCUP,<sup>94</sup> unpublished NHLBI tabulation).



- In 2018, there were 9 728 000 all-listed discharges for essential hypertension (HCUP;<sup>94</sup> unpublished NHLBI tabulation).
- In 2018, 33 610 000 of 860 386 000 physician office visits had a primary diagnosis of essential hypertension (*ICD-9-CM* 401; NAMCS,<sup>95</sup> unpublished NHLBI tabulation). A total of 914 000 of 143 454 000 ED visits in 2018 (HCUP;<sup>94</sup> unpublished NHLBI tabulation) and 3 743 000 of 125 721 000 hospital outpatient visits in 2011 were for essential hypertension (NHAMCS,<sup>96</sup> unpublished NHLBI tabulation).
- Among REGARDS study participants  $\geq 65$  years of age taking antihypertensive medication, 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;  $P < 0.001$ ) and more cardiologist visits (0.50 versus 0.35 per year;  $P = 0.014$ ). 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%).<sup>97</sup>

## Cost

### (See Table 8-1)

- The estimated direct and indirect cost of HBP for 2017 to 2018 (annual average) was \$51.1 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.<sup>98</sup>
- From 2003 to 2014, the annual mean additional medical cost for a person with hypertension was \$1920 compared with costs for a person without hypertension, according to data from MEPS.<sup>99</sup>
- According to data from MEPS for 2011 to 2014, among individuals with a diagnosis code for hypertension who were  $\geq 18$  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  $\geq 3$  comorbidities.<sup>100</sup>
- 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.<sup>101</sup>

## 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 except Oceania and eastern, central, and western sub-Saharan Africa.<sup>102</sup>
- In a meta-analysis of population-based studies conducted in Africa, the prevalence of hypertension was 55.2% among adults  $\geq 55$  years of age.<sup>103</sup>
- 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%).<sup>104</sup>
- 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).<sup>105</sup>
- The GBD 2020 Study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020. Age-standardized mortality rates attributable to high SBP were highest in Central and Southeast Asia, Eastern and Central Europe, and parts of Africa and the Middle East (Chart 8-6).
- In 2015, the prevalence of SBP  $\geq 140$  mm Hg was estimated to be 20 526 per 100 000. This represents an increase from 17 307 per 100 000 in 1990.<sup>107</sup> 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  $\geq 140$  mm Hg.<sup>107</sup>
- It has been estimated that 7.834 million deaths and 143.037 million DALYs in 2015 could be attributed to SBP  $\geq 140$  mm Hg.<sup>107</sup> 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.<sup>107</sup>
- Between 1990 and 2015, the number of deaths related to SBP  $\geq 140$  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.<sup>107</sup>
- 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%.<sup>108</sup>
  - 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.<sup>109</sup>
  - 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.<sup>110</sup>

**Table 8-1. HBP in the United States**

Population group	Prevalence, 2015–2018, age ≥20 y	Mortality,* 2019, all ages	Hospital discharges,† 2018, all ages	Estimated cost, 2017–2018
Both sexes	121 500 000 (47.3%) (95% CI, 45.4%–49.2%)	102 072	1 331 000	\$51.1 Billion
Males	63 100 000 (51.7%)	49 451 (48.4%)‡		...
Females	58 400 000 (42.8%)	52 621 (51.6%)‡		...
NH White males	51.0%	33 788	...	...
NH White females	40.5%	37 835	...	...
NH Black males	58.3%	9 604	...	...
NH Black females	57.6%	8 999	...	...
Hispanic males	50.6%	3 949	...	...
Hispanic females	40.8%	3 659	...	...
NH Asian males	51.0%	1 490§	...	...
NH Asian females	42.1%	1 688§	...	...
NH American Indian/Alaska Native people	...	679	...	...

Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A subject was considered to have hypertension if SBP was ≥130 mm Hg or 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.<sup>47</sup> 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, DBP was ≥80 mm Hg, or 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.

DBP indicates diastolic blood pressure; ellipses (...), data not available; HBP, high blood pressure; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

\*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. Large increase in hospital discharges is attributable to *International Classification of Diseases, 10th Revision* coding changes for heart failure using Agency for Healthcare Research and Quality Prevention Quality Indicator 08, heart failure admission rate.

‡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.<sup>6</sup> Percentages for racial and 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.<sup>72</sup> These data represent underlying cause of death only. Mortality for NH Asian people includes Pacific Islander people. Hospital discharges: Unpublished NHLBI tabulation using HCUP.<sup>94</sup> Cost: Unpublished NHLBI tabulation using Medical Expenditure Panel Survey<sup>111</sup>; includes estimated direct costs for 2017 to 2018 (annual average) and indirect costs calculated by NHLBI for 2017 to 2018 (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 and Ethnicity**

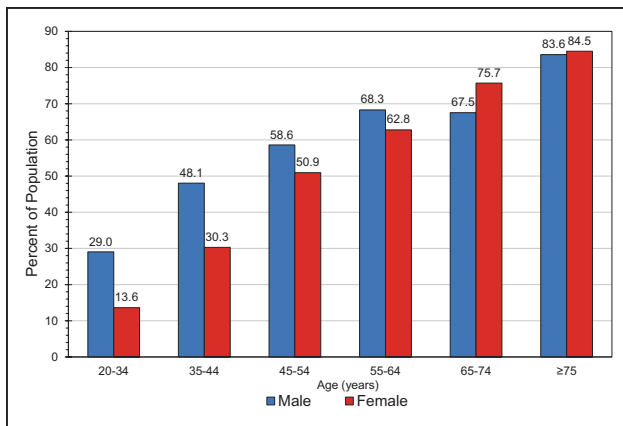
	Awareness, %			Treatment, %			Control, %		
	1999–2002	2007–2010	2015–2018	1999–2002	2007–2010	2015–2018	1999–2002	2007–2010	2015–2018
Overall	48.9	61.2	61.2	37.7	52.5	50.4	12.0	24.1	21.6
NH White males	42.7	58.0	60.3	31.4	48.7	45.9	10.9	22.2	20.2
NH White females	56.7	66.1	64.8	45.9	59.2	57.7	14.8	28.7	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

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  $\geq 130$  mmHg, diastolic blood pressure (DBP) was  $\geq 80$  mmHg, or if the subject said “yes” to taking antihypertensive medication. Controlled hypertension is considered SBP  $< 130$  mmHg or DBP  $< 80$  mmHg. Total includes race and 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 used only starting in 2007. Consequently, for long-term trend data, the category of Mexican American people is used. Total includes race and ethnicity groups not shown (other Hispanic, other race, and multiracial).

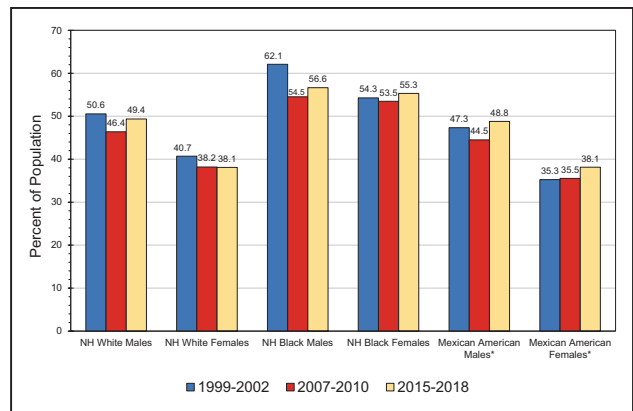
Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>6</sup>



**Chart 8-1. Prevalence of hypertension in US adults  $\geq 20$  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  $\geq 130$  mmHg or diastolic blood pressure  $\geq 80$  mmHg, 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.<sup>6</sup>



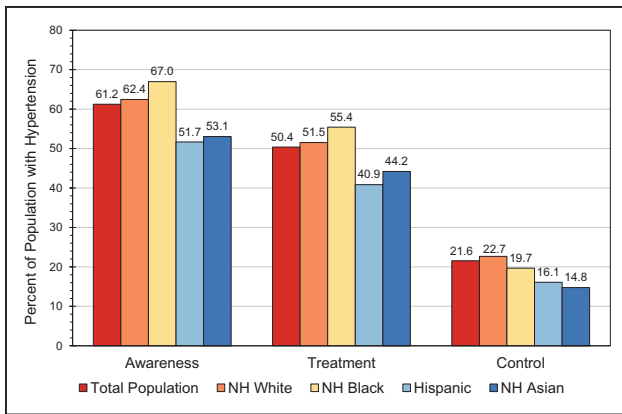
**Chart 8-2. Age-adjusted prevalence trends for hypertension in US adults  $\geq 20$  years of age, by race and ethnicity, sex, and survey year (NHANES, 1999–2002, 2007–2010, and 2015–2018).**

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  $\geq 130$  mmHg or diastolic blood pressure  $\geq 80$  mmHg 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.<sup>6</sup>

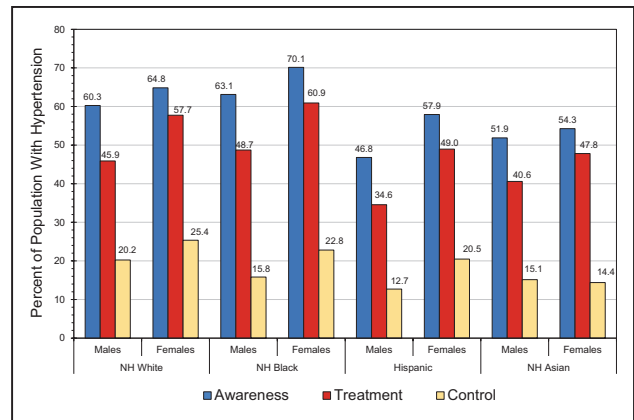


**Chart 8-3. Extent of awareness, treatment, and control of high blood pressure, by race and ethnicity, United States (NHANES, 2015–2018).**

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  $\geq 130$  mm Hg or diastolic blood pressure  $\geq 80$  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.<sup>6</sup>

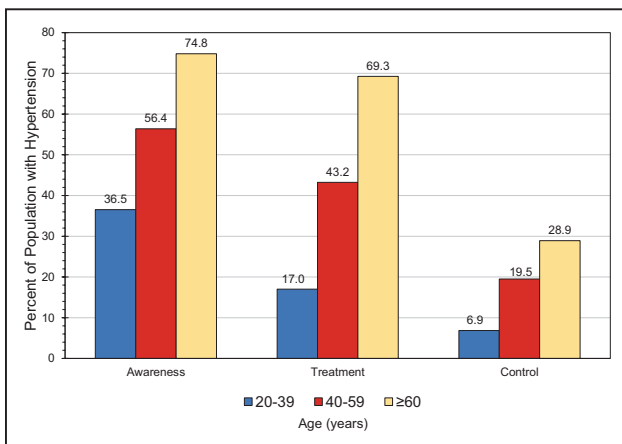


**Chart 8-5. Extent of awareness, treatment, and control of high blood pressure, by race and ethnicity and sex, United States (NHANES, 2015–2018).**

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  $\geq 130$  mm Hg or diastolic blood pressure  $\geq 80$  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.<sup>6</sup>



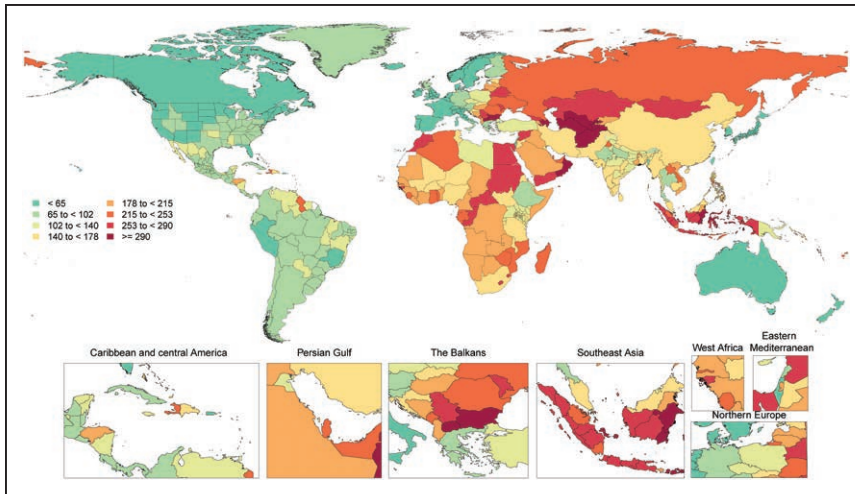
**Chart 8-4. Extent of awareness, treatment, and control of high blood pressure, by age, United States (NHANES, 2015–2018).**

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  $\geq 130$  mm Hg or diastolic blood pressure  $\geq 80$  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.<sup>6</sup>





**Chart 8-6. Age-standardized global mortality rates attributable to high systolic blood pressure per 100 000, both sexes, 2020.**

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. Additional information is available on the Global Burden of Disease Study website.<sup>112</sup>

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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, and type 1 diabetes, which constitutes 5% to 10% of cases of diabetes.<sup>1</sup> For this chapter, diabetes type (ie, type 1 diabetes or type 2 diabetes) is used when reported as such in the original data source; otherwise, the broader term diabetes is used and may include different diabetes types, of which the vast majority will be type 2 diabetes. Diabetes is defined on the basis of FPG  $\geq 126$  mg/dL, 2-hour postchallenge glucose  $\geq 200$  mg/dL during an oral glucose tolerance test, random glucose  $\geq 200$  mg/dL with presentation of hyperglycemia symptoms, or HbA1c  $\geq 6.5\%$ <sup>2</sup> and may be classified as diagnosed by a health care professional or undiagnosed (ie, meeting glucose or HbA1c criterion but without a clinical diagnosis). Prediabetes increases the risk of diabetes and is defined as FPG of 100 to 125 mg/dL, 2-hour postchallenge glucose of 140 to 199 mg/dL during an oral glucose tolerance test, or HbA1c of 5.7% to 6.4%. Diabetes is a major risk factor for CVD, including CHD and stroke.<sup>3</sup> The AHA has identified untreated FPG levels of  $< 100$  mg/dL for children and adults as 1 of the 7 components of ideal CVH.<sup>4</sup>

### Prevalence

#### Youth

- Approximately 210 000 people  $< 20$  years of age were diagnosed with diabetes in 2018, of whom 187 000 had type 1 diabetes.<sup>1</sup>
- 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).<sup>5</sup>

- 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.<sup>6</sup>
- 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%]).<sup>7</sup>

#### Adults

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

- Among adults  $\geq 18$  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.<sup>8</sup>
- On the basis of data from NHANES 2015 to 2018,<sup>9</sup> an estimated 28.2 million adults (10.4%) had diagnosed diabetes, 9.8 million adults (3.8%) had undiagnosed diabetes, and 113.6 million adults (45.8%) had prediabetes.
- After adjustment for population age differences, NHANES 2015 to 2018<sup>9</sup> data for people  $\geq 20$  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.<sup>1</sup>
- On the basis of NHANES 2015 to 2018 data,<sup>9</sup> the age-adjusted prevalence of diagnosed diabetes in adults  $\geq 20$  years of age varies by race and ethnicity and years of education. NH White adults with more than a high school education had the lowest prevalence (8.3%), and Hispanic adults with less than a high school education had the highest prevalence (16.8%; Chart 9-2).
- Among US adults  $\geq 20$  years of age in NHANES 2011 to 2016, the prevalence of diabetes varied within racial and 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%).<sup>10</sup>
- 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.<sup>11</sup>

The 2022 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 2022. 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.

- Geographic variations in diabetes prevalence have been reported in the United States:
  - From state-level data from BRFSS<sup>12</sup> 2019, Mississippi (13.3%) and West Virginia (13.0%) had the highest age-adjusted prevalence of diagnosed diabetes, and Montana (6.4%) and Colorado (6.6%) had the lowest prevalence. The age-adjusted prevalence of diagnosed diabetes was highest in the US territories of Guam (13.3%) and Puerto Rico (14.4%; Chart 9-3).

## 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.<sup>1</sup>
- On the basis of 2014 to 2015 data from SEARCH, a population-based registry of 69 457 475 youths <20 years of age from Arizona, California, Colorado, New Mexico, Ohio, South Carolina, and Washington, the incidence rate (per 100 000) of type 1 and type 2 diabetes was 22.3 (95% CI, 21.0–23.6) and 13.8 (95% CI, 12.4–15.3), respectively.<sup>13</sup>
  - 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.<sup>13</sup>
  - 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.<sup>13</sup>

### 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).<sup>1</sup>
- 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.<sup>1</sup>
- During 2017 to 2018, adults with less than a 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 a high school education (5.6 per 1000 [95% CI, 4.7–6.7]).<sup>1</sup>

## Secular Trends

### (See Charts 9-4 and 9-5)

- In the SEARCH study, the incidence rate of type 1 diabetes increased by 1.9% annually and the incidence of type 2 diabetes increased by 4.8% annually from 2002 to 2015.<sup>13</sup>
  - The annual increase in diabetes varied by race and 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<sup>13</sup> (Chart 9-4).
- 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%]).<sup>1</sup>
- The prevalence of diagnosed diabetes in adults was higher for both males and females in the NHANES 2015 to 2018 data than in the NHANES 1988 to 1994 data. Males had a higher prevalence of both diagnosed diabetes and undiagnosed diabetes than females in 2015 to 2018 (Chart 9-5).
- 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.<sup>1</sup>

## 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 HbA1c 5.7% to 6.4%.<sup>14</sup>
- 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]).<sup>15</sup>

- 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.<sup>16</sup>
- 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  $\leq 6$  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).<sup>17</sup>
- Lifestyle factors (higher alcohol consumption, lower PA, higher sedentary time, and unhealthy diet) were independently associated with diabetes risk over a median 3.8 years of follow-up. Adults with the least favorable lifestyle profile had an increased risk for diabetes compared with those with the most favorable lifestyle profile, regardless of the number of metabolic risk components for WC, triglycerides, HDL-C, BP, and FPG (0–2 metabolic risk components RR, 1.29 [95% CI, 1.15–1.45]; 3 metabolic risk components RR, 1.21 [95% CI, 1.06, 1.38]; 4–5 metabolic risk components RR, 1.21 [95% CI, 1.07, 1.37]).<sup>18</sup>
- In a meta-analysis of 14 studies, adults with the most favorable combined lifestyle factors had a lower diabetes risk than those with the least favorable combined lifestyle factors (HR, 0.25 [95% CI, 0.18–0.35]).<sup>19</sup>
- In analyses adjusted for PA, total sedentary behavior (RR, 1.01 [95% CI, 1.00–1.01]) and television viewing (RR, 1.09 [95% CI, 1.07–1.12]) were associated with diabetes risk in a systematic review and meta-analysis.<sup>20</sup>
- In a meta-analysis of prospective cohort studies, SSB intake was associated with an increased risk of diabetes (RR per 250 mL/d, 1.19 [95% CI, 1.13–1.25]). ASB intake was also associated with diabetes risk (RR per 250 mL/d, 1.15 [95% CI, 1.05–1.26]).<sup>21</sup>
- In NHANES 2007 to 2014, the prevalence of gestational diabetes was 7.6%, with 19.7% of females 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%).<sup>22</sup>
- In the NHS II, the risk of diabetes was also 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.<sup>23</sup>

## Social Determinants

- 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  $\geq 65$  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.<sup>24</sup>
- In NHANES 2011 to 2016, 83.4% of adults with diabetes had an HbA1c test in the past year. Testing rates were higher for individuals with health insurance (86.6%) than for those without health insurance (55.9%).<sup>25</sup>
- According to data from BRFSS 2013, individuals with private health insurance were more likely than those without health insurance to have had HbA1c 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.<sup>26</sup>
- 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 HbA1c  $>9.0\%$  (OR, 2.37 [95% CI, 1.10–5.09]).<sup>27</sup>

## Risk Prediction

- Several risk prediction algorithms for type 2 diabetes have been developed.<sup>28–30</sup> The updated version of the QDiabetes risk prediction algorithm had C statistics between 0.81 and 0.89.<sup>31</sup>
- Risk prediction algorithms for CVD among individuals with diabetes have also been developed.<sup>32,33 34</sup> 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.<sup>33</sup>
- 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.<sup>35</sup>
- A diabetic kidney disease risk prediction model including age, BMI, smoking, diabetic retinopathy, HbA1c, SBP, HDL-C, triglycerides, and ACR performed well in a validation cohort (C statistic, 0.77 [95% CI, 0.71–0.82]).<sup>36</sup>

## 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.<sup>37,38</sup> In the FHS, having a parent or sibling with diabetes conferred a

3.4-fold increased risk of diabetes, which increased to 6.1 if both parents were affected.<sup>39</sup> On the basis of data from NHANES 2009 to 2014, individuals with diabetes had an adjusted PR for family history of diabetes of 4.27 (95% CI, 3.57–5.12) compared with individuals without diabetes or prediabetes.<sup>40</sup>

- There are monogenic forms of diabetes such as maturity-onset diabetes of the young (caused by variants in *GCK* [glucokinase] and other genes) 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.<sup>41</sup> Genetic testing can be considered if maturity-onset diabetes is suspected and can guide the 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 >500 genetic variants associated with diabetes,<sup>42</sup> with ORs in a GWAS of 74 124 cases with type 2 diabetes and 824 006 controls ranging from 1.04 to 8.05,<sup>43</sup> the most consistent being a common intronic variant in the *TCF7L2* (transcription factor 7 like 2) gene.<sup>44–47</sup> These common variants in aggregate account for 18% of type 2 diabetes risk.<sup>43</sup> Several of these variants have also been associated with gestational diabetes.<sup>48</sup>
- Other risk loci for diabetes identified from GWASs include variants in the *SLC30A8* and *HHEX* genes (related to  $\beta$ -cell development or function) and in the *NAT2* (N-acetyltransferase 2) gene, associated with insulin sensitivity.<sup>46,49</sup>
- Sequencing studies to identify rare variants for type 2 diabetes have identified a small number of additional genes. In a study of 20 791 cases and 24 440 controls, 4 novel variants were identified, with the *SLC30A8* signal consisting of 90 missense variants associated with lower type 2 diabetes risk.<sup>50</sup>
- 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),<sup>46,51</sup> a variant in the *DNER* gene associated with diabetes in Native Americans,<sup>52</sup> a variant in the *G6PD* gene,<sup>53</sup> and a rare variant in the *HBB* gene<sup>54</sup> 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.<sup>55</sup> A meta-analysis of East Asian >77 000 individuals with type 2 diabetes identified 61 novel loci for diabetes.<sup>56</sup>
- A diabetes GRS composed of >6 million diabetes-associated variants was associated with incident

diabetes in >130 000 individuals in the FinnRisk study (HR, 1.74 [95% CI, 1.72–1.77];  $P < 1 \times 10^{-300}$ ), with the GRS showing improved reclassification over a clinical model (net reclassification index, 4.5% [95% CI, 3.0%–6.1%]).<sup>57</sup>

- 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.<sup>58</sup>
- 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, GRSs associated with body fat distribution were associated with a higher risk of diabetes.<sup>59</sup> 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 GRS has been developed that includes these genetic markers and was found to be associated with the effect of intensive glycemic treatment of cardiovascular outcomes.<sup>60</sup>
- Although most variants identified from GWASs are common, genes that harbor rare variants associated with diabetes have also been identified.<sup>50</sup> These include rare loss-of-function variants in the *SLC30A8* gene that protect against diabetes risk,<sup>50</sup> with carriers having a 65% lower risk,<sup>61</sup> 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<sup>62</sup> and variants in the *ANGPTL4* gene associated with reduced diabetes risk.<sup>63</sup>
- 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  $\approx 50\%$  of the genetic risk.<sup>64</sup> Other studies have identified additional genes associated with type 1 diabetes risk, including rare variants.<sup>65</sup>
- 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).<sup>66</sup> In a study of 7798 high-risk children, a risk score combining type 1 diabetes genetic variants, autoantibodies and clinical factors improved prediction of incident type 1 diabetes (AUC  $\geq 0.9$ ).<sup>67</sup>
- 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<sup>68</sup>; and a GWAS in latent autoimmune diabetes in adults found overlap of many genetic signals with type 1 and type 2 diabetes.<sup>69</sup>

- The risk of complications from diabetes is also heritable:
  - 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.<sup>70</sup>
  - Genetic variants have also been identified that increase the risk of CAD or dyslipidemia in patients with diabetes<sup>71,72</sup> and that are associated with end-organ complications in diabetes (retinopathy,<sup>73</sup> nephropathy,<sup>74</sup> and neuropathy<sup>75</sup>).
  - A GRS of type 2 diabetes variants was associated with diabetes-related retinopathy (OR of highest GRS decile compared with lowest GRS decile, 1.59 [95% CI, 1.44–1.77]), CKD (OR, 1.16 [95% CI, 1.07–1.26]), PAD (OR, 1.20 [95% CI, 1.11–1.29]), and neuropathy (OR, 1.21 [95% CI, 1.12–1.30]).<sup>42</sup>
- Epigenetic changes in DNA are associated with diabetes, although these changes are tissue specific and vary over time. In a study of whole-genome bisulfite sequencing in islets from 6 patients with type 2 diabetes compared with 8 patients without diabetes, >25 000 differentially methylated regions were identified covering genetic loci with known islet function (eg, *PDX1*, *TCF7L2*).<sup>76</sup>
- In a mendelian randomization analysis, prediabetes (determined by SNPs for glycemic traits) was not associated with diabetes (OR, 0.91 [95% CI, 0.73–1.14]).<sup>77</sup>

### Role of Nongenetic Factors

- Metabolomic profiling has identified several strong type 2 diabetes markers that appear to have causal effects on diabetes:
  - Branched chain amino acids are associated with insulin resistance,<sup>78</sup> incident type 2 diabetes risk (OR, 7.60 [95% CI, 2.14–27.07] for top versus bottom branched chain amino acid quartiles),<sup>79</sup> and response to weight loss interventions.<sup>80</sup> Circulating glycine levels are associated with lower diabetes risk (meta-analysis RR, 0.89 [95% CI, 0.81–0.96]).<sup>81</sup> Other metabolites associated with type 2 diabetes include complex lipid species such as triacylglycerols<sup>82</sup> and alpha amino-adipic acid.<sup>83</sup>
- The potential role of the microbiome in diabetes is becoming increasingly recognized. Bacterial metabolic pathways, including lactobacilli species<sup>84</sup> and *Clostridium* species<sup>85</sup> (which produce short-chain fatty acids), have been shown to be enriched in the microbiome of patients with diabetes. Microbial taxa

may also mediate the effects of metformin therapy in patients with diabetes.<sup>86</sup>

### Prevention

- Among adults without diabetes in NHANES 2007 to 2012, 37.8% met the moderate-intensity PA goal of  $\geq 150$  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.<sup>87</sup>
- 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.<sup>88</sup>
- In the DPP 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 those receiving 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.<sup>89</sup>
- Acarbose was associated with a lower diabetes risk (RR, 0.82 [95% CI, 0.71–0.94]) compared with placebo among adults with impaired glucose tolerance and CHD over a median 5 years of follow-up.<sup>90</sup>

### Awareness, Treatment, and Control

#### (See Chart 9-6)

#### Awareness

- 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.<sup>1</sup>

#### Treatment

- According to NHANES 2015 to 2018 data for adults with diabetes, 21.1% had their diabetes treated and controlled with a fasting glucose  $< 126$  mg/dL (unpublished NHLBI tabulation; Chart 9-6).
- Among those with diagnosed diabetes, the age-adjusted percentage of those with HbA1c of 6.0% to 6.9% increased from 26.9% in 2004 to 30.9% in 2016.<sup>91</sup>
- In NHANES 2003 through 2016, among adults with diagnosed and undiagnosed diabetes, the proportion taking any medication increased from 58% in 2003 through 2004 to 67% in 2015 through 2016, with an increase in the use of metformin and insulin analogs and a decrease in the use of sulfonylureas, thiazolidinediones, and human insulin.<sup>92</sup>

- Among 1.66 million privately insured and 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%.<sup>93</sup>
- In NHANES, the percentage of adults 40 to 75 years of age with diabetes who were taking a statin was 48.5% in 2011 through 2014 and 53% in 2015 through 2018 ( $P=0.133$ ).<sup>94</sup>
- 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.<sup>95</sup>

### Control

- 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 HbA1c, 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.<sup>96</sup>
- Among adults with diagnosed diabetes in NHANES 2013 to 2016, 9.9% had an HbA1c  $\geq 10.0\%$ , and this was more prevalent among adults 18 to 44 years of age (16.3% [95% CI, 10.8%–23.9%]) than adults  $\geq 65$  years of age (4.3% [95% CI, 2.9%–6.5%]).<sup>1</sup>
- According to data from NHANES 1988 through 2018, among adults with newly diagnosed type 2 diabetes, there was a significant increase in the proportion of individuals with HbA1c  $< 7\%$  (59.8% for 1998–1994 and 73.7% for 2009–2018) and decreases in mean HbA1c (7.0% and 6.7%), mean BP (130.1/77.5 and 126.0/72.1 mm Hg), and mean TC (219.4 and 182.4 mg/dL). The proportion with HbA1c  $< 7.0\%$ , BP  $< 140/90$  mm Hg, and TC  $< 240$  mg/dL improved from 31.6% to 56.2%.<sup>97</sup>
- Among HCHS/SOL study participants with diabetes, 43.0% had HbA1c  $< 7.0\%$ , 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.<sup>98</sup>
- In a national cohort of 1 140 634 veterans with diabetes, in adjusted models, odds of HbA1c  $\geq 8.0\%$  compared with HbA1c  $< 7\%$  was higher among NH Black people (OR, 1.11 [95% CI, 1.09–1.14]) and Hispanic people (OR, 1.36 [95% CI, 1.32–1.41]) compared with NH White people.<sup>99</sup>

- In MEPS, 70% (95% CI, 68%–71%), 67% (95% CI, 66%–69%), and 68% (95% CI, 66%–70%) of US adults with diabetes received appropriate diabetes care (HbA1c measurement, foot examination, and an eye examination) in 2002, 2007, and 2013, respectively.<sup>100</sup>
- Among those with type 1 diabetes in the SEARCH study, 60% reported having  $\geq 3$  HbA1c measurements in the past year. Other screening tests reported were as follows: 93% for BP, 81% for eye examination, 71% for lipid levels, 64% for foot examination, and 63% for albuminuria screening.<sup>101</sup>

### Mortality

#### (See Table 9-1)

- Diabetes was listed as the underlying cause of mortality for 87 647 people (49 512 males and 38 135 females) in the United States in 2019 (Table 9-1).<sup>102</sup>
- The 2019 overall age-adjusted death rate attributable to diabetes was 21.6 per 100 000. For males, the age-adjusted death rates per 100 000 population were 24.8 for NH White people, 46.4 for NH Black people, 31.2 for Hispanic people, 19.8 for NH Asian/Pacific Islander people, and 48.2 for NH American Indian/Alaska Native people. For females, the age-adjusted death rates per 100 000 population were 14.2 for NH White people, 32.1 for NH Black people, 21.0 for Hispanic people, 14.0 for NH Asian/Pacific Islander people, and 35.7 for NH American Indian/Alaska Native people (unpublished NHLBI tabulation using CDC WONDER<sup>103</sup>). In 2019, diabetes was the seventh leading cause of death in the United States.<sup>104</sup>
- 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 and ethnic group.<sup>105</sup>
- 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]).<sup>106</sup> 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]).<sup>107</sup>
- 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]).<sup>108</sup>

- In the Swedish National Diabetes Register, compared with individuals without diabetes, the aHR 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).<sup>109</sup> Individuals with type 2 diabetes who met all risk factor targets (HbA1c, LDL-C, BP, urine ACR, and nonsmoker) had similar risks of death, MI, and stroke compared with those without diabetes.<sup>110</sup>
- In the Swedish National Diabetes Register, 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 and those without diabetes observed among those with BMI  $\geq 40$  kg/m<sup>2</sup> (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).<sup>111</sup>
- In the NHIS from 1985 to 2014, there was a decrease in major CVD deaths, with 25% greater 10-year percentage reduction among adults with diabetes than among adults without diabetes.<sup>112</sup>
- In the NHIS from 1985 to 1994 and 2010 to 2015, among adults with diabetes, there was a decline in all-cause mortality from 23.1 (95% CI, 20.1–26.0) to 15.2 (95% CI, 14.6–15.8) per 1000 person-years. This represents a 20% decline every 10 years. Over this same time period, death attributable to vascular causes decreased from 11.0 (95% CI, 9.2–12.2) to 5.2 (95% CI, 4.8–5.6) per 1000 person-years, a 32% decline every 10 years.<sup>113</sup>
- 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.<sup>114</sup>
- In NIS 2017, the mortality rate for diabetic ketoacidosis was higher among males (40.5 per 10000 admissions) compared with females (35.3 per 10000 admissions, respectively) and NH Black people (39.1 per 10000 admissions) compared with

NH White people (36.2 per 10000 admissions) and Hispanic people (36.3 per 10000 admissions).<sup>115</sup>

## Complications

### (See Chart 9-7)

#### Microvascular Complications

##### Peripheral Artery Disease

- In a cohort study of patients in Denmark undergoing coronary angiography, those with diabetes but not CAD had an increased risk of PAD (HR, 1.73 [95% CI, 1.51–1.97]) and lower limb revascularization (HR, 1.73 [95% CI, 1.51–1.97]) compared with those with neither diabetes nor CAD.<sup>116</sup> Patients with both diabetes and CAD also had an increased risk of PAD (HR, 3.90 [95% CI, 3.55–4.28]) and lower limb revascularization (HR, 4.61 [95% CI, 3.85–5.52]).<sup>116</sup>
- In the Freemantle Diabetes Study of adults with type 2 diabetes, the rate of incident hospitalization for diabetic foot ulcers increased between the 2 study phases (1993–1996 and 2008–2011) from 1.9 (95% CI, 0.9–3.3) per 1000 person-years to 4.5 (95% CI, 3.0–6.4) per 1000 person-years.<sup>117</sup>
- On the basis of analyses of data from the NIS and NHIS between 2000 and 2016 (Chart 9-7), declines in hospitalization for lower extremity amputations were observed between 2000 and 2010, with subsequent increases from 2010 to 2016.<sup>91</sup>
- 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.<sup>118</sup>
- According to data from Medicare fee-for-service claims from 2000 to 2017, among beneficiaries with diabetes, the rate of nontraumatic lower-extremity amputation decreased from 8.5 in 2000 to 4.4 in 2009 but then increased to 4.8 in 2017.<sup>119</sup>
- From data from NIS and NHIS 2000 through 2015, the age-adjusted rate of nontraumatic lower-extremity amputation among individuals with diabetes decreased from 5.38 (95% CI, 4.93–5.84) per 1000 adults with diabetes in 2000 to 3.07 (95% CI, 2.79–3.34) per 1000 adults in 2009 and then increased to 4.62 (95% CI, 4.25–5.00) per 1000 adults in 2015. The increase was greatest among individuals 18 to 44 and 45 to 64 years of age.<sup>120</sup>

##### Retinopathy

- Among those  $\leq 21$  years of age with newly diagnosed diabetes in a US managed care network, 20.1% 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.<sup>121</sup>
- 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.<sup>122</sup>
  - 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%).<sup>1</sup>
  - 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.<sup>123</sup>
  - According to NHIS 2016 and 2017, among individuals with young-onset diabetes (diagnosed before 40 years of age), individuals with type 1 diabetes had a higher prevalence of retinopathy (24.7% [95% CI, 17.1%–32.2%]) compared with those with type 2 diabetes (11.4% [95% CI, 8.9%–13.9%]) but similar rates of kidney disease, CHD, MI, and stroke.<sup>124</sup>

### Chronic Kidney Disease

- 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.<sup>125</sup> 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.<sup>125</sup>
- 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%).<sup>126</sup>
- 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%).<sup>127</sup>

- According to data from NHANES 1988 through 2018, among adults with newly diagnosed diabetes, there was a significant decrease in the prevalence of any CKD (40.4% for 1988–1994 and 25.5% for 2009–2018). This was driven by a decrease in albuminuria (38.9% to 18.7%). There was no significant change in the prevalence of reduced eGFR (7.5% to 9.9%).<sup>97</sup>
- According to data from 142 countries representing 97.3% of the world population, the global annual incidence of ESRD increased from 375.8 to 1016.0 per million with diabetes from 2000 to 2015. The percentage of individuals with ESRD with diabetes increased from 19.0% to 29.7% over this same period.<sup>128</sup>

### Neuropathy

- In the T1D Exchange Clinic Registry, from 2016 to 2018, the prevalence of self-reported diabetic peripheral neuropathy was 11%.<sup>129</sup>

### CVD Complications

#### (Chart 9-7)

- According to data from NHANES 1988 through 2018, among adults with newly diagnosed diabetes, there was no significant change in self-reported CVD (19.0% for 1988–1994 and 16.5% for 2009–2018).<sup>97</sup>
- 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]).<sup>130</sup>
- 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.<sup>131</sup>
- In the UK Biobank, the association between previously diagnosed diabetes and MI was stronger in females (HR, 2.33 [95% CI, 1.96–2.78]) than in males (HR, 1.81 [95% CI, 1.63–2.02]).<sup>132</sup>
- On the basis of analyses of data from the NIS and NHIS between 2000 and 2016 (Chart 9-7), substantial declines were observed in the age-standardized rates of hospitalizations for IHD and HF among those with diagnosed diabetes. Declines in hospitalization for stroke were observed between 2000 and 2010, with subsequent increases from 2010 to 2016.<sup>91</sup>



- In the REGARDS study, 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.<sup>133</sup> 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.<sup>134</sup>
  - 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.
- In the Freemantle Diabetes Study of adults with type 2 diabetes, the rate of first hospitalizations for MI, stroke, and HF improved between the 2 study phases (1993–1996 and 2008–2011), with IRRs of 0.61 (95% CI, 0.47–0.78), 0.55 (95% CI, 0.35–0.85), and 0.62 (95% CI, 0.50–0.77), respectively.<sup>135</sup>
- In MESA, 63% of participants with diabetes had a CAC score >0 compared with 48% of those without diabetes.<sup>136</sup> 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.<sup>137</sup>
- 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).<sup>138</sup>

### Hypoglycemia

- 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]).<sup>139</sup>
- In the LEADER trial, patients with type 2 diabetes who experienced a severe hypoglycemic event had an increased risk of MACEs, defined as cardiovascular death, nonfatal MI, or nonfatal stroke (HR, 2.2 [95% CI, 1.6–3.0]), and CVD death (HR, 3.7 [95% CI, 2.6–5.4]).<sup>140</sup> Similarly, in the EXAMINE trial, severe hypoglycemia was associated with an increased risk of MACEs (HR, 2.42 [95% CI, 1.27–4.60]).<sup>141</sup>

- In ARIC, in data from 1996 through 2013, 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]).<sup>142</sup> In a similar ARIC analysis using individuals with diabetes who attended the 2011 to 2013 visit and had follow-up data through 2018, severe hypoglycemia was associated with incident or recurrent CVD (IRR, 2.19 [95% CI, 1.24–3.88]).<sup>143</sup>
- In a cohort of adults with diabetes receiving care at a large integrated health care system, severe hypoglycemia was associated with ASCVD events, with an unadjusted HR of 3.2 (95% CI, 2.9–3.6) and aHR of 1.3 (95% CI, 1.2–1.5).<sup>144</sup>
- 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.<sup>145</sup>

### COVID-19

- Individuals with diabetes are at increased risk of severe disease, hospitalization, and death resulting from COVID-19.
  - Studies from Northern California and New York reported a prevalence of diabetes among individuals hospitalized with COVID-19 of 31% to 36%.<sup>146–149</sup>
  - In a study of individuals with COVID-19 in 2 hospitals in Wuhan, China, comparing 153 individuals with diabetes and sex- and age-matched control subjects, those with diabetes had a higher proportion of ICU admission (17.6% versus 7.8%) and more fatal cases (20.3% versus 10.5%).<sup>150</sup>
  - According to data from the Vanderbilt University Medical Center data warehouse of 6451 individuals with COVID-19, compared with individuals without diabetes, individuals with diabetes had a higher rate of hospitalization (OR, 3.90 [95% CI, 1.75–8.69] for type 1 diabetes and 3.36 [95% CI, 2.49–4.55] for type 2 diabetes) and greater illness severity (OR, 3.35 [95% CI, 1.53–7.33] for type 1 diabetes and 3.42 [95% CI, 2.55–4.58] for type 2 diabetes).<sup>151</sup>
  - Among 450 patients with COVID-19 at Massachusetts General Hospital, 178 (39.6%) had diabetes. In adjusted models, diabetes was associated with greater odds of ICU admission (OR, 1.59 [95% CI, 1.01–2.52]), mechanical ventilation (OR, 1.97 [95% CI, 1.21–3.20]), and death (OR, 2.02 [95% CI, 1.01–4.03]) within 14 days of presentation to care.<sup>152</sup>

- Among 7337 individuals with COVID-19 hospitalized in Hubei Province, China, 952 had type 2 diabetes. Individuals with diabetes required more medical interventions and had greater mortality (7.8% versus 2.7%). Well-controlled blood glucose during the hospitalization was associated with lower mortality.<sup>153</sup>
- Among 453 individuals admitted with COVID-19 to a hospital in Wuhan, China, mortality was higher among individuals with hyperglycemia (HR, 3.29 [95% CI, 0.65–16.6]), newly diagnosed diabetes (HR, 9.42 [95% CI, 2.18–40.7]), and known diabetes (HR, 4.63 [95% CI, 1.02–21.0]).<sup>154</sup>
- In a report from the Chinese Center for Disease Control and Prevention, among 44 672 confirmed cases of COVID-19 in China, the overall case fatality rate was 2.3%, whereas the case fatality rate among individuals with diabetes was 7.3%.<sup>155</sup>
- In a nationwide retrospective study in England, the adjusted ORs for in-hospital COVID-19–related death were 2.86 (95% CI, 2.58–3.18) for individuals with type 1 diabetes and 1.80 (95% CI, 1.76–1.86) for individuals with type 2 diabetes.<sup>156</sup> Among individuals hospitalized with COVID-19, patients with type 2 diabetes were at increased risk of death (HR, 1.23 [95% CI, 1.14–1.32]).<sup>157</sup>

## Health Care Use (See Table 9-1)

- 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).<sup>1</sup>
- According to NEDS and NIS 2014, there were 185 255 ED visits or inpatient admissions among adults for diabetic ketoacidosis and 27 532 for hyperglycemic hyperosmolar state. The majority of encounters for diabetic ketoacidosis were for individuals with type 1 diabetes (70.6%), and the majority of encounters for hyperglycemic hyperosmolar state were for individuals with type 2 diabetes (88.1%). Rates of diabetic ketoacidosis and hyperglycemic hyperosmolar state increased from 2009 to 2015 in all age groups and among both males and females.<sup>158</sup>
- In 2018, there were 678 000 principal diagnosis discharges for diabetes (HCUP,<sup>159</sup> unpublished NHLBI tabulation; Table 9-1).
- 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).<sup>1</sup>

- 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.<sup>160</sup> According to data from the Optum Labs Data Warehouse, adults with diabetes hospitalized between 2009 and 2014 had a 10.8% 30-day readmission rate.<sup>161</sup> Thirty-day readmission rates were 10.2% among White people, 12.2% among NH Black people, 10.9% among Hispanic people, and 9.9% among Asian people.<sup>162</sup>

## Cost

- According to data from MEPS, spending in the United States on glucose-lowering medications increased by \$40.6 billion between 2005 through 2007 and 2015 through 2017, an increase of 240%.<sup>163</sup> From 2007 to 2018, list prices of branded insulins increased by 262% and for branded noninsulin antidiabetic agents by 165%.<sup>164</sup> In the Optum Labs Data Warehouse data from 2016 to 2019, there were higher rates of initiation of newer diabetes agents among individuals with commercial health plans compared with Medicare Advantage plans.<sup>165</sup>
- In 2016, of 154 health conditions evaluated, diabetes had the third highest health care spending (\$111.2 billion), the highest public insurance spending (\$55.4 billion), the fifth highest private insurance spending (\$49.1 billion), and the eighth highest out-of-pocket payments (\$6.7 billion).<sup>166</sup>
- In 2017, the cost of diabetes was estimated at \$327 billion, up 26% from 2012, accounting for 1 in 4 health care dollars.<sup>167</sup> Of these costs, \$237 billion was 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 per capita medical expenditure of \$16 752 per year for people with diabetes, of which \$9601 was attributed to diabetes.<sup>167</sup>
- Informal care is estimated to cost \$1 192 to \$1 321 annually per person with diabetes.<sup>168</sup>
- 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.<sup>169</sup>
- 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.<sup>170</sup> The diabetes-related preventable hospitalization rate has decreased slightly<sup>170</sup> or stayed stable.<sup>171</sup>

- A systematic review estimated that CVD costs account for 20% to 49% of the total direct costs of diabetes care.<sup>172</sup>

## Global Burden of Diabetes

### (See Table 9-2 and Charts 9-8 through 9-10)

- The GBD 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020. The number of prevalent cases of diabetes increased by 230.14% (95% UI, 224.38%–236.15%) for males and 217.98% (95% UI, 213.12%–223.12%) for females between 1990 and 2020. Overall, 243.30 (95% UI, 224.54–262.00) million males and 229.01 (95% UI, 211.71–246.67) million females worldwide had diabetes. In 2020, there were 1.64 (95% UI, 1.50–1.75) million deaths attributable to diabetes (Table 9-2).
  - The age-standardized prevalence of diabetes was estimated to be highest in Oceania, high-income North America, North Africa and the Middle East, the Caribbean, and Central Latin America (Chart 9-8).
- Age-standardized mortality rates attributable to high FPG were highest in Oceania and sub-Saharan Africa, Central Latin America, and locations in South and Southeast Asia (Chart 9-9).
- Age-standardized mortality estimated for diabetes was highest in Oceania, southern sub-Saharan Africa, central sub-Saharan Africa, and Central Latin America (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.<sup>174</sup> Approximately 4.2 million deaths (11.1% of deaths) worldwide among individuals 20 to 79 years of age are attributable to diabetes according to 2019 estimates.<sup>175</sup> 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.<sup>176</sup>

**Table 9-1. Diabetes in the United States**

Population group	Prevalence of diagnosed diabetes, 2015–2018: age ≥20 y	Prevalence of undiagnosed diabetes, 2015–2018: age ≥20 y	Prevalence of prediabetes, 2015–2018: age ≥20 y	Incidence of diagnosed diabetes, 2018: age ≥18 y	Mortality, 2019: all ages*	Hospital discharges, 2018: all ages	Cost, 2017
Both sexes	28 200 000 (10.4%)	9 800 000 (3.8%)	113 600 000 (45.8%)	1 500 000	87 647	678 000	\$327 billion
Males	15 500 000 (12.1%)	5 500 000 (4.5%)	63 100 000 (52.9%)	...	49 512 (56.5%)†	...	...
Females	12 700 000 (9.0%)	4 300 000 (3.2%)	50 500 000 (38.9%)	...	38 135 (43.5%)†	...	...
NH White males	10.8%	4.1%	56.5%	...	33 492	...	...
NH White females	7.5%	2.9%	37.3%	...	23 833	...	...
NH Black males	12.8%	4.7%	35.5%	...	7901	...	...
NH Black females	13.2%	3.3%	30.3%	...	7567	...	...
Hispanic males	15.3%	6.0%	49.8%	...	5617	...	...
Hispanic females	13.1%	4.6%	41.2%	...	4549	...	...
NH Asian males	14.3%	5.5%	52.5%	...	1763	...	...
NH Asian females	10.1%	3.1%	42.3%	...	1612	...	...
NH American Indian or Alaska Native	...	...	...	...	1077	...	...

Undiagnosed diabetes is defined as those whose fasting glucose is  $\geq 126$  mg/dL but who did not report being told by a health care professional 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.

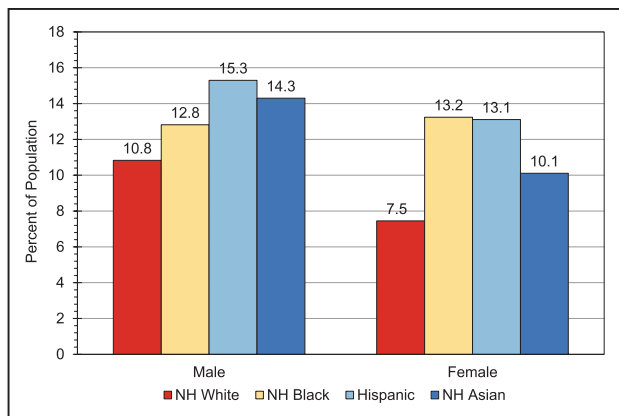
Sources: Prevalence: Prevalence of diagnosed and undiagnosed diabetes: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey.<sup>9</sup> Percentages for sex and racial and ethnic groups are age adjusted for Americans  $\geq 20$  years of age. Incidence: Centers for Disease Control and Prevention, National Diabetes Statistics Report, 2020.<sup>1</sup> Mortality: Unpublished NHLBI tabulation using National Vital Statistics System.<sup>102</sup> 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.<sup>159</sup> Cost: American Diabetes Association.<sup>167</sup>

**Table 9-2. Global Prevalence and Mortality of Diabetes, 2020**

	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), 2020	1.64 (1.50 to 1.75)	472.32 (436.74 to 508.85)	0.80 (0.73 to 0.87)	243.30 (224.54 to 262.00)	0.83 (0.75 to 0.90)	229.01 (211.71 to 246.67)
Percent change in total number, 1990–2020	150.70 (130.68 to 170.77)	224.13 (218.97 to 229.14)	173.44 (142.96 to 199.54)	230.14 (224.38 to 236.15)	132.08 (107.05 to 156.56)	217.98 (213.12 to 223.12)
Percent change in total number, 2010–2020	41.78 (34.51 to 49.34)	50.57 (48.22 to 52.84)	43.30 (33.15 to 53.44)	50.87 (48.53 to 53.26)	40.35 (30.82 to 49.76)	50.26 (47.72 to 52.76)
Rate per 100 000, age standardized, 2020	20.07 (18.48 to 21.44)	5608.54 (5190.63 to 6043.72)	21.87 (20.01 to 23.61)	6000.46 (5544.21 to 6461.51)	18.60 (16.81 to 20.21)	5244.91 (4854.99 to 5648.90)
Percent change in rate, age standardized, 1990–2020	13.03 (4.41 to 22.27)	63.79 (61.18 to 66.46)	20.42 (7.47 to 31.34)	65.77 (62.92 to 68.76)	6.18 (–5.07 to 17.12)	61.40 (58.84 to 64.06)
Percent change in rate, age standardized, 2010–2020	5.80 (0.38 to 11.33)	19.23 (17.39 to 20.97)	6.20 (–1.13 to 13.83)	19.52 (17.66 to 21.33)	5.05 (–2.19 to 12.23)	18.82 (16.82 to 20.68)

UI indicates uncertainty interval.

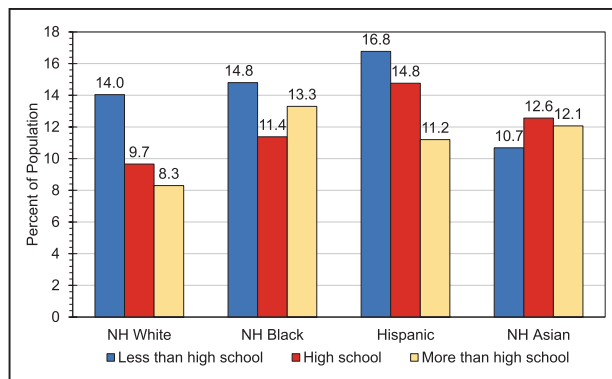
Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington.



**Chart 9-1. Age-adjusted prevalence of diagnosed diabetes in US adults ≥20 years of age, by race and ethnicity and sex (NHANES, 2015–2018).**

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

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>9</sup>

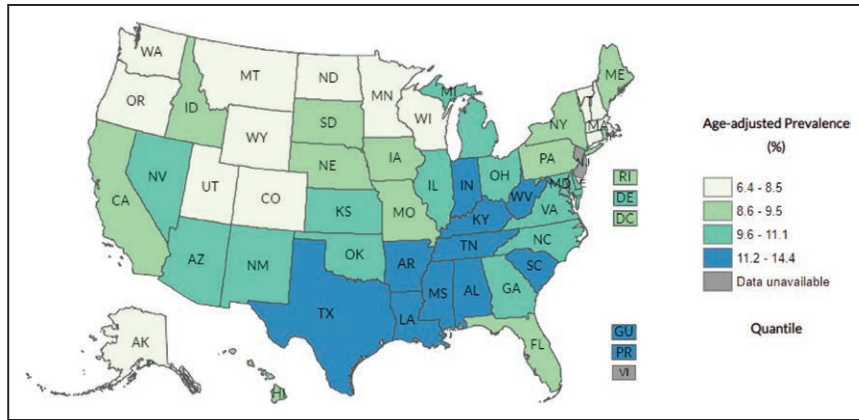


**Chart 9-2. Age-adjusted prevalence of diagnosed diabetes in US adults ≥20 years of age, by race and ethnicity and years of education (NHANES, 2015–2018).**

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

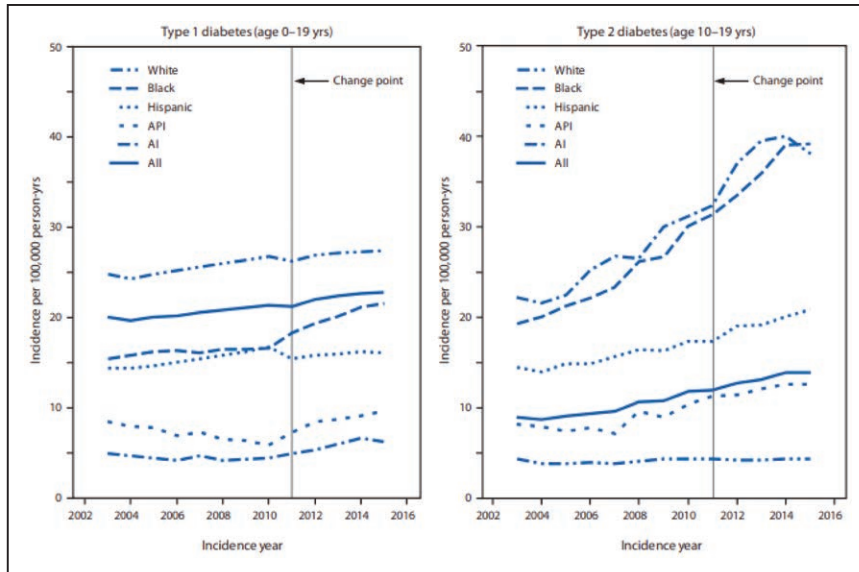
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>9</sup>





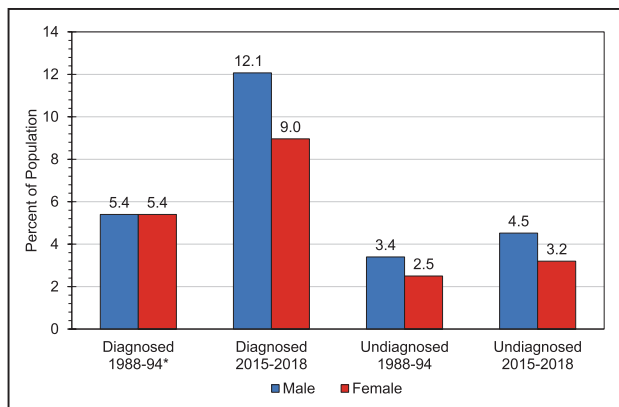
**Chart 9-3. Age-adjusted percentage of adults with diagnosed diabetes, US states and territories, 2019.**

Reprinted image has been altered to remove background colors and page headers and footers. Source: Reprinted from Behavioral Risk Factor Surveillance System prevalence and trends data.<sup>12</sup>



**Chart 9-4. Incidence of type 1 and type 2 diabetes, overall and by race and ethnicity, among US youths ≤19 years of age (SEARCH study, 2002–2015).**

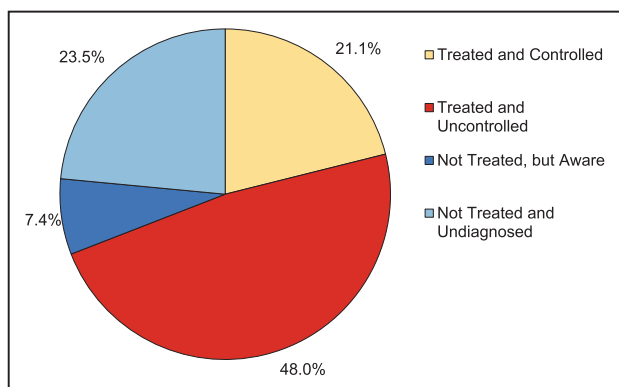
AI indicates American Indian; API, Asian/Pacific Islander; and SEARCH, Search for Diabetes in Youth. Models included a change point at the year 2011 to compare trends in incidence rates between 2002 to 2010 and 2011 to 2015. People who were AI were from primarily 1 southwestern tribe. SEARCH includes data on youths (<20 years of age) in Colorado (all 64 counties plus selected Indian reservations in Arizona and New Mexico under the direction of Colorado), Ohio (8 counties), South Carolina (all 46 counties), and Washington (5 counties) and in California for Kaiser Permanente Southern California health plan enrollees in 7 counties. Source: Reprinted from Divers et al.<sup>13</sup>



**Chart 9-5. Prevalence of diagnosed and undiagnosed diabetes in US adults ≥20 years of age by sex (NHANES, 1988–1994 and 2015–2018).**

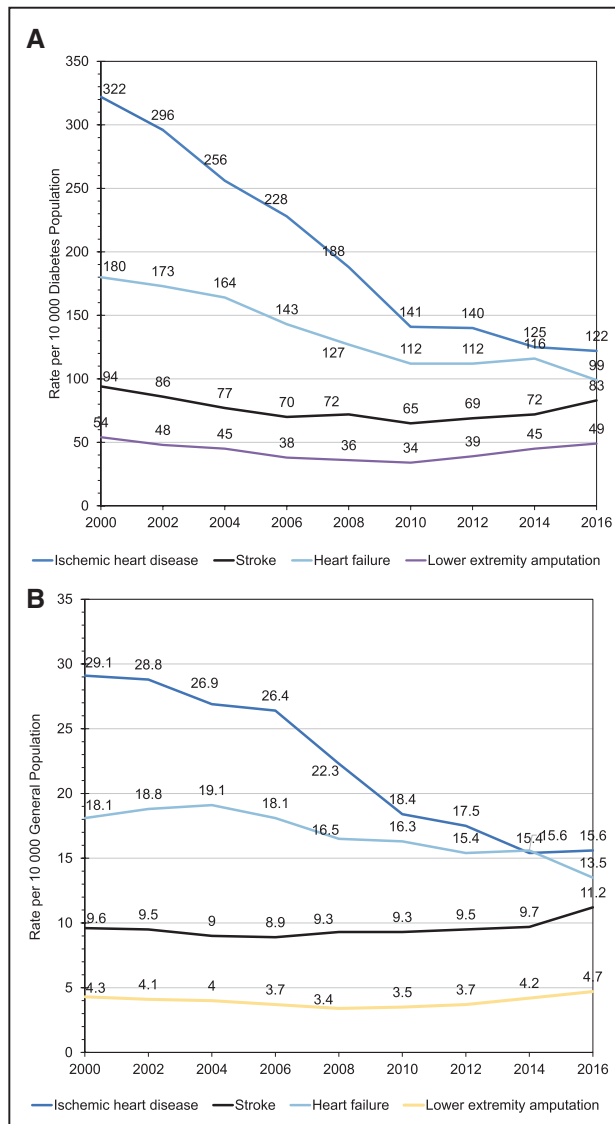
The definition of diabetes changed in 1997 (from glucose ≥140 to ≥126 mg/dL).

NHANES indicates National Health and Nutrition Examination Survey. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>9</sup>



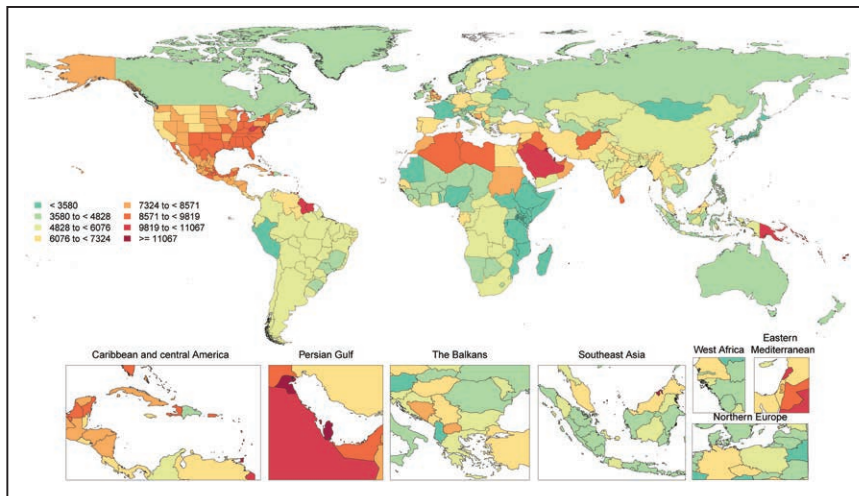
**Chart 9-6. Awareness, treatment, and control of diabetes in US adults ≥20 years of age (NHANES, 2015–2018).**

Controlled is defined as currently treated (taking insulin or diabetic pills to lower blood sugar) and fasting glucose <126 mg/dL. Uncontrolled is defined as currently treated (taking insulin or diabetic pills to lower blood sugar) and fasting glucose ≥126 mg/dL. NHANES indicates National Health and Nutrition Examination Survey. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>9</sup>



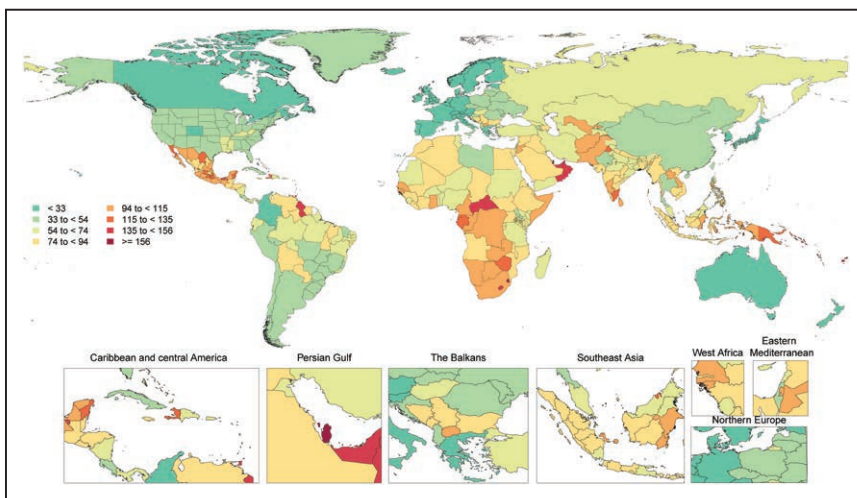
**Chart 9-7. Trends in age-standardized hospitalization rates for diabetes-related complications among US adults ≥18 years of age from 2000 to 2016.**

**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. Source: Centers for Disease Control and Prevention Diabetes Atlas<sup>91</sup> using data from NIS<sup>177</sup> and NHIS.<sup>178</sup>



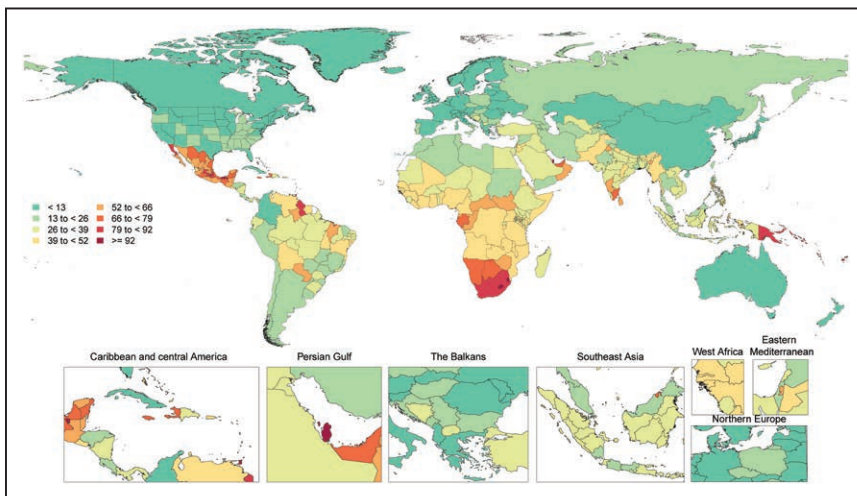
**Chart 9-8. Age-standardized global prevalence rates of diabetes per 100 000, both sexes, 2020.**

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. Additional information is available on the Global Burden of Disease Study website.<sup>179</sup>



**Chart 9-9. Age-standardized global mortality rates attributable to high FPG per 100 000, both sexes, 2020.**

High FPG is defined as serum fasting plasma glucose of >4.8 to 5.4 mmol/L. FPG indicates fasting plasma glucose. Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. Additional information is available on the Global Burden of Disease Study website.<sup>179</sup>



**Chart 9-10. Age-standardized global mortality rates of diabetes per 100 000, both sexes, 2020.**

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## 10. METABOLIC SYNDROME

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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 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<sup>1</sup>:
  - FPG  $\geq 100$  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  $\geq 150$  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. Current recommendations for WC cut points also may overestimate MetS in US Hispanic/Latina women.<sup>2</sup>
  - SBP  $\geq 130$  mm Hg or DBP  $\geq 85$  mm Hg or undergoing drug treatment for hypertension or anti-hypertensive 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 pro-inflammatory and prothrombotic state.<sup>3</sup>

- Type 2 diabetes, defined as FPG  $\geq 126$  mg/dL, random or 2-hour postchallenge glucose  $\geq 200$  mg/dL, HbA1c  $\geq 6.5\%$ , 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).<sup>4</sup>
- 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.<sup>5</sup>
- 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<sup>6</sup> and waist-height ratio<sup>7</sup> 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%.<sup>6</sup>

#### 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%).<sup>8</sup> 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  $\geq 60$  years of age.
- In a meta-analysis of 26 609 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.<sup>9</sup>
- 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.<sup>10</sup>
- 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).<sup>11</sup>
- The prevalence of MetS has been noted to be high in individuals with certain conditions, including schizophrenia spectrum disorders<sup>12</sup> and

The 2022 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 2022. 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.

bipolar disorder<sup>13</sup>; prior solid organ transplantations<sup>14</sup>; prior hematopoietic cell transplantation<sup>15,16</sup>; HIV infection<sup>17</sup>; COPD<sup>18</sup>; prior treatment for blood cancers<sup>16,19</sup>; systemic inflammatory disorders such as psoriasis,<sup>20,21</sup> systemic lupus erythematosus,<sup>22</sup> ankylosing spondylitis,<sup>23</sup> and rheumatoid arthritis<sup>24,25</sup>; multiple sclerosis<sup>26</sup>; type 1 diabetes<sup>27,28</sup>; latent autoimmune diabetes in adults<sup>28</sup>; prior gestational diabetes<sup>29</sup>; prior pregnancy-induced hypertension<sup>30</sup>; acne keloidalis nuchae<sup>31</sup>; periodontitis<sup>32,33</sup>; gallstones<sup>34</sup>; cerebral palsy<sup>35</sup>; war-related bilateral lower-limb amputation<sup>36</sup> or spinal cord injury<sup>37</sup> in veterans; and chronic opiate dependence,<sup>38</sup> as well as individuals in select professions, including law enforcement,<sup>39</sup> commercial truck driving,<sup>40</sup> and firefighting.<sup>41</sup>

## 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).<sup>42</sup>

### Adults

#### (See Charts 10-4 through 10-6)

- Secular trends in MetS differ according to the definition used.<sup>8,43,44</sup> Chart 10-4<sup>43</sup> demonstrates trends using the harmonized MetS criteria in NHANES 1988 to 2012; Chart 10-5<sup>8</sup> 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).<sup>45</sup>

## 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.<sup>46</sup> 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.<sup>47</sup>

- In a single-center retrospective case-control study among children and adolescents <18 years of age, bipolar disorder was associated with prevalent MetS compared with healthy controls (OR, 2.33 [95% CI, 1.37–4.0]).<sup>48</sup>

### Respiratory Exposures

- 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.<sup>49</sup>
- Among 9897 children and adolescents 10 to 18 years of age in China, long-term exposure to ambient air pollution (eg, PM<sub>2.5</sub>, fine particulate matter <10- $\mu$ m diameter, and NO<sub>2</sub>) was positively associated with the prevalence of MetS. For every 10- $\mu$ g/m<sup>3</sup> increase in PM<sub>2.5</sub>, fine particulate matter <10- $\mu$ m diameter, and NO<sub>2</sub>, the odds of MetS increased by 31%, (OR, 1.31 [95% CI, 1.05–1.64]), 32% (OR, 1.32 [95% CI, 1.08–1.62]), and 33%, (OR, 1.33 [95% CI, 1.03–1.72]), respectively.<sup>50</sup>

### Diet and PA

- 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.<sup>51</sup>
- Among 6009 children and adolescents 9 to 18 years of age with objectively measured accelerometer data from the International Children's Accelerometry Database, total PA and moderate to vigorous PA were directly associated with prevalent MetS according to the IDF definition.<sup>52</sup> The odds of MetS decreased by 17% (OR, 0.83 [95% CI, 0.76–0.91]) for every 100-count per minute increase in total PA and by 9% (OR, 0.91 [95% CI, 0.84–0.99]) for every 10-minute increase in moderate to vigorous PA independently of sedentary time.

### Serum Biomarkers

- 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]).<sup>53</sup> 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]).<sup>54</sup>

- In ERICA, a cross-sectional multicenter study of Brazilian adolescents 12 to 17 years of age, serum adiponectin levels were inversely associated with MetS z score ( $\beta = -0.40$  [95% CI,  $-0.66$  to  $-0.14$ ];  $P = 0.005$ ).<sup>55</sup> Total serum adiponectin, but not high-molecular-weight adiponectin, levels were inversely associated with MetS according to modified WHO criteria in Mexican children 8 to 11 years of age.<sup>56</sup>

## Adults

### Incident MetS

#### Diet

- Dietary habits are directly associated with incident MetS, including a Western diet,<sup>57</sup> high inflammatory diet pattern,<sup>58–60</sup> and consumption or intake of soft drinks,<sup>61</sup> energy-dense beverages,<sup>62</sup> SSBs,<sup>63</sup> fructose,<sup>64</sup> magnesium<sup>65</sup> carbohydrates,<sup>66</sup> total fat,<sup>67</sup> meats (total, red, and processed but not white meat),<sup>68,69</sup> and fried foods.<sup>70</sup> In addition, restrained and emotional eating behaviors<sup>71</sup> and a problematic relationship with eating and food<sup>72</sup> are risk factors for incident MetS.
- Dietary habits are also inversely associated with incident MetS, including alcohol use,<sup>73</sup> fiber intake,<sup>74</sup> Mediterranean diet,<sup>75–77</sup> fruit consumption ( $\geq 4$  servings/d versus  $< 1$  serving/d),<sup>78</sup> dairy consumption (particularly yogurt and low-fat dairy products),<sup>79,80</sup> consumption of animal or fat protein,<sup>81</sup> coffee consumption,<sup>58,59,82,83</sup> vitamin D intake,<sup>84</sup> intake of tree nuts,<sup>85</sup> walnut intake,<sup>86</sup> and intake of long-chain omega-3 PUFAs.<sup>87</sup>

#### Physical Activity

- In prospective or retrospective cohort studies, low levels of PA<sup>88</sup> and physical fitness<sup>89</sup> 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.<sup>90</sup> For every increase of 10 MET-h/wk (equal to  $\approx 150$  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,<sup>91</sup> aerobic training,<sup>92</sup> and cardiorespiratory fitness (eg, maximal oxygen uptake).<sup>93</sup> Each 1000-steps/d increase is associated with lower odds of having MetS (OR, 0.90 [95% CI, 0.83–0.98]) in American males.<sup>94</sup>

#### Blood Biomarkers

- In Chinese adults, increased high-sensitivity CRP levels were associated with a higher risk of MetS in

females (OR, 4.82 [95% CI, 1.89–12.3] for highest versus lowest quartile) but not in males (OR, 3.15 [95% CI, 0.82–12.1]).<sup>95</sup>

- Blood biomarkers that are inversely associated with incident MetS include insulin sensitivity,<sup>96</sup> total testosterone,<sup>96,97</sup> serum 25-hydroxyvitamin D,<sup>98–102</sup> total and indirect bilirubin,<sup>103</sup> follicle-stimulating hormone in postmenopausal women,<sup>104</sup> and sex hormone-binding globulin.<sup>96,97</sup>

#### Other

- Risk factors for incident MetS include age,<sup>105</sup> smoking,<sup>106,107</sup> childhood MetS,<sup>108</sup> childhood cancer,<sup>109</sup> obesity or high BMI,<sup>110</sup> weight gain,<sup>111</sup> and weight fluctuation.<sup>112</sup>
- There is a bidirectional association between MetS and depression. In prospective studies, depression increased the risk of MetS (OR, 1.49 [95% CI, 1.19–1.87]), and MetS increased the risk of depression (OR, 1.52 [95% CI, 1.20–1.91]).<sup>113</sup>
- There is also a bidirectional association between MetS and osteoarthritis. In a meta-analysis, osteoarthritis increased the odds of incident MetS in females (OR, 2.34 [95% CI, 1.54–3.56]) but not in males (OR, 0.86 [95% CI, 0.61–1.16]), and MetS increased the odds of incident osteoarthritis (pooled OR, 1.45 [95% CI, 1.27–1.66]).<sup>114</sup>
- In a meta-analysis, incident MetS was associated with perinatal factors, including low birth weight (pooled OR, 1.79 [95% CI, 1.39–2.31]) and preterm birth (pooled OR, 1.72 [95% CI, 1.12–2.65]).<sup>115</sup>
- Among perimenopausal women (mean age,  $55 \pm 5.4$  years),  $> 12$  months of breastfeeding significantly reduced the odds of incident MetS in midlife (aOR, 0.76 [95% CI, 0.60–0.95]).<sup>116</sup>
- 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),  $\gamma$ -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.<sup>117</sup>

#### Prevalent MetS

#### Diet

- In cross-sectional studies, prevalent MetS was directly associated with a high-salt diet,<sup>118</sup> white rice consumption,<sup>119</sup> a high DII,<sup>120,121</sup> high dietary acid load,<sup>122</sup> high insulin load or insulin index diet,<sup>123</sup> a long-chain food supply (compared with a short-chain food supply),<sup>124</sup> excessive dietary calcium ( $> 1200$  mg/d) in males,<sup>125</sup> and inadequate energy intake among patients undergoing dialysis.<sup>126</sup>



- Prevalent MetS is inversely associated with total antioxidant capacity from diet and dietary supplements,<sup>127</sup> animal-based oils such as butter and ghee,<sup>128</sup> and organic food consumption.<sup>129</sup>

### Physical Activity

- In cross-sectional studies, prevalent MetS is directly associated with low cardiorespiratory fitness<sup>99,130</sup> and low levels of PA<sup>131,132</sup> and is inversely associated with “weekend warrior” and regular PA patterns,<sup>133</sup> any length of moderate- to vigorous-intensity PA,<sup>132</sup> and handgrip strength.<sup>134–136</sup>
- The relationship between PA and MetS may be moderated by lean muscle mass in males. Males and females with high lean muscle mass had low risk of MetS regardless of PA. However, males with low lean muscle mass exhibited a U-shaped relationship between vigorous PA and MetS risk (0 h/wk versus 4–8 h/wk aOR, 2.1 [95% CI, 1.1–4.3]; >12 h/wk versus 4–8 h/wk aOR, 4.3 [95% CI, 1.7–11.0]). No interaction between lean muscle mass and PA was seen in women.<sup>137</sup>

### Blood Biomarkers

- Blood biomarkers directly associated with prevalent MetS include proinflammatory cytokines such as IL-6 and tumor necrosis factor- $\alpha$ <sup>138</sup>; retinol binding protein 4<sup>139</sup>; cancer antigen 19-9<sup>130,140</sup>; serum liver chemistries, including alanine transaminase<sup>141</sup>, aspartate transaminase, alanine transaminase/aspartate transaminase ratio, alkaline phosphatase, and  $\gamma$ -glutamyl transferase<sup>142</sup>; serum vitamin levels,<sup>143</sup> including retinol and  $\alpha$ -tocopherol; serum thyrotropin in individuals with euthyroidism<sup>144</sup>; erythrocyte parameters<sup>145</sup> such as hemoglobin level and red blood cell distribution width; other blood parameters such as platelet and white blood cell counts<sup>146</sup>; non-HDL-C<sup>147</sup>; and ratio of lymphocytes to HDL-C.<sup>148</sup>
- In cross-sectional studies, prevalent MetS is inversely associated with testosterone levels in males,<sup>149</sup> anti-inflammatory cytokines (IL-10),<sup>138</sup> ghrelin,<sup>138</sup> adiponectin,<sup>138</sup> and antioxidant factors (paraoxonase-1).<sup>138</sup>
- In NHANES 1999 to 2004, high serum anti-Müllerian hormone was inversely associated with specific MetS components, including WC, diabetes status, and insulin resistance, in overweight and obese US adult men.<sup>150</sup> However, anti-Müllerian hormone was not associated with having  $\geq 3$  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.<sup>150</sup>

### Other

- Prevalent MetS is also directly associated with stress<sup>151</sup>; elevated intraocular pressure among

people without glaucoma<sup>152</sup>; sensorineural hearing loss among people with Turner syndrome<sup>153</sup>; exposure to pesticides<sup>154</sup>; exposure to antiretroviral therapy among adults living with HIV<sup>155</sup>; elevated urine sodium<sup>156</sup>; poor sleep characteristics<sup>157</sup>; OSA<sup>158</sup>; snoring<sup>159</sup>; microalbuminuria<sup>160</sup>; sarcopenia in middle-aged and older nonobese adults<sup>161</sup>; visceral fat level<sup>162</sup>; hypoactive sexual desire disorder among postmenopausal women<sup>163</sup>; high heavy metal exposure<sup>164</sup>; and high occupational noise exposure.<sup>165</sup>

- In cross-sectional studies, prevalent MetS is inversely associated with the ratio of muscle mass to visceral fat in college students,<sup>166</sup> vacation frequency,<sup>167</sup> and marijuana use.<sup>168</sup>
- In Korea NHANES 2013 to 2017, which included 24 695 eligible participants, a higher density of physicians (2.71 per 1000 population versus 2.64 per 1000 population) was significantly associated with a lower prevalence of MetS (OR, 0.86 [95% CI, 0.76–0.98]).<sup>169</sup>
- In data from 8272 adults in China, there was a U-shaped relationship between sleep duration and MetS. Sleep duration <6 or >9 hours was associated with higher risk of MetS (OR, 1.10–2.15).<sup>170</sup>
- In NHANES 2003 to 2008, high neighborhood racial and ethnic diversity<sup>171</sup> 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.

### Social Determinants of Health

- Prior studies have reported higher MetS incidence among individuals with lower educational attainment, lower SES,<sup>172</sup> more experiences of everyday discrimination,<sup>173</sup> and long-term work stress. In HCHS/SOL, SES was inversely associated with prevalent MetS among Hispanic/Latino adults of diverse ancestry groups.<sup>174</sup> Higher income and education and full-time employment status versus unemployed status were associated with a 4%, 3%, and 24% decreased odds of having MetS, respectively. The association between income was significant only among females and those with current health insurance.
- In NHANES 2007 to 2014, females in households with low and very low food security were at increased risk for prevalent MetS compared with females in households with full food security (OR, 1.43 [95% CI, 1.13–1.80] and 1.71 [95% CI, 1.31–2.24], respectively).<sup>175</sup>
- In the HELENA study among 1037 European adolescents 12.5 to 17.5 years of age, those with low-educated mothers showed a higher MetS risk ( $\beta$  estimate, 0.54 [95% CI, 0.09–0.98]) compared with those with high-educated mothers. Adolescents

who accumulated  $>3$  disadvantages (defined as low-educated parents, low family affluence, migrant origin, unemployed parents, or nontraditional families) had a higher MetS risk score compared with those who did not experience disadvantage. ( $\beta$  estimate, 0.69 [95% CI, 0.08–1.31]).<sup>176</sup>

## Subclinical Disease

### (See Chart 10-6)

- In the ARIC study (1987–1998), with the use of a sex- and race and 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).<sup>45</sup>
- Isolated MetS, which could be considered an earlier form of overt MetS, has been defined as  $\geq 3$  MetS components but without overt hypertension and diabetes. In a population-based random sample of 2042 residents of Olmsted County, Minnesota, 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 ( $P < 0.05$ ).<sup>177</sup>

## Genetics and Family History

### (See also Chapters 6 [Overweight and Obesity], 8 [High Blood Pressure], and 9 [Diabetes])

- Genetic factors are associated with the individual components of MetS. In a candidate gene study of 3067 children, variants in the *FTO* gene were associated with MetS.<sup>178</sup>
- 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 and ethnic populations that could explain some of the correlated architecture of MetS traits.<sup>179–183</sup>
- The A allele of the *TNF $\alpha$*  (-308 A/G) rs1800629 polymorphic gene, which is associated with higher levels of circulating tumor necrosis factor- $\alpha$ , has been associated with higher prevalence of MetS in Egyptians.<sup>184</sup>
- 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.<sup>185</sup>

- SNPs of inflammatory genes (encoding IL-6, IL-1 $\beta$ , and IL-10) and plasma fatty acids, as well as interactions among these SNPs, are differentially associated with odds of MetS.<sup>186</sup>
- A UK Biobank study of 291 107 individuals performed GWASs for the clustering of MetS traits and found 3 loci associated with all 5 MetS components (near *LINC0112*, *C5orf67*, and *GIP*), of which *C5orf67* has been associated with individual MetS components.<sup>187</sup>

## Prevention and Awareness of MetS

- Identification of MetS represents a call to action for the health care professional 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.<sup>188</sup>
- Despite the high prevalence of MetS, the public's recognition of MetS is limited.<sup>189</sup> Communicating with patients about MetS and its clinical assessment may increase risk perception and motivation toward a healthier behavior.<sup>190</sup>

## 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.<sup>191</sup>
- In the HAPIEE study of 4257 participants 45 to 72 years of age with a mean follow-up of 11 years, MetS increased the risk of a first CVD event among males (HR, 1.53 [95% CI, 1.18–1.97]) and females (HR, 1.56 [95% CI, 1.14–2.15]).<sup>192</sup>
- 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, elevated blood pressure, 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.<sup>110</sup>
- 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  $\geq 3$  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.<sup>193</sup>

- In the Three-City Study, among 7612 participants  $\geq 65$  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.<sup>194</sup>
- 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.<sup>195</sup>
- In patients with chest pain undergoing invasive coronary angiography, presence of MetS and increasing number of MetS factors were independently associated with obstructive CAD in females (aOR, 1.92 [95% CI, 1.31–2.81]) but not in males (aOR, 0.97 [95% CI, 0.61–1.55]).<sup>196</sup>
- 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.<sup>197</sup>
- MetS is associated with risk of stroke.<sup>198</sup> 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]). Last, 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 a combined analysis from the ARIC and JHS study, among 13 141 White and Black individuals with a mean follow-up of 18.6 years, risk of ischemic stroke increased consistently with MetS severity z score (HR, 1.75 [95% CI, 1.35–2.27]) for those above the 75th percentile compared with those below the 25th percentile. Risk was highest for White females (HR, 2.63 [95% CI, 1.70–4.07]) although without significant interaction by sex and race.<sup>199</sup>
- 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];  $P < 0.001$ ).<sup>200</sup> 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]).<sup>201</sup>
- In a meta-analysis of 20 prospective cohort studies that included 57 202 adults  $\geq 60$  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).<sup>202</sup> 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.<sup>203</sup> 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  $\geq 6$  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.<sup>204</sup>
- 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).<sup>205</sup> MetS severity score was also strongly associated with early onset of diabetes.<sup>206</sup>

- 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.<sup>108</sup> 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 the 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]) with the same definition.
- Among 2798 adolescents 11 to 19 years of age in the Tehran lipid and glucose study with a mean follow-up of 11.3 years, those with MetS in adolescence had a 2.8 times increased hazard of incident type 2 diabetes in adulthood (incidence rate, 33.78 per 10 000 per years; HR, 2.82 [95% CI, 1.41–5.64]) independently of baseline age and sex, adulthood BMI, and family history of diabetes.<sup>207</sup>
- 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.<sup>208</sup>
- 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.<sup>209</sup>

## Adults

### MetS and Subclinical CVD

- MetS has also been associated with incident AF,<sup>210,211</sup> HF,<sup>212</sup> and PAD.<sup>213</sup>
- In MESA, among 6603 people 45 to 84 years of age (1686 [25%] with MetS without diabetes and 881 [13%] with diabetes), subclinical atherosclerosis prevalence and progression assessed by CAC were more severe in people with MetS and diabetes than in those without these conditions, and the extent and progression of CAC were strong predictors of CHD and CVD events in these groups.<sup>214,215</sup> There appears to be a synergistic relationship among MetS, NAFLD, and prevalence of CAC,<sup>216</sup> as well as a synergistic relationship with smoking.<sup>217</sup>
- Individuals with MetS have a higher degree of endothelial dysfunction than individuals with a similar burden of traditional cardiovascular risk factors.<sup>218</sup> Furthermore, individuals with both MetS and diabetes have demonstrated increased microvascular

and macrovascular dysfunction.<sup>219</sup> MetS is associated with increased thrombosis, including increased resistance to aspirin<sup>220</sup> and clopidogrel loading.<sup>221</sup>

- In a meta-analysis of 8 population-based studies that included 19 696 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 (pooled OR, 1.61 [95% CI, 1.29–2.01];  $P<0.0001$ ) than in individuals without MetS.<sup>222</sup>
- 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<sup>223</sup>; increased visceral fat<sup>224</sup>; increased ascending aortic diameter<sup>225</sup>; high-risk coronary plaque features, including increased necrotic core<sup>226</sup>; impaired coronary flow reserve<sup>227</sup>; abnormal indexes of LV strain<sup>228</sup>; LV diastolic dysfunction<sup>229</sup>; LV dyssynchrony<sup>230</sup>; and subclinical RV dysfunction.<sup>231</sup>

### 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.<sup>232</sup> 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]).<sup>233</sup>

#### 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.<sup>234</sup>
- In RENIS-T6, MetS was associated with a mean 0.30-mL/min per year (95% CI, 0.02–0.58) faster decline in GFR than in individuals without MetS.<sup>235</sup>

#### Cancer

- MetS is also associated with cancer (in particular breast, endometrial, prostate, pancreatic, hepatic,



colorectal, and renal),<sup>236–238</sup> as well as with gastroenteropancreatic neuroendocrine tumors.<sup>239</sup>

- MetS is linked to poorer cancer outcomes, including increased risk of recurrence and overall mortality.<sup>240</sup>  
<sup>241</sup> In a meta-analysis of 24 studies that included 132 589 males with prostate cancer (17.4% with MetS), MetS was associated with worse oncological outcomes, including biochemical recurrence and more aggressive tumor features.<sup>242</sup> Among 94 555 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]).<sup>243</sup>
- In a meta-analysis of 17 prospective longitudinal studies that included 602 195 females and 15 945 cases of breast cancer, MetS was associated with increased risk of incident breast cancer in postmenopausal females (aRR, 1.25 [95% CI, 1.12–1.39]) but significantly reduced breast cancer risk in premenopausal females (aRR, 0.82 [95% CI, 0.76–0.89]). The association between MetS and increased risk of breast cancer was observed only among White and Asian females, whereas there was no association in Black females.<sup>244</sup>
- 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).<sup>245</sup>
- In 25 038 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]).<sup>236</sup> 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]).<sup>246</sup>

### 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 is 21.9%.<sup>247</sup> The global prevalence of NAFLD is estimated at 25.2%.<sup>248</sup> 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]).<sup>249</sup> 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.<sup>247,250</sup>

- MetS has been associated with cirrhosis,<sup>251</sup> colorectal adenomas,<sup>252</sup> acute pancreatitis,<sup>253</sup> and Barrett esophagus.<sup>254</sup>

### Other

- Among 725 Chinese adults  $\geq 90$  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, 1.17–4.32]).<sup>255</sup>
- In a cross-sectional analysis of data from the PREDIMED-Plus multicenter randomized trial, MetS was associated with adverse health-related quality of life as measured by the Short Form-36 in the aggregated physical dimensions, body pain in females, and general health in males; however, this adverse association was absent for the psychological dimensions of health-related quality of life.<sup>256</sup>
- MetS is associated with dementia<sup>257</sup> (particularly Alzheimer dementia<sup>258</sup>), cognitive decline,<sup>259</sup> and lower cognitive performance in older adults at risk for cognitive decline.<sup>260</sup>
- 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.<sup>261,262</sup>
- In males, MetS has been associated with decreased sperm total count, sperm concentration, sperm normal morphology, sperm progressive motility, and sperm vitality and an increase in sperm DNA fragmentation and mitochondrial membrane potential, as well as lower semen quality, which may contribute to male infertility.<sup>263</sup>
- MetS and its components are associated with more severe infection with severe acute respiratory syndrome coronavirus 2 and high risk for poor outcomes in COVID-19 illness.<sup>264–267</sup>

### 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  $\approx 24\%$  for each additional MetS component present.<sup>268</sup>
- 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.<sup>245,269–273</sup>

## 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,<sup>274</sup> Latin America,<sup>275</sup> Aruba,<sup>276</sup> India,<sup>277–280</sup> Bangladesh,<sup>281</sup> Iran,<sup>282–284</sup> Ghana,<sup>285</sup> the Gaza Strip,<sup>286</sup> Jordan,<sup>287</sup> Ethiopia,<sup>288,289</sup> Nigeria,<sup>290,291</sup> South Africa,<sup>292</sup> Ecuador,<sup>293</sup> and Vietnam,<sup>294</sup> as well as many other countries.
- Global prevalence of MetS in military personnel is estimated at 21% (95% CI, 17%–25%; n=37 studies: 15 in America, 13 in Europe and 9 in Asia).<sup>295</sup>
- MetS among children and adolescents is an emerging public health challenge in low- to middle-income countries. In a meta-analysis including data from 76 studies with 142 142 children and adolescents residing in low- to middle-income countries, the pooled prevalence of MetS was 4.0% (IDF), 6.7% (ATP III), and 8.9% (de Ferranti).<sup>296</sup> Among obese or overweight children and adolescents, pooled prevalence was estimated at 24.1%, 36.5%, and 56.3% with the IDF, ATP III, and de Ferranti criteria, respectively.

### Latin America

- In a systematic review of 10 Brazilian studies, the weighted mean prevalence of MetS in Brazil was 29.6%.<sup>297</sup>
- 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%;  $P=0.02$ ).<sup>298</sup>
- In a report from a representative survey of the northern state of Nuevo León, Mexico, the prevalence of MetS in adults ( $\geq 16$  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%).<sup>299</sup> Among older Mexican adults ( $\geq 65$  years of age), the prevalence was 72.9% (75.7% in males, 70.4% in females).<sup>300</sup>

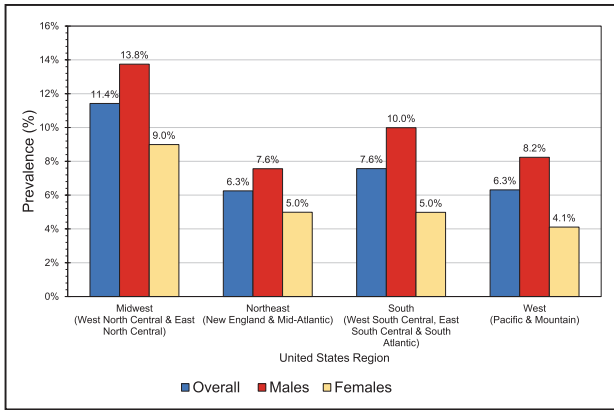
- MetS is highly prevalent in modern indigenous populations, notably in Brazil and Australia. The prevalence of MetS was estimated to be 41.5% in indigenous groups in Brazil,<sup>297,299</sup> 33.0% in Australian Aborigines, and 50.3% in Torres Strait Islanders.<sup>301</sup>

### Europe

- 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).<sup>302</sup>
- 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.<sup>303</sup>

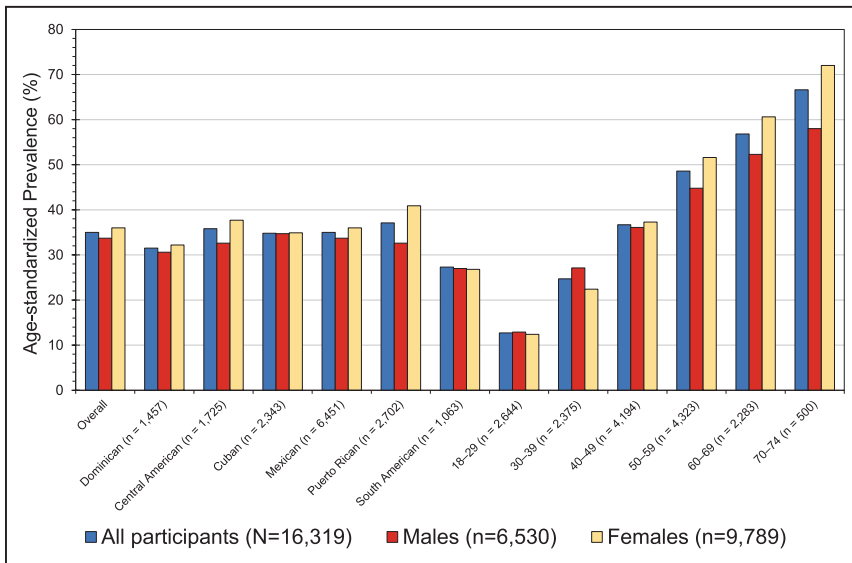
### Asia and Middle East

- On the basis of data from NIPPON DATA (1990–2005), the age-adjusted prevalence of MetS in a Japanese population was 19.3%.<sup>197</sup> In a partially representative Chinese population, the 2009 age-adjusted prevalence of MetS in China was 21.3%,<sup>304</sup> whereas in northwest China, the prevalence for 2010 was 15.1%,<sup>305</sup> and in 2018, the prevalence in Chinese adults in Hong Kong was 14.1%.<sup>306</sup>
- 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 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.<sup>307</sup>



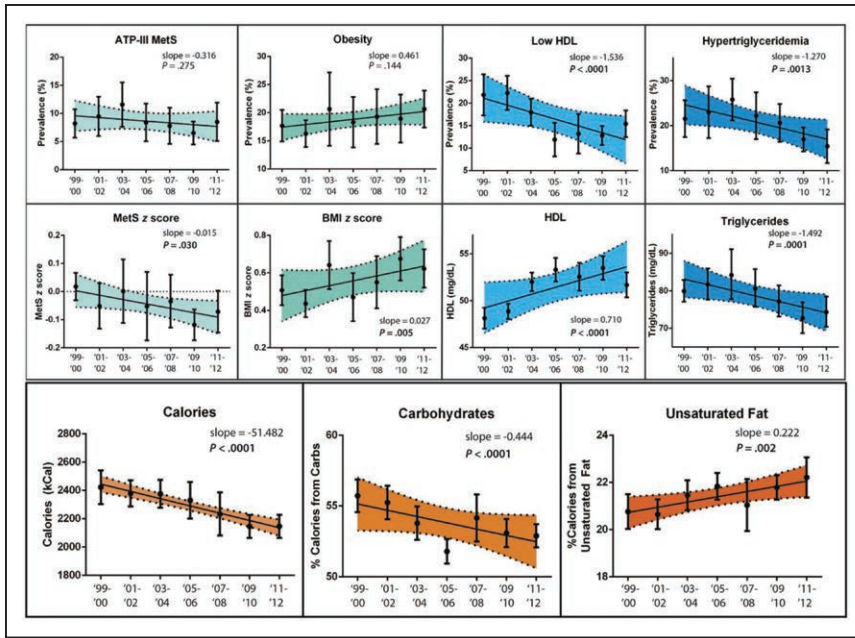
**Chart 10-1. Prevalence of metabolic syndrome, by sex and US region among adolescents 12 to 19 years of age (NHANES, 1999–2014).**

NHANES indicates National Health and Nutrition Examination Survey. Source: Data derived from DeBoer et al.<sup>4</sup>

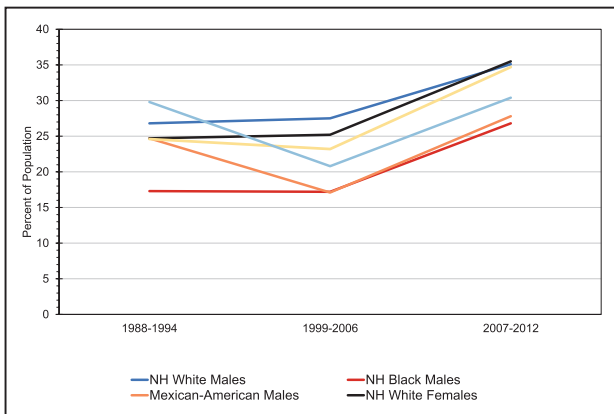


**Chart 10-2. Age-standardized prevalence of MetS, by age and sex in Hispanic/Latino people in HCHS/SOL, United States, 2008 to 2011.**

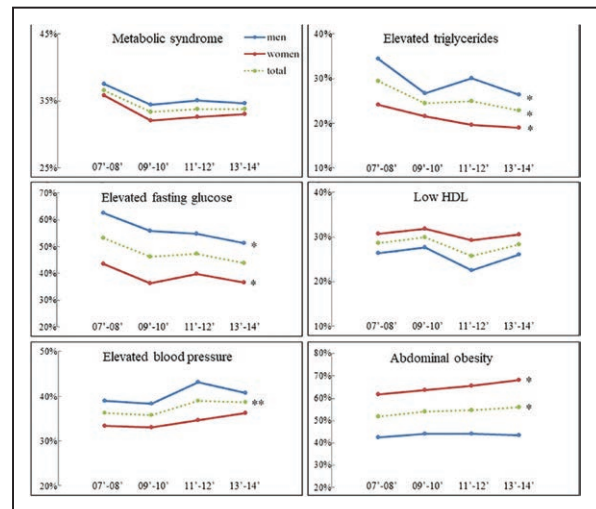
Values were weighted for survey design and nonresponse and were age standardized to the population described by the 2010 US census. HCHS/SOL indicates Hispanic Community Health Study/Study of Latinos; and MetS, metabolic syndrome. Source: Data derived from Heiss et al.<sup>10</sup>



**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-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; and NHANES, National Health and Nutrition Examination Survey. Source: Reproduced with permission from Lee et al.<sup>42</sup> Copyright © 2016 American Academy of Pediatrics.

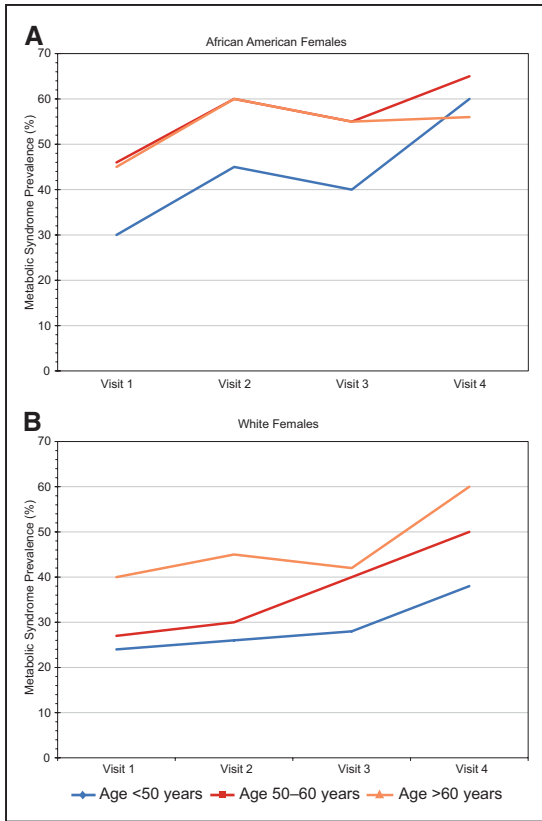


**Chart 10-4. Prevalence of MetS among US adults using the harmonized MetS criteria (NHANES, 1998–2012).** MetS was defined using the criteria agreed to jointly by the International Diabetes Federation; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity. MetS indicates metabolic syndrome, NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey. Source: Data derived from Moore et al.<sup>43</sup>



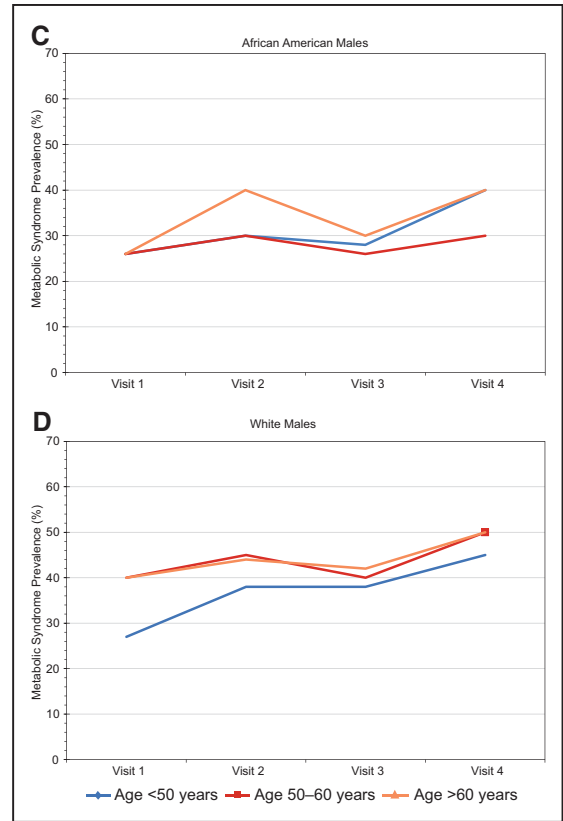
**Chart 10-5. Sex-stratified trends in the age-adjusted weighted prevalence of MetS using ATP III criteria and its components among US adults (NHANES, 2007–2014).** MetS was defined using modified National Cholesterol Education Program–ATP III criteria. ATP III indicates Adult Treatment Panel III; HDL, high-density lipoprotein; MetS, metabolic syndrome; 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. Source: Reprinted from Shin et al<sup>8</sup> with permission from Elsevier. Copyright © 2018 Elsevier.





**Chart 10-6. Ten-year progression of MetS in the ARIC study, stratified by age, sex, and race and ethnicity, United States, 1987 to 1998.**

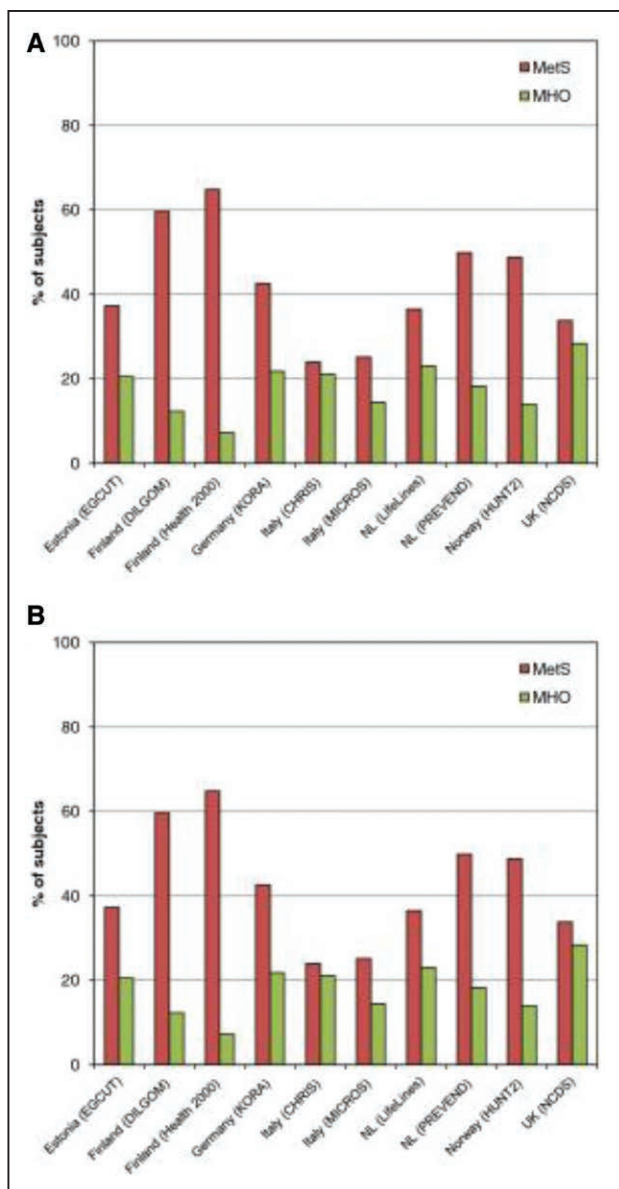
**A,** African American females. **B,** White females. (*Continued*)



**Chart 10-6. Continued. 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; and MetS, metabolic syndrome.

Source: Data derived from Vishnu et al.<sup>45</sup>

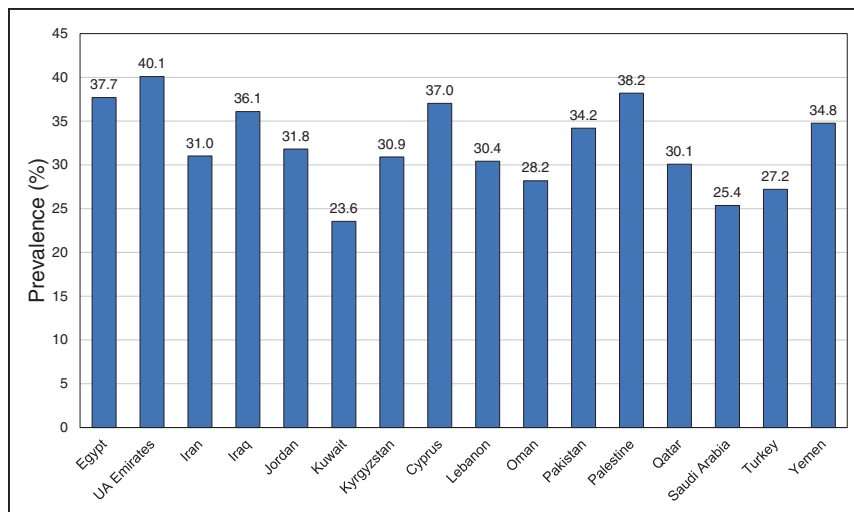


**Chart 10-7. Age-standardized prevalence of MetS and MHO among obese (body mass index  $\geq 30$  kg/m<sup>2</sup>) people in different European cohorts, 1995 to 2012 (global data).**

**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.

Source: Reprinted from van Vliet-Ostapchouk et al.<sup>302</sup> Copyright © 2014 van Vliet-Ostapchouk et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.



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

MetS indicates metabolic syndrome; and UA, United Arab.

\*Pooled prevalence estimates obtained using random-effects model.

Source: Data derived from Ansari-Moghaddam et al.<sup>307</sup>

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## 11. ADVERSE PREGNANCY OUTCOMES

See Table 11-1 and Charts 11-1 through 11-10

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APOs include gestational hypertension, preeclampsia, gestational diabetes, PTB, and delivery of an infant who is SGA. The processes leading to these interrelated disorders reflect a response to the “stress test” of pregnancy, and they are associated with risk of poor future CVH outcomes in females and offspring, including CHD, stroke, and HF. Furthermore, growing rates of pregnancy-related morbidity and mortality in the United States are attributed predominantly to CVD. Because of this, the AHA has recognized the importance of raising awareness about these disorders in comprehensive CVH promotion and CVD prevention in females.<sup>1</sup> Furthermore, the AHA, in partnership with the American College of Obstetricians and Gynecologists, 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 health for both females and offspring.<sup>2</sup>

This chapter focuses only on complications of pregnancy-related mortality, CVD, CVH (risk factors), and brain health in females and offspring; complications in other organ systems are important sources of APO-related morbidity and mortality in females (eg, acute kidney injury) and offspring (eg, necrotizing enterocolitis) 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 22 [Cardiomyopathy and Heart Failure] for pregnancy-related HF and PPCM and Chapter 17 [Congenital Cardiovascular Defects and Kawasaki Disease] for pregnancy-related risk factors for congenital HD).

### 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 is defined as gestational hypertension.

- 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.
- The threshold for treatment of BP differs in pregnant and nonpregnant individuals. The American College of Obstetricians and Gynecologists defines HDP as a BP of  $\geq 140/90$  mmHg in pregnancy. In contrast, the AHA and ACC adopted a lower threshold in nonpregnant adults of  $\geq 130/80$  mmHg in 2017. In a retrospective cohort study, lowering the BP threshold to diagnose gestational hypertension would increase the prevalence from 6.0% to 13.8% in a sample of 137 398 females from an integrated health system between 2009 and 2014.<sup>3</sup>
- Gestational diabetes: De novo diabetes that develops after week 20 of pregnancy is considered gestational diabetes.
- PTB: PTB includes spontaneous or indicated delivery before 37 weeks' gestation.
- Infant with SGA: An infant with a birth weight  $\leq 10$ th percentile for gestational age is considered to be SGA. SGA is called intrauterine growth restriction during gestation; an alternative definition for an infant with LBW includes birth weight  $< 2500$  g.
- Pregnancy loss: Spontaneous loss of an intrauterine pregnancy is classified as pregnancy loss and is further categorized according to gestational age at which loss occurs.
  - Stillbirth: loss occurs at  $\geq 20$  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.<sup>4</sup>

#### Risk Factors (Including Social Determinants)

(See Chart 11-1)

- According to a meta-analysis of individual participant data from 265 270 females from 39 European, North American, and Oceanic cohort studies, the risk of any APO was greater with higher categories of prepregnancy BMI and greater degree of GWG, with an aOR of 2.51 (95% CI, 2.31–2.74) for females with prepregnancy obesity and high ( $\geq 1.0$  SD) GWG (Chart 11-1).<sup>5</sup>

The 2022 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 2022. 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.



- 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 prepregnancy overweight or obesity, defined as BMI  $\geq 25.0$  kg/m<sup>2</sup>.<sup>6</sup>
- 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 PTB, gestational diabetes, or HDP, with an aOR of 1.95 (95% CI, 1.15–3.29).<sup>7</sup>

### **Pregnancy-Related Complications: Mortality and CVD**

#### **Mortality**

- The pregnancy-related mortality rate was 17.4 per 100 000 live births in 2018.<sup>8</sup> Maternal or pregnancy-related mortality is defined by the NCHS as death while pregnant or within 42 days of being pregnant; late maternal or pregnancy-related deaths occurring between 43 days and 1 year are not included as part of the definition.
  - Pregnancy-related mortality rates were higher in older age groups for females  $\geq 40$  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 pregnancy-related mortality rate for NH Black females 2.5-fold and 3-fold greater than for 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 or pregnancy-related mortality, accounting for 26.5% of deaths according to an observational study using 2011 to 2013 data from the CDC Pregnancy Mortality Surveillance System.<sup>9,10</sup>

#### **Cardiovascular Risk Factors and CVD**

- Among 4484 females from the nuMoM2b Heart Health Study, a prospective observational cohort, APOs 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]).<sup>11</sup>
- Among 48 113 participants from the WHI, 13 482 (28.8%) reported  $\geq 1$  APOs (defined as HDP,

gestational diabetes, PTB, LBW, and high birth weight).<sup>12</sup> Females who reported any APO were more likely to have ASCVD (1028 [7.6%]) compared with those without APOs (1758 [5.8%]), and each APO was individually associated with future ASCVD (gestational diabetes: aOR, 1.32 [95% CI, 1.02–1.67]; LBW: aOR, 1.25 [95% CI, 1.12–1.39]; PTB: aOR, 1.23 [95% CI, 1.10–1.36]; HDP: aOR, 1.38 [95% CI, 1.19–1.58]; except for high birth weight: aOR, 1.07 [95% CI, 0.91–1.25]).

### **Hypertensive Disorders of Pregnancy**

#### **Incidence, Prevalence, and Secular Trends**

##### **(See Charts 11-2 and 11-3)**

- 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).<sup>13</sup>
- There is substantial geographic heterogeneity in rates of HDP across the United States (Chart 11-3). In 2019, the highest rate of HDP was observed in Louisiana with a rate of 116 per 1000 live births.
- Rates of chronic hypertension before pregnancy increased significantly between 2007 to 2018.<sup>14</sup> Among 47 949 381 live births to females 15 to 44 years of age, the overall prevalence of prepregnancy hypertension increased from 10.9 to 20.5 per 1000 live births; significant disparities were observed with higher prevalence of prepregnancy hypertension in rural compared with urban areas (rate ratio in 2018, 1.18 [95% CI, 1.16–1.20]).

#### **Risk Factors (Including Social Determinants)**

- Among 2304 female-newborn dyads in the multinational HAPO study, lower CVH (based on 5 metrics: BMI, BP, cholesterol, glucose, and smoking) at 28 weeks' gestation was associated with higher risk of preeclampsia; aRRs were 3.13 (95% CI, 1.39–7.06), 5.34 (95% CI, 2.44–11.70), and 9.30 (95% CI, 3.95–21.86) for females with  $\geq 1$  intermediate, 1 poor, or  $\geq 2$  poor (versus all ideal) CVH metrics during pregnancy, respectively.<sup>15</sup> Conversely, each 1-point higher (more favorable) CVH score was associated with 33% lower risk for preeclampsia (aRR, 0.67 [95% CI, 0.61–0.73]).
- In a meta-analysis of 25 356 688 pregnancies from 92 studies published between 2000 and 2015, the following factors at  $\leq 16$  weeks' gestation were associated with significantly elevated risks for preeclampsia (reported as pooled unadjusted RR): 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]);

pregnancy diabetes (3.7 [95% CI, 3.1–4.3]); prepregnancy obesity (BMI >30 kg/m<sup>2</sup> versus <30 kg/m<sup>2</sup>: 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<sup>2</sup> (23.8% [95% CI, 22.0%–25.6%]) and prior preeclampsia (22.8% [95% CI, 19.6%–26.3%]).<sup>16</sup>

### Weight Gain

- 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<sup>2</sup>], 11.5–16 kg for normal weight [BMI, 18.5–24.9 kg/m<sup>2</sup>], 7.0–11.5 kg for overweight [BMI, 25.0–29.9 kg/m<sup>2</sup>], and 5.0–9.0 kg for obese [BMI >30.0 kg/m<sup>2</sup>]) 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]).<sup>17</sup> Among 8296 nulliparous females in the nuMoM2b study, higher HDP risks were observed for excess weight gain in midpregnancy (from 5–13 to 16–21 weeks' gestation; aRR, 1.16 [95% CI, 1.01–1.35]) and late pregnancy (from 16–21 to 22–29 weeks' gestation; aRR, 1.19 [95% CI, 1.02–1.40]) but not in early pregnancy (from prepregnancy to 5–13 weeks' gestation; aRR, 0.95 [95% CI, 0.83–1.08]).<sup>18</sup>
- In a meta-analysis of 12 studies, interpregnancy weight gain was associated with increased HDP risk; each 1-kg/m<sup>2</sup> increase in BMI from the start of one pregnancy to the next was associated with 31% higher OR for HDP (0.31 [95% CI, 0.11–0.53]).<sup>19</sup>

### Blood Pressure

- Among 586 females with a mean age of 28.5 years (SD, 4.5 years) followed up from preconception through early pregnancy, each 2-mmHg higher mean arterial pressure during preconception was associated with a higher risk of HDP (aRR, 1.08 [95% CI, 1.01–1.14]); in addition, each 2-mmHg increase in mean arterial pressure from preconception to 4 weeks' gestation was associated with a higher risk of preeclampsia (aRR, 1.13 [95% CI, 1.02–1.25]), and each 2-mmHg increase in mean arterial pressure from preconception to 20 weeks' gestation was associated with a higher risk of HDP (aRR, 1.14 [95% CI, 1.06–1.22]) and higher risk of

preeclampsia (aRR, 1.20 [95% CI, 1.08–1.34]) after adjustment for age, parity, BMI, and aspirin use.<sup>20</sup>

### Diet

- Among 62 774 females with singleton pregnancies in the Danish National Birth Cohort, sodium intake during pregnancy (reported at 25 weeks' gestation) was associated with risk for HDPs; females with >3.5 g/d sodium intake had 54% (95% CI, 16%–104%) higher risk for gestational hypertension and 20% (95% CI, 1%–42%) higher risk for preeclampsia compared with females with <2.8 g/d sodium intake.<sup>21</sup>
- Among 8259 pregnant females in the nuMoM2b cohort, periconceptional dietary quality was associated with HDP risk. The HDP rate was 25.9% for females in the lowest quartile (poorest quality) of the HEI-2010 compared with 20.3% for females in the highest quartile (aRR, 1.16 [95% CI, 1.02–1.31]).<sup>22</sup>

### Race and Ethnicity

- Among 9470 nulliparous pregnant females in nuMoM2b (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, 0.77 [95% CI, 0.64–0.91]; and 8.5%, OR, 0.60 [95% CI, 0.41–0.87]), respectively, versus NH White females).<sup>23</sup> These differences were largely attenuated after adjustment for age, BMI, smoking, and medical comorbidities.
- In meta-analysis, immigrant (versus nonimmigrant) status has been associated with lower risk of HDPs (RR, 0.74 [95% CI, 0.67–0.82]).<sup>24</sup> Similarly, in the nuMoM2b Study, greater acculturation (defined as born in the United States with high English proficiency versus born or not born in the United States with low proficiency in English or use of Spanish as the preferred language) was associated with higher risk of preeclampsia or eclampsia (aOR, 1.31 [95% CI, 1.03–1.67]) and gestational hypertension (aOR, 1.48 [95% CI, 1.22–1.79]).<sup>25</sup>

### Other

- In a meta-analysis of 10 studies, PM2.5 exposure during pregnancy was associated with higher risk for HDP (OR, 1.52 [95% CI, 1.24–1.87] per 10 µg/m<sup>3</sup>).<sup>26</sup>

### Genetics/Family History

- 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 (aRR ratio, 2.55 [95% CI, 1.87–3.47] and 1.44 [95% CI, 1.23–1.69], respectively) and gestational hypertension (aRR ratio, 1.37 [95% CI, 1.09–1.71] and 1.36 [95% CI, 1.24–1.49], respectively).<sup>18,27</sup>

- Heritability estimates for preeclampsia range from 31% to 54%.<sup>28,29</sup> In 1 study, daughters of females who had preeclampsia had a >2 times higher risk of preeclampsia themselves compared with other females (OR, 2.2 [95% CI, 2.0–2.4]).<sup>30</sup>
- Many genetic risk factors for HDP may overlap with traditional CVD risk factors. According to data from the UK Biobank, polygenic risk scores for SBP (aOR per SD, 1.22 [95% CI, 1.17–1.27]), DBP (aOR per SD, 1.22 [95% CI, 1.17–1.26]), and BMI (aOR per SD, 1.06 [95% CI, 1.02–1.10]) were significantly associated with HDP risk, whereas those for heart rate, type 2 diabetes, smoking, and LDL-C were not. Analysis of genetic instruments related to BP-lowering pathways suggested that nitric oxide signaling might be particularly relevant for HDP risk (*GUCY1A3* SNP was associated with an aOR of 0.21 per 5-mmHg lowering of SBP versus polygenic risk score for systolic BP; aOR, 0.65 per 5-mmHg lowering of SBP; *P* for heterogeneity=0.037).<sup>31</sup>
- 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,<sup>32</sup> 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.<sup>33</sup>

### Genetic Variants

- Studies have identified variants associated with preeclampsia, some of which share susceptibility with cardiovascular risk. A GWAS of preeclampsia analyzed 4380 offspring of females 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.<sup>34</sup> *FLT1* encodes a transmembrane tyrosine kinase receptor that mediates angiogenesis by binding placental growth factor.
- Another GWAS meta-analysis of 7219 European preeclampsia cases and 155 660 controls and 2296 Central Asian preeclampsia cases and 2059 controls found commonality between hypertension genes and preeclampsia, including variants at

*ZNF831* and *FTO* associated with preeclampsia.<sup>35</sup> Furthermore, a GRS for hypertension was associated with preeclampsia ( $P=1.2\times 10^{-12}$ , effect [log OR]=0.18 [95% CI, 0.13–0.23], with effect corresponding to the increase in the risk of preeclampsia per SD in GRS).<sup>35</sup>

- The role of GRS composed of preeclampsia risk factor variants in preeclampsia is supported by a study of 498 preeclampsia cases; a hypertension GRS and a BMI GRS were associated with increased risk of preeclampsia (OR, 1.11 [95% CI, 1.01–1.21] and 1.10 [95% CI, 1.00–1.20], respectively).<sup>36</sup>
- *TTN* variants, present in DCM and PPCM, are enriched in patients with preeclampsia, suggesting a shared genetic architecture among preeclampsia, PPCM, and DCM. In a study of 181 primarily White females 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 variants found in the *TTN* gene<sup>37</sup> (see Chapter 22 [Cardiomyopathy and Heart Failure]).

## Prevention

### Lifestyle Modifications

- PA is recommended for pregnant females without obstetric or medical complications.<sup>38–41</sup> 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%.<sup>42</sup>
- 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).<sup>43</sup>

### 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]).<sup>44</sup>
- 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%]).<sup>45</sup>

### 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.<sup>46</sup>
- In an analysis of 65 286 425 females from the NIS from January 1, 1998, through December 31, 2014, females with HDP had higher risk of stroke compared with those without HDP (34.5% versus 6.9%;  $P < 0.0001$ ).<sup>47</sup> A significant interaction with race and ethnicity was observed with significantly higher risk of stroke in Black females (aRR, 2.07 [95% CI, 1.86–2.30]) and Hispanic females (aRR, 2.19 [95% CI, 1.98–2.43]) compared with NH White females.
- 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: HR, 1.67 [95% CI, 1.54–1.81]; HF: HR, 2.13 [95% CI, 1.64–2.76]; AF: HR, 1.73 [95% CI, 1.38–2.16]; and cardiovascular mortality: HR, 2.12 [95% CI, 1.49–2.99]).<sup>48</sup>
- In a national cohort study from Norway, in 508 422 females 16 to 49 years of age at first birth between 1980 and 2004, preeclampsia was associated with a significantly higher risk for HF (HR, 2.00 [95% CI, 1.50–2.68]) compared with normotension.<sup>49</sup>
- 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; for example, the standardized mean difference in FMD before the clinical diagnosis of preeclampsia was significantly different (–0.92 [95% CI, –1.24 to –0.60]). This suggests a mechanistic link between vascular dysfunction and risk of preeclampsia and future CVD.<sup>50</sup>

### 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]).<sup>51</sup>

- 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<sup>2</sup> [95% CI, 0.04–0.68]; 13 studies, 53 293 individuals, 1752 exposed).<sup>52</sup> 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 11-4)

- The national prevalence of gestational diabetes was 6.0% in 2016, an increase of 0.4% from 2012 according to birth data from the NVSS. In 2016, the prevalence of preexisting diabetes complicating pregnancies was 0.9% (Table 11-1).<sup>53</sup>
  - 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.<sup>54</sup>
  - 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 and ethnicity (Chart 11-4).

### Risk Factors (Including Social Determinants)

- 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<sup>2</sup> 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 associated with



higher risks of gestational diabetes.<sup>5</sup> 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]).

- In the nuMoM2b study, 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 and ethnicity, employment schedule, BMI, and snoring.<sup>55</sup>
- In a cohort of 595 pregnant females in 4 US cities, perceived discrimination (self-reported as based on sex, race, income level or social status, age, and physical appearance) was associated with development of gestational diabetes. Gestational diabetes occurred in 12.8% of females in the top quartile of a self-reported discrimination scale versus 7.0% in all others (aOR, 2.11 [95% CI, 1.03–4.22], adjusted for age, income, parity, race and ethnicity, and study site); 22.6% of this association was statistically mediated by obesity.<sup>56</sup>

### Genetics/Family History

- Although gestational diabetes is thought to be heritable, estimates for gestational diabetes from twin or familial clustering studies are not available. Korean females with gestational diabetes had a greater parental history of type 2 diabetes compared with pregnant females with normal glucose tolerance (13.2% versus 30.1%;  $P<0.001$ ).<sup>57</sup>
- Many of the genetic risk factors for type 2 diabetes overlap with those for gestational diabetes (see Chapter 10 [Metabolic Syndrome] for genetics/family history of MetS and type 2 diabetes). For example, in a cohort of 283 Danish females 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.<sup>58</sup>
- In a case-control study of 2636 females with gestational diabetes and 6086 females 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]).<sup>59</sup>

- Association of diabetes GRS with gestational diabetes is consistent in other ancestries; in a study of 832 South Asian females from the START and UK Biobank cohorts, a diabetes GRS optimized to South Asian ancestry was associated with gestational diabetes (OR, 2.51 [95% CI, 1.82–3.47];  $P=1.75\times 10^{-8}$ ; and OR, 2.66 [95% CI, 1.51–4.63];  $P=0.0006$ , respectively, for the top 25% of GRS compared with the bottom 75%).<sup>60</sup>
- Genetic discovery studies to identify gestational diabetes risk variants have identified primarily known diabetes genetic variants. For example, a GWAS of gestational diabetes in a discovery cohort of 468 Korean females with gestational diabetes and 1242 females 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;  $P=6.7\times 10^{-16}$ ; and a variant near *MTNR1B*: OR, 1.45;  $P=2.5\times 10^{-13}$  in joint analyses).<sup>61</sup> In a meta-analysis of 14 candidate gene and GWAS studies, *MTNR1B* was most strongly associated with gestational diabetes (OR, 1.24 [95% CI, 1.19–1.29]).<sup>62</sup>

### 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).<sup>63</sup>

### Complications: Maternal Cardiovascular Risk Factors, Subclinical CVD, and CVD

- Among females in CARDIA 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];  $P=0.01$ ),<sup>64</sup> and adverse cardiac structure and function were higher in >20 years of follow-up.<sup>65</sup>
- In a meta-analysis of 20 studies that included 1 332 373 individuals, the RR for diabetes was estimated as 10 times higher (95% CI, 7.14–12.67) in females with a history of gestational diabetes compared with females without gestational diabetes.<sup>66</sup>
- Among 1133 females without diabetes at baseline in CARDIA, the risk of CAC was consistently higher among females with a history of gestational diabetes, even among those with normoglycemia in follow-up (aHR, 2.34 [95% CI, 1.34–4.09] with gestational diabetes/normoglycemia in follow-up; aHR, 2.13 [95% CI, 1.09–4.17] for gestational diabetes/prediabetes in follow-up; and aHR, 2.02 [95% CI, 0.98–4.19] for gestational diabetes/incident diabetes).<sup>67</sup>

- 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.<sup>46</sup>

### Complications: Offspring Morbidity and Mortality

- 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.<sup>68</sup> 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]).<sup>69</sup>
- 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]).<sup>70</sup> 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.

## Preterm Birth

### Incidence, Prevalence, and Secular Trends

#### (See Chart 11-5)

- In 2016, PTB accounted for 9.9% of all births with a similar proportion of PTBs (10.0%) reported in 2018 from a total of 3 791 712 live births (or a birth rate of 11.6 per 1000 population).<sup>71,72</sup>
  - PTB rates were higher among NH Black females (14.1%) compared with NH White (9.1%) and Hispanic (9.7%) females in 2018 (Chart 11-5).<sup>72</sup>
- Among all singleton deliveries at a single US tertiary care center, compared with the overall PTB rate before the COVID-19 pandemic (11.1% among 17 687 deliveries from January 1, 2018–January 31, 2020), the rate was significantly lower during the pandemic (10.1% among 5396 deliveries from April 1, 2020–October 27, 2020;  $P=0.039$  for comparison); spontaneous PTB rates also decreased during the pandemic (from 5.7% to 5.0%;  $P=0.074$ ). However, decreases in spontaneous PTB occurred only among females from more (versus less) advantaged neighborhoods (from 4.4% to 3.8% versus from 7.2% to 7.4%), White (versus Black) females (from 5.6% to 4.7%, versus from 6.6% to 7.1%), and females receiving care from clinics that do not

(versus do) provide prenatal care to those eligible for Medical Assistance (from 5.5% to 4.8% versus from 6.3% to 6.7%).<sup>73</sup>

### Risk Factors (Including Social Determinants)

- In a meta-analysis of studies reported between December 2019 and June 2020, maternal COVID-19 infection (versus no COVID-19 infection) was associated with higher odds of PTB (OR, 3.0 [95% CI, 1.15–7.85]); the rates among COVID-19–infected females were 17% (95% CI, 13%–21%) for overall PTB and 6% (95% CI, 3%–9%) for spontaneous PTB.<sup>74</sup> In another US study using a surveillance database, among 4442 pregnant females with COVID-19 from March to October 2020, the PTB rate was 12.9%; this was higher than the rate in the general population in 2019 (10.2%).<sup>75</sup>
- 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) PTB were elevated even with mild stage 1 hypertension (SBP from 130–135 mmHg or DBP from 80–85 mmHg; 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]).<sup>76</sup>
- Among 8259 pregnant females in the nuMoM2b cohort, periconceptional dietary quality was associated with PTB risk. The PTB rate was 9.5% for females in the lowest quartile (poorest quality) of the HEI-2010 compared with 6.9% for females in the highest quartile (aRR, 1.27 [95% CI, 1.01–1.60]).<sup>22</sup>
- In a meta-analysis of 6 studies, objectively measured SDB (OSA) was associated with a higher risk of PTB, with an aOR of 1.6 (95% CI, 1.2–2.2).<sup>77</sup>

### Environmental Exposures

- In a systematic review of studies examining air pollution, significant associations were found with PTB for 19 of 24 studies (examining a total of >7 million births). The risk was higher by a median of 11.5% (range, 2.0%–19.0%) for whole-pregnancy PM<sub>2.5</sub> exposure per IQR higher exposure, and risk was greater among NH Black females compared with NH White females.<sup>78</sup>
- In a systematic review, 4 of 5 studies (>800 000 births) examining heat demonstrated that risk for PTB was higher by a median of 15.8% (range, 9.0%–22.0%) for whole-pregnancy heat exposure per 5.6°C higher weekly mean temperature.<sup>78</sup> Similarly, in a meta-analysis of 47 studies including international populations, the odds of PTB were 1.05 times higher (95% CI, 1.03–1.07) per 1°C higher environmental temperature and were 1.16 times higher (95% CI, 1.10–1.23) during heat waves (defined in this analysis as ≥2 days with temperatures ≥90th percentile).<sup>79</sup>

- In a meta-analysis of 4 studies, more favorable environmental characteristics such as access to green space or greater environmental greenness (based on a standardized measure commonly used to indicate presence and level of green space: normalized difference vegetation index) within a 100-m buffer were associated with a lower risk for PTB (pooled standardized OR, 0.98 [95% CI, 0.97–0.99]).<sup>80</sup>

### Race and Ethnicity

- Among 9470 nulliparous pregnant females (60.4% NH White, 13.8% NH Black, 16.7% Hispanic, 4.0% Asian, 5.0% other), PTB 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]).<sup>23</sup> 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 PTB was 1.21 (95% CI, 1.01–1.44).
- Examination of state Medicaid expansion noted an association with improvement in relative disparities between Black people and White people in rates of PTB 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 for Black infants compared with White infants.<sup>81</sup>
- Black-White disparities in PTB are also present among females of high SES; among 2 170 686 singleton live births in the United States from 2015 to 2017 to college-educated females with private insurance who were not receiving Women, Infants, and Children benefits, PTB rates for females who identified as NH White, mixed NH White/Black, and NH Black were 5.5% versus 6.1% versus 9.9% for PTB at <37 weeks' gestation and 0.2% versus 0.4% versus 1.2% for PTB at <28 weeks' gestation, respectively.<sup>82</sup>

### Social Determinants

- Among infants born to females who were evicted in Georgia from 2000 to 2016, eviction during gestation (versus infants born to females who experienced an eviction before they were pregnant) was associated with 1.14 (95% CI, 0.21–2.06) percentage points higher rate of PTB after covariate adjustment (crude rates, 15.28% versus 13.36%, respectively).<sup>83</sup>
- In a cohort of 3801 females with 9075 live singleton births, latent class analysis revealed a stress/

anxiety/depression class that was associated with increased risk for PTB (OR, 1.87 [95% CI, 1.20–2.30]).<sup>84</sup>

### Genetics/Family History

- Heritability estimates for birth weight and length of gestation range from 25% to 40%.<sup>85</sup> 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%).<sup>86</sup>
- A maternal GWAS of gestational duration and PTB analyzed a discovery set of 43 568 females 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.<sup>87</sup> 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, that was associated with gestational duration.<sup>88</sup>
- An international study that evaluated haplotype genetic scores known to be associated with adult height, BMI, BP, blood glucose, and type 2 diabetes in 10 734 female-infant duos of European ancestry found that taller genetic maternal height was associated with longer gestational duration (0.14 d/cm [95% CI, 0.10–0.18];  $P=2.2 \times 10^{-12}$ ), lower PTB risk (OR, 0.7/cm [95% CI, 0.96–0.98];  $P=2.2 \times 10^{-9}$ ), and higher birth weight (15 g/cm [95% CI, 13.7–16.3];  $P=1.5 \times 10^{-11}$ ).<sup>89</sup> Genetically determined maternal BMI was associated with higher birth weight (15.6 g/[kg/m<sup>2</sup>] [95% CI, 13.5–17.7];  $P=1.0 \times 10^{-47}$ ) but not gestational duration or PTB risk.

### Complications: Maternal CVD and Mortality

- 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]).<sup>90</sup>
- 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.<sup>91</sup>
- In a separate study from the Swedish national birth registry among 2 189 190 females with singleton delivery from 1973 to 2015, the aHR for IHD for females who experienced PTB was 2.47 (95% CI, 2.16–2.82) in the 10 years after delivery, 1.86 (95% CI, 1.73–1.99) in the 10 to 19 years after



delivery, 1.52 (95% CI, 1.45–1.59) in the 20 to 29 years after delivery, and 1.38 (95% CI, 1.32–1.45) in the 30 to 43 years after delivery.<sup>92</sup>

- 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.<sup>46</sup>
- Among 2 189 477 females with a singleton delivery in 1973 to 2015, risk of all-cause mortality was higher among those with PTB (<37 weeks' gestational age) with an aHR of 1.73 (95% CI, 1.61–1.87) in the 10 years after delivery; a dose-dependent relationship was observed with higher risk based on delivery at earlier gestational ages (extremely preterm, 22–27 weeks: 2.20 [95% CI, 1.63–2.96]; very preterm, 28–33 weeks: 2.28 [95% CI, 2.01–2.58]; late preterm delivery, 34–36 weeks: 1.52 [95% CI, 1.39–1.67]; early term, 37–38 weeks: 1.19 [95% CI, 1.12–1.27]) compared with full-term delivery between 39 and 41 weeks.<sup>93</sup>

### Complications: Offspring Morbidity and Mortality

- In a meta-analysis of 4 cohort studies, PTB was associated with increased risk for MetS (pooled OR, 1.72 [95% CI, 1.12–2.65]).<sup>94</sup>
- In analyses of Swedish national birth register data (>2 million → 4 million individuals), gestational age at birth was inversely associated with the risks for type 1 diabetes (aHR, 1.21 [95% CI, 1.14–1.28] at <18 years of age and 1.24 [95% CI, 1.13–1.37] at 18–43 years of age), type 2 diabetes (aHR, 1.26 [95% CI, 1.01–1.58] at <18 years of age and 1.49 [95% CI, 1.31–1.68] at 18–43 years of age), hypertension (aHR, 1.24 [95% CI, 1.15–1.34] at <18 years of age, 1.28 [95% CI, 1.21–1.36] at 18–29 years of age, and 1.25 [95% CI, 1.18–1.31] at 30–43 years of age), and lipid disorders (aHR, 1.23 [95% CI, 1.16–1.29] at 0–44 years of age) among individuals born preterm versus term.
  - In cosibling analyses, associations remained significant for type 1 and 2 diabetes but were largely attenuated for hypertension and lipid disorders (suggesting that shared familial genetic and lifestyle risk factors for PTB and hypertension or lipid disorders accounted for much of their associations).<sup>95–97</sup>

### Cardiac Remodeling and HF

- In a 2020 meta-analysis of 32 studies, individuals born preterm had higher LV mass (increase versus controls of 0.71 g/m<sup>2</sup> [95% CI, 0.20–1.22] per year from childhood), smaller LV diastolic dimension (percent WMD in young adulthood, –4.9%;  $P=0.006$ ), lower LV stroke volume index (percent WMD in young adulthood, –8.2%;  $P<0.001$ ), poorer LV diastolic function (e' percent WMD in childhood/young adulthood, –5.9%;  $P<0.001$ ), and poorer RV

systolic function (longitudinal strain percent WMD, –14.3%;  $P<0.001$ ) compared with term-born individuals.<sup>98</sup>

- In a study of 4 193 069 individuals born in Sweden during 1973 through 2014, PTB was associated with higher risk of HF at <1 year of age (aHR, 4.49 [95% CI, 3.86–5.22]), 1 to 17 years of age (aHR, 3.42, [95% CI, 2.75–4.27]), and 18 to 43 years of age (aHR, 1.42 [95% CI, 1.19–1.71]) compared with individuals born full-term; a dose-dependent relationship with prematurity was observed with further stratification in the group 18 to 43 years of age with highest risk for HF among those born extremely preterm (22–27 weeks; HR, 4.72 [95% CI, 2.75–4.27]).<sup>99</sup>
- Among 2 613 030 individuals without congenital malformations born in Sweden from 1987 to 2012 with median follow-up 13.1 years, gestational age at birth was inversely associated with risk of early-onset HF (median age at diagnosis, 16.5 years [IQR, 5.2–19.7 years]). Incidence rates were 1.34 per 100 000 person-years for ≥37 weeks of gestational age (referent), 2.32 for 3 to 36 weeks (aRR, 1.54 [95% CI, 1.11–2.12]), 4.71 for 28 to 31 weeks (aRR, 2.60 [95% CI, 1.33–5.08]), and 20.1 for <28 weeks (aRR, 12.9 [95% CI, 7.06–23.7]).<sup>100</sup>

### CVD and Mortality

- Among 1 306 943 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]).<sup>101</sup>
- 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 (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]).<sup>102</sup> Cosibling analyses supported an association that was independent of familial shared genetic and environmental factors.
- Among 4 296 814 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.<sup>103</sup> Relative to full-term birth (39–41 weeks), PTB (<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]).

## SGA Delivery

### *Incidence, Prevalence, and Secular Trends*

#### *(See Chart 11-6)*

- The percentage of LBW (defined as delivered at <2500 g) deliveries was 8.3% for 2017 to 2018, which has increased slightly since 2014 (8.0%). Prevalence of LBW by race is shown in Chart 11-6.<sup>104</sup>

### *Risk Factors (Including Social Determinants)*

- 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 of 130–135 mm Hg or DBP of 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 Hypertension Clinical Practice Guidelines.<sup>76</sup>
- In an individual participant data meta-analysis of 265 270 births from 39 cohorts in Europe, North America, and Australia, prepregnancy overweight BMI (BMI <18.5 kg/m<sup>2</sup>; OR, 1.67 [95% CI, 1.58–1.76]) was associated with higher risks for SGA delivery.<sup>5</sup> 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).
- Among 8259 pregnant females in the nuMoM2b cohort, periconceptional dietary quality was associated with risks for SGA (birth weight <10th percentile for gestational age) and LBW (<2500 g). The SGA and LBW rates were 12.8% and 7.7%, respectively, for females in the lowest quartile (poorest quality) of the HEI-2010 compared with 9.5% and 5.4% for females in the highest quartile (aRRs, 1.24 [95% CI, 1.02–1.51] and 1.32 [95% CI, 1.02–1.71], respectively).<sup>22</sup>
- Among 3435 females in a health system with routine urine toxicology screening at the first prenatal visit, cannabis exposure (detected in 8.2% of females) was associated with SGA delivery, with an aRR of 1.69 (95% CI, 1.22–2.34) after adjustment for maternal race and ethnicity, prepregnancy BMI, age, and cigarette smoking. In stratified analyses,

the aRR for SGA associated with cannabis exposure was 1.42 (95% CI, 0.32–2.15) in females who did not also smoke cigarettes and 2.38 (95% CI, 1.35–4.19) in females who also smoked cigarettes during pregnancy.<sup>105</sup>

### *Environmental Exposures*

- In a systematic review of studies examining associations of air pollution, significant associations were found with LBW for 25 of 29 studies (examining a total of >18 million births) in the United States.<sup>78</sup>
- The median risk was 10.8% higher (range, 2.0%–36.0%) for whole-pregnancy PM<sub>2.5</sub> exposure per IQR greater exposure, and in 1 study, risk was higher by 3% for each 5-km closer proximity to a solid waste plant.<sup>78</sup>
- In a systematic review examining heat, 3 of 3 studies (2.7 million births) demonstrated the median risk for LBW was 31.0% higher (range, 13.0%–49.0%) for whole-pregnancy heat exposure per 5.6°C higher weekly mean temperature, and in 1 study, whole-pregnancy ambient local temperature >95th percentile was associated with an RR of 2.49 (95% CI, 2.20–2.83).<sup>78</sup>
- In a meta-analysis of 5 studies, more favorable environmental characteristics such as greater access to green space or greater environmental greenness (based on a standardized measure commonly used to indicate presence and level of green space: normalized difference vegetation index) within a 100- to 500-m buffer was associated with lower risk for LBW or SGA (pooled standardized OR, 0.94 [95% CI, 0.92–0.97]).<sup>80</sup>

### *Race and Ethnicity*

- Among 9470 nulliparous pregnant females in the nuMoM2b study (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]).<sup>23</sup> 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 the lowest quartile of perceived social support compared with the upper 3 quartiles).
- Among >23 million singleton live births in the United States, the excess risks of intrauterine growth restriction and SGA related to race and ethnicity were partly mediated by the adequacy of

prenatal care: 13%, 12%, and 10% for intrauterine growth restriction and 7%, 6%, and 5% for SGA among Black, Hispanic, and other race and ethnicity females, respectively, compared with White females.<sup>106</sup>

- Examination of state Medicaid expansion noted an association with improvement in relative disparities between Black people and White people in rates of infants with LBW among states that expanded compared with those that did not. Difference-in-difference models between 2011 and 2016 estimated a decline of  $-0.53$  percentage points (95% CI,  $-0.96$  to  $-0.10$ ) for LBW for Black infants compared with White infants.<sup>81</sup>

### Social Determinants

- Among infants born to females who were evicted in Georgia from 2000 to 2016, eviction during gestation (versus infants born to females who experienced an eviction before they were pregnant) was associated with 0.88 (95% CI, 0.23–1.54) percentage points higher rate of LBW (<2500 g) after covariate adjustment (crude rates, 11.59% versus 10.24%, respectively).<sup>83</sup>

### Complications: Maternal CVD

- There is limited weak evidence for a relationship between infant birth weight and maternal CVD, which may be attributable in part to heterogeneity in definitions of LBW and SGA. In a meta-analysis examining 4 studies that defined LBW (<2500 g at term), females with a history of an infant with LBW 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 (OR, 1.29 [95% intrinsic CI, 0.91–1.83]), but there was significant between-study heterogeneity.<sup>46</sup>
- In data from 11 110 females in the prospectively collected Vasterbotten Intervention Program and population-based registries in Sweden, LBW 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 LBW did not improve risk reclassification for CVD in prediction models.<sup>107</sup>

### Complications: Offspring Morbidity and Mortality

- In a meta-analysis of 6 cohort studies, LBW was associated with higher risk for MetS in either childhood or adulthood (pooled OR, 1.79 [95% CI, 1.39–2.31]).<sup>94</sup>
- Among 4 193 069 individuals born in Sweden during 1973 to 2014, SGA birth (weight <10th percentile for gestational age) was associated with

risk for type 2 diabetes; aHRs were 1.61 (95% CI, 1.38–1.89) at <18 years of age and 1.79 (95% CI, 1.65–1.93) at 18 to 43 years of age.<sup>95</sup>

- A 2018 meta-analysis examined associations between birth weight and adult cardiometabolic outcomes.<sup>108</sup>
  - 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 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.
  - 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.
- 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).<sup>109</sup>

## Pregnancy Loss

### Incidence, Prevalence, and Secular Trends

#### (See Charts 11-7 and 11-8)

- In 2013, the stillbirth ( $\geq 20$  weeks' gestation) rate in the United States was 5.96 per 1000 live births and fetal deaths, with relative stability since 2006.<sup>110</sup>
  - Stillbirth rates were highest among NH Black females (10.53), intermediate among American Indian or Alaska Native females (6.22) and Hispanic females (5.22), and lowest among NH White (4.88) and Asian or Pacific Islander (4.68) females.
  - Stillbirth rates were highest for females <15 years of age (15.88) and  $\geq 45$  years of age (13.76) and were lowest among females 25 to 29 years of age (5.34).
  - Geographic differences were observed in stillbirth rates (analyzed for  $\geq 24$  weeks' gestation),

with the highest rates in Alabama (6.02) and Mississippi (5.87) and the lowest rates in New Mexico (2.62).

- Fetal mortality rates declined between 2000 and 2006 but were stagnant between 2006 and 2012 (Chart 11-7).
- Between 2014 and 2016, stillbirth or late fetal death (at  $\geq 28$  weeks' gestation) was unchanged (2.88 in 2016 versus 2.83 in 2014 per 1000 live births and fetal deaths; Chart 11-8).<sup>111</sup>

### Risk Factors (Including Social Determinants)

- Maternal cardiovascular risk factors, including diabetes (6–35 per 1000 live births and stillbirths), chronic hypertension (6–25 per 1000 live births and stillbirths), prepregnancy obesity (13–18 per 1000 live births and stillbirths), and smoking (10–15 per 1000 live births and stillbirths), as well as exposure to secondhand smoke, are associated with increased risk of stillbirth compared with total population rates (6.4 per 1000 live births and stillbirths).<sup>112</sup>
- 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  $\geq 10$  weeks) in a meta-analysis of 212 184 females (including 770 with antiphospholipid syndrome) from 8 studies.<sup>113</sup>
- In a systematic review of studies examining associations of air pollution in US populations, significant associations with stillbirth risk were found for 4 of 5 studies (examining a total of  $> 5$  million births) in which the median risk for stillbirth was 14.5% higher (range, 6.0%–23.0%) for whole-pregnancy PM<sub>2.5</sub> exposure per IQR greater exposure, and risk was higher by 42% (95% CI, 6%–91%) with high third-trimester PM<sub>2.5</sub> exposure.<sup>78</sup>
- In a systematic review of 2 US studies ( $> 200\,000$  births) examining heat, the risk for stillbirth was 6% higher per 1°C higher ambient temperature the week before delivery during the warm season.<sup>78</sup> Similarly, in a separate meta-analysis of 8 studies (including international populations), the odds of stillbirth were 1.05 times higher (95% CI, 1.01–1.08) per 1°C higher environmental temperature.<sup>79</sup>
- Contrasting findings have been noted for rates of stillbirth before and during the COVID-19 pandemic. At 1 hospital in London, UK, that examined 1681 births before the pandemic and 1718 births during the pandemic, the incidence of stillbirth was 9.31 per 1000 births compared with 2.38 per 1000 births.<sup>114</sup> However, in a follow-up study from the National Health Service in England, there was no change in stillbirth deliveries (4.1 per 1000 live births [95% CI, 3.8–4.5] versus 4.0 per 1000 live births [95% CI, 3.7–4.4]) between April 1, 2020,

and June 30, 2020, compared with the same period in 2019 (IRR, 1.02 [95% CI, 0.91–1.15]).<sup>115</sup>

### Genetics/Family History

- The heritability of any pregnancy loss has been reported at 29% (95% CI, 20%–38%) for any miscarriage.<sup>116</sup>
- 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 females  $\geq 35$  years of age with recurrent pregnancy loss versus 70% in females with nonrecurrent pregnancy loss).<sup>117</sup>
- Fetal single-gene disorders may also play a role in recurrent pregnancy loss; for example, 1 study found that 3.3% of stillbirths carried pathogenic variants in LQTS genes compared with a prevalence of  $< 0.05\%$  in the general population.<sup>118</sup>
- A study to identify novel genetic risk factors for recurrent pregnancy loss analyzed rare variants using whole-exome sequencing in 75 females with either recurrent pregnancy loss or lack of achieving clinical pregnancy and identified presence of rare variants in 13% of the females with recurrent pregnancy loss.<sup>119</sup>
- In a GWAS of 69 054 females with sporadic pregnancy loss, 750 females with recurrent pregnancy loss, and 359 469 controls, only 1 genome-wide significant variant was found for sporadic pregnancy loss (OR, 1.4 [95% CI, 1.2–1.6];  $P=3.2 \times 10^{-8}$ ), and 3 were found for recurrent pregnancy loss (OR, 1.7–3.8), including variants in *FGF9*, *TLE1*, *TLE4*, *E2F8*, and *SIK1*.<sup>116</sup>

### 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.<sup>120</sup>
- In 79 121 postmenopausal females from the WHI,  $\approx 35\%$  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.<sup>121</sup>

### Health Care Use

- 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/LBW.

- 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/LBW.
- 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]).<sup>122</sup>

## 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.<sup>123</sup>

## Global Burden

### (See Charts 11-9 and 11-10)

- According to WHO data from 2013, an estimated 20 million infants with LBW globally are born every year.<sup>124</sup>
- 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 infants who were SGA in low- and middle-income countries that were concentrated in South Asia.<sup>125</sup>
- In an analysis of data from the WHO Global Survey for Maternal and Perinatal Health (conducted in African, Latin American, and Asian countries), higher risks for gestational hypertension (aOR among nulliparous females, 1.56 [95% CI, 0.94–2.58] and among multiparous females, 1.73 [95% CI, 1.25–2.39]) were observed for females with

severe anemia (hemoglobin <7 mg/dL) at delivery compared with females with hemoglobin ≥7 mg/dL at delivery; the risk for preeclampsia/eclampsia was also higher with severe anemia (hemoglobin <7 mg/dL) at delivery compared with hemoglobin ≥7 mg/dL at delivery (aOR among nulliparous females, 3.74 [95% CI, 2.90–4.81] and among multiparous females, 3.45 [95% CI, 2.79–4.25]).<sup>126</sup>

- 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' gestation 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.<sup>127</sup>
- Based on data from 204 countries in the 2020 GBD study, the global incidence of maternal hypertensive disorders is shown in Chart 11-9. Incidence of maternal hypertensive disorders was highest throughout sub-Saharan Africa. The incidence of maternal hypertensive disorders among females 15 to 49 years of age was 17.89 (95% UI, 15.17–21.34) million cases with an average rate of 916.72 (95% UI, 777.29–1093.49) per 100 000 female population 15 to 49 years of age. (Data courtesy of the GBD Study.)
- Based on data from the 2020 GBD study, global incidence of neonatal PTBs is shown in Chart 11-10. The highest rates of neonatal PTB were found in South Asia, followed by the Caribbean, Oceania, and some parts of North Africa, the Middle East, and sub-Saharan Africa. The incidence of neonatal PTBs was 21.62 (95% UI, 21.60–21.63) million cases with an average rate of 17 198.15 (95% UI, 17 183.86–17 212.03) per 100 000 births. (Data courtesy of the GBD Study.)



**Table 11-1. Unadjusted Prevalence of Preexisting Diabetes and Gestational Diabetes Among Females 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	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 females within a characteristic group (eg, age group) might not sum to the total number of females because of missing information.

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

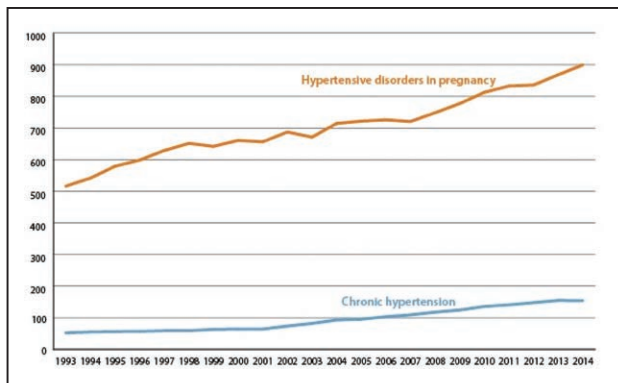
§Prepregnancy BMI was classified as underweight (BMI <18.5 kg/m<sup>2</sup>), normal weight (BMI, 18.5–24.9 kg/m<sup>2</sup>), overweight (BMI, 25.0–29.9 kg/m<sup>2</sup>), obesity class 1 (BMI, 30.0–34.9 kg/m<sup>2</sup>), obesity class 2 (BMI, 35.0–39.9 kg/m<sup>2</sup>), and obesity class 3 (BMI ≥40.0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

Source: Data derived from Table 1 of Deputy et al.<sup>53</sup>

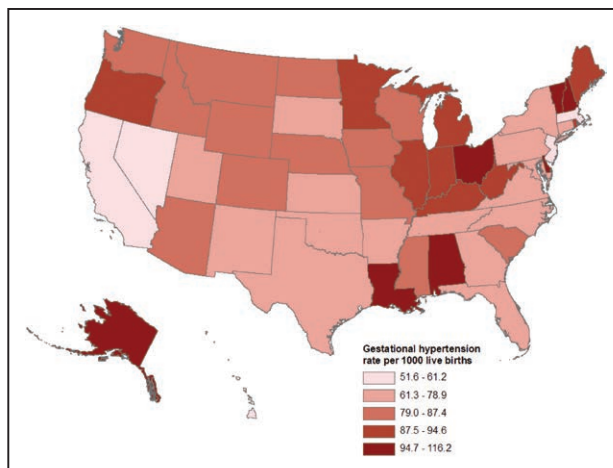
Pre-Pregnancy Body Mass Index Category	Gestational Weight Gain Category		
	Low (≤ 1.1 SD)	Medium (-1.0 to 0.9 SD)	High (≥1.0 SD)
Underweight	1.09 (0.94 – 1.26)	1.04 (0.96 – 1.12)	1.13 (0.98 – 1.30)
Normal weight	1.04 (1.01 – 1.08)	Referent	1.10 (1.06 – 1.14)
Overweight	1.23 (1.16 – 1.32)	1.38 (1.33 – 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 APO, by prepregnancy BMI and 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 (birth weight >90th percentile) size for sex, and gestational age at birth. Prepregnancy BMI categories are as follows: underweight, <18.5 kg/m<sup>2</sup>; normal weight, 18.5 to 24.9 kg/m<sup>2</sup>; overweight, 25.0 to 29.9 kg/m<sup>2</sup>; and obesity, ≥30 kg/m<sup>2</sup>. GWG values corresponding to the SD cutoffs were not provided by the source, but the median GWG was 14.0 kg (95% CI, 3.9–27.0 kg). APO indicates adverse pregnancy outcome; BMI, body mass index; and GWG, gestational weight gain.  
Source: Data derived from Santos et al.<sup>5</sup>

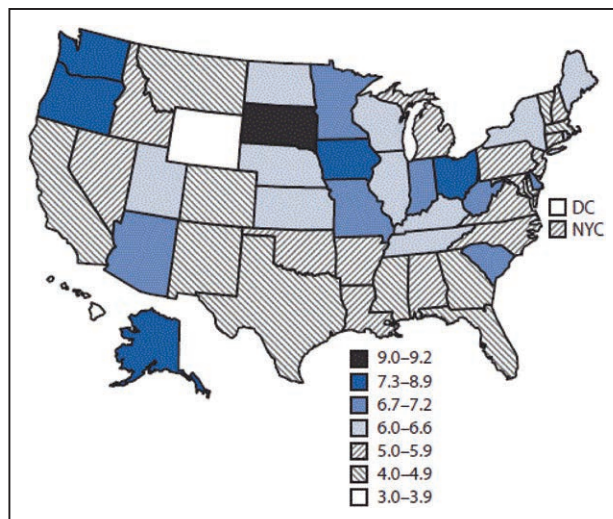


**Chart 11-2. Trends in the rates of hypertensive disorders per 10000 delivery hospitalizations, United States, 1993 to 2014.**  
Source: Reprinted from Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion.<sup>13</sup>



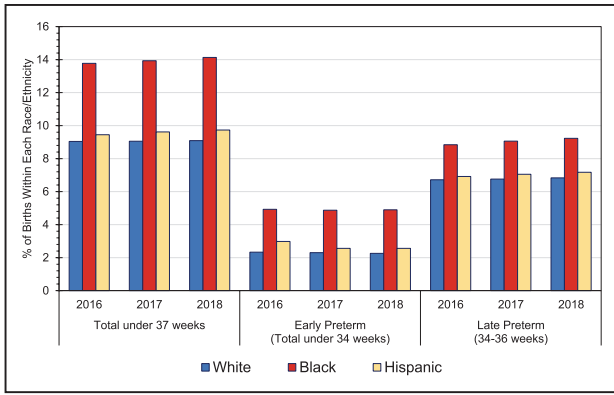
**Chart 11-3. State-level rates of de novo hypertension in pregnancy per 1000 live births, United States, 2019.**

Unadjusted rates are calculated for each state based on 3736 144 females 15 to 44 years of age with a live birth.  
Source: Unpublished map using CDC WONDER.<sup>129</sup>



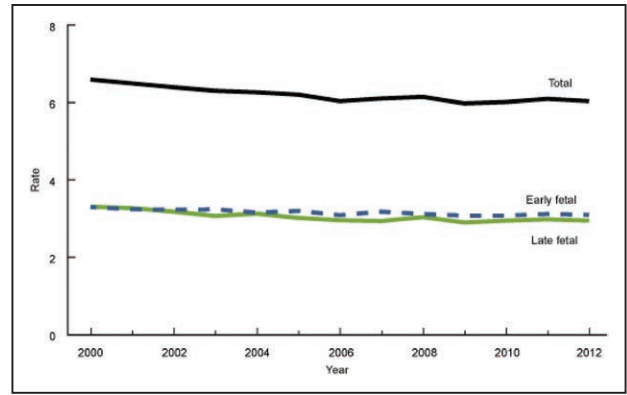
**Chart 11-4. Standardized\* prevalence of gestational diabetes among females who had a live birth, by state, United States, 2016.**

NYC indicates New York City.  
\*Standardized to age and race and ethnicity distribution of US resident females with a live birth in 2012.  
Source: Reprinted from Deputy et al.<sup>53</sup>



**Chart 11-5. Trends in the rates of preterm birth by gestational age (weeks) in the United States by maternal race and ethnicity, 2016 to 2018.**

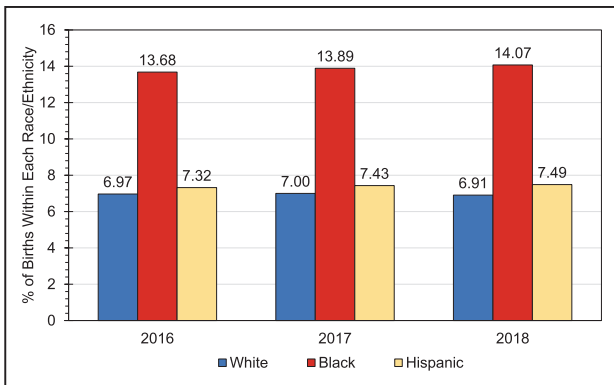
Source: Data derived from Martin et al.<sup>104</sup>



**Chart 11-7. Total, early, and late fetal mortality rates, United States, 2000 to 2012.**

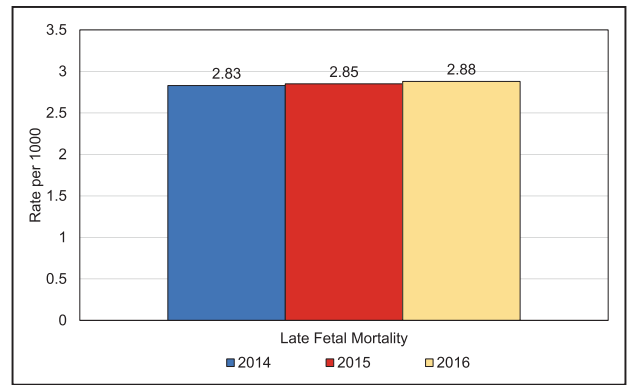
Total fetal mortality rate is the number of fetal deaths at  $\geq 20$  weeks of gestation per 1000 live births and fetal deaths. Early fetal mortality rate is the number of fetal deaths at 20 to 27 weeks per 1000 live births and fetal deaths at 20 to 27 weeks. Late fetal mortality rate is the number of fetal deaths at  $\geq 28$  weeks of gestation per 1000 live births and fetal deaths at  $\geq 28$  weeks of gestation.

Source: Reprinted from Gregory et al.<sup>130</sup>



**Chart 11-6. Trends in the rates of infants with low birth weight (<2500 g) in the United States, by race and ethnicity of females with a live birth, 2016 to 2018.**

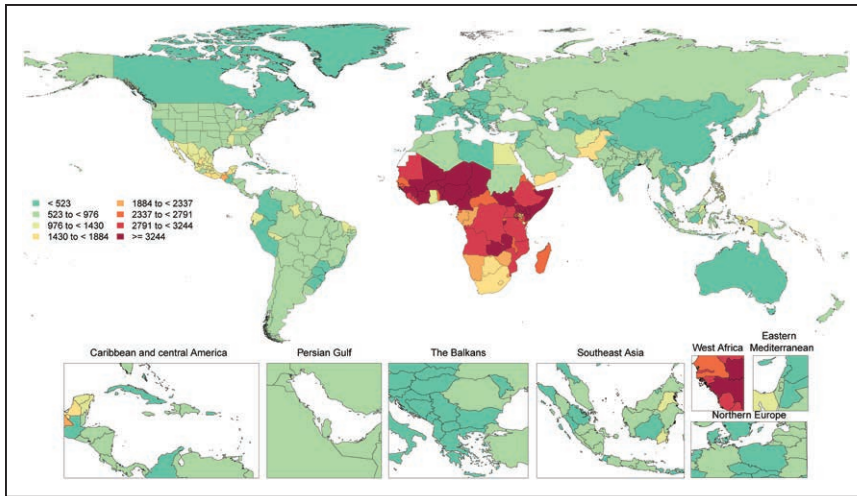
Source: Data derived from Martin et al.<sup>104</sup>



**Chart 11-8. Late fetal mortality rates, United States, 2014 to 2016.**

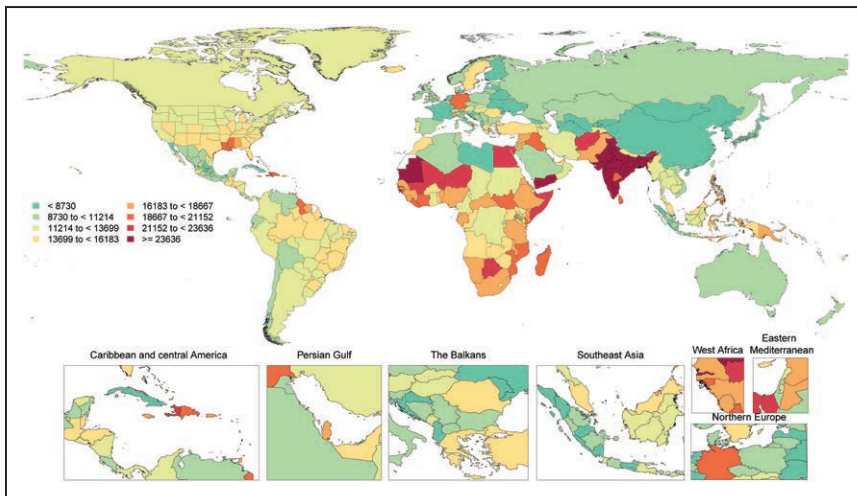
Late fetal mortality rate is the number of fetal deaths at  $\geq 28$  weeks of gestation per 1000 live births and fetal deaths at  $\geq 28$  weeks of gestation.

Source: Data derived from Gregory et al.<sup>111</sup>



**Chart 11-9. Global incidence rates of maternal hypertensive disorders per 100 000 females, 15 to 49 years of age, 2020.**

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. Additional information is available on the Global Burden of Disease Study website.<sup>131</sup>



**Chart 11-10. Global incidence rates of neonatal preterm births per 100 000, both sexes, at birth, 2020.**

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. Additional information is available on the Global Burden of Disease Study website.<sup>131</sup>



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## 12. KIDNEY DISEASE

ICD-10 N18.0. See Charts 12-1 through 12-11

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### Definition

(See Chart 12-1)

CKD, defined as reduced eGFR ( $<60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$ ), excess urinary albumin excretion (ACR  $\geq 30 \text{ mg/g}$ ), 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.<sup>1</sup>

- eGFR is usually determined from serum creatinine level with equations that account for age, sex, and race. Given that race is a social construct and its inclusion in eGFR equations may perpetuate bias by wrongly ascribing biological differences to race, efforts are underway to re-evaluate the use of race in eGFR equations and the impact on CKD identification and outcomes.<sup>2-4</sup>
- 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).<sup>5,6</sup>
- ESRD is defined as severe CKD requiring long-term kidney replacement therapy such as hemodialysis, peritoneal dialysis, or kidney transplantation.<sup>6</sup> Individuals with ESRD are an extremely high-risk population for CVD morbidity and mortality.

### Prevalence

(See Charts 12-1 through 12-3)

- With the use of data from NHANES 2015 to 2018, 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  $<60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$  or ACR  $\geq 30 \text{ mg/g}$ ; shown

in yellow, orange, and red in Chart 12-1) in 2015 to 2018 was 14.9%.<sup>1</sup>

- The overall prevalence of CKD increases substantially with age, with 9% of adults  $<65$  years of age and 38.6% of adults  $\geq 65$  years of age having CKD in 2015 to 2018.<sup>1</sup>
- According to NHANES 2015 to 2018, the prevalence of ACR  $\geq 30 \text{ mg/g}$  was 12.4% for NH Black adults, 10.2% for Hispanic adults, and 9.4% for NH White adults. In contrast, the prevalence of eGFR  $<60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$  was lowest among Hispanic adults (3.0%) followed by NH Black adults (6.4%) and NH White adults (8.4%).<sup>1</sup>
- In 2018, the age-, race-, and sex-adjusted prevalence of ESRD in the United States was 2242 per million people.<sup>1</sup>
- ESRD prevalence varied by race and ethnicity (Chart 12-2). In 2018, ESRD prevalence was highest in Black adults followed by American Indian/Alaska Native adults, Asian adults, and White adults. ESRD prevalence also was higher among Hispanic people than among NH people.
- Among those with prevalent ESRD, the use of in-center hemodialysis was highest among those  $\geq 75$  years of age (80.2%) and lowest among those  $<18$  years of age (15.0%). In contrast, peritoneal dialysis was highest among those  $<18$  years of age (13.7%) and lowest among those  $\geq 75$  years of age (6.4%).<sup>1</sup>
  - In 2018, 12.5% of all patients on dialysis used home dialysis, although this varied geographically with higher use in the West and Midwest (Chart 12-3).

### Incidence

(See Chart 12-4)

- For US adults 30 to 49, 50 to 64, and  $\geq 65$  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.<sup>7</sup>
- According to 2019 data from the Veterans Affairs Health System, the CKD incidence rate (categories 3–5) increased with age. The incidence rate per 1000 patient-years was 1.2 (20–29 years of age), 3.2 (30–39 years of age), 11.4 (40–49 years of age), 26.7 (50–59 years of age), 59.8 (60–69 years of age), and 113.5 ( $\geq 70$  years of age).<sup>8</sup>
- In 2018, the age-, race-, and sex-adjusted incidence of ESRD was 374.8 per million, an increase of 0.2% from the previous year. The incidence of ESRD was highest among Black individuals and lowest among White individuals (Chart 12-4).<sup>1</sup>

The 2022 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 2022. 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.

## Secular Trends

### (See Charts 12-2 and 12-4 through 12-6)

- Among Medicare beneficiaries, the prevalence of CKD (based on coded diagnosis) increased from 1.8% in 1999 to 13.5% in 2018 (Chart 12-5).<sup>1</sup>
- According to NHANES data, the overall prevalence of reduced eGFR and excess ACR across categories was generally similar from 2003 to 2018 (Chart 12-6).<sup>1</sup>
- The prevalence of ESRD increased across most racial and ethnic groups from 2000 to 2018 primarily because of improved survival (Chart 12-2), whereas the incidence rate appeared to stabilize or decrease (Chart 12-4).<sup>1</sup>
  - Disparities in ESRD incidence persisted by sex, race, and ethnicity (Chart 12-4).
- 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.<sup>9</sup>

## Risk Factors

- Many traditional CVD risk factors are also risk factors for CKD, including older age, male sex, HBP, diabetes, smoking, and family history of CVD. In NHANES 2015 to 2018, the prevalence of CKD was 31.9% in adults with HBP, 36.9% in adults with diabetes, and 17.5% in adults with obesity (BMI  $\geq 30$  kg/m<sup>2</sup>).<sup>1</sup>
- 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.<sup>10</sup>
- OSA was associated with increased 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]).<sup>11</sup>
- In the ARIC study, incident hospitalization with any major CVD event (HF, AF, CHD, or stroke) was associated with an increased risk of ESRD (HR, 6.63 [95% CI, 4.88–9.00]). In analyses by CVD event type, the association with ESRD risk was more pronounced for HF (HR, 9.92 [95% CI, 7.14–13.79]) than CHD (HR, 1.80 [95% CI, 1.22–2.66]), AF (HR, 1.10 [95% CI, 0.76–1.60]), and stroke (HR, 1.09 [95% CI, 0.65–1.85]).<sup>12</sup>
- In the Framingham Offspring study, maintaining Life's Simple 7 factors in the intermediate or ideal levels for 5 years was associated with lower risk of incident CKD during a median follow-up of 16 years (HR, 0.75 [95% CI, 0.63–0.89]).<sup>13</sup>

- 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 alternative 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.<sup>14</sup>
- In a meta-analysis of 23 studies, preeclampsia was associated with increased risk of ESRD (RR, 4.90 [95% CI, 3.56–6.74]) and CKD (RR, 2.11 [95% CI, 1.72–2.59]).<sup>15</sup>

## Social Determinants of CKD

- According to NHANES 2015 to 2018, the prevalence of CKD was 19.5% for adults with less than a high school education, 17.2% for those with a high school degree or equivalent, and 13.1% for those with some college or more.<sup>1</sup>
- 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 and ethnicity, and this association was stronger in 2005 to 2010 than 1995 to 2004.<sup>16</sup>
- 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.<sup>17</sup> 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.<sup>18</sup>

## Genetics/Family History

- It is estimated that  $\approx 30\%$  of early-onset CKD is caused by single-gene variants, and several hundred loci have been implicated in monogenic CKD.<sup>19,20</sup>
- GWASs in >1 million individuals have revealed >260 candidate loci for CKD phenotypes, including eGFR and serum urate.<sup>21–24</sup>
- Use of polygenic risk scores based on 35 blood and urine biomarkers measured in >363 000 UK Biobank participants, including renal biomarkers, was found to improve genetic risk stratification for CKD.<sup>25</sup>
- 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.<sup>26</sup> SNPs in *APOL1* that are present in individuals of African ancestry but absent in

other racial groups might have been subjected to positive selection, conferring protection against trypanosome infection but leading to increased risk of renal disease, potentially through disruption of mitochondrial function.<sup>27</sup>

- Although certain variants of *APOL1* increase risk, this explains only a portion of the racial disparity in ESRD risk.<sup>26</sup> 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.<sup>28</sup>
- 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.<sup>29</sup>

### Awareness, Treatment, and Control

- Despite improvements in CKD awareness from 7.2% in NHANES 2003 to 2006 to 12.1% in 2015 in 2018, the vast majority of individuals with kidney disease remain unaware of underlying kidney disease.<sup>1</sup>
- Treatment and control of BP among those with CKD and hypertension improved from 31.1% in 2003 to 2006 to 37.5% in 2015 to 2018.<sup>1</sup>
- In 2015 to 2018, 69% of those with CKD and diabetes had HbA1c <8%, and 11% of them had fasting LDL-C levels <70 mg/dL.<sup>1</sup>
- Among patients with CKD with hypertension, intensive BP <130 mmHg versus standard BP <140 mmHg 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.<sup>30</sup>

### Complications

- DALYs for CKD were 457.25 per 100 000 in 2002 versus 536.85 per 100 000 in 2019.<sup>31</sup>

### Cost

- In 2018, Medicare spent >\$81 billion caring for people with CKD and \$49.2 billion caring for people with ESRD.<sup>1</sup>
- Medicare spending per person per year for beneficiaries with ESRD increased from \$86 939 to \$93 191 for hemodialysis, from \$67 196 to \$78 741 for peritoneal dialysis, and from \$33 613 to \$37 304 for kidney transplantation.<sup>1</sup>
- Medicare expenditures for inpatient care for patients with CKD was \$23.3 billion in 2018, and hospitalizations for infection or cardiovascular causes accounted for 45% of hospitalization costs.<sup>1</sup>

- Total hospitalization expenditures in Medicare fee-for-service beneficiaries with ESRD increased from \$10.4 billion in 2009 to \$11.9 billion in 2018.<sup>1</sup>
- 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).<sup>32</sup>

### Global Burden of Kidney Disease

#### (See Charts 12-7 and 12-8)

- The GBD 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020. (Data courtesy of the GBD study.)
  - In 2020, the total prevalence of CKD was 674.11 (95% UI, 628.85–721.47) million people, a 25.00% (95% UI, 24.10%–25.92%) increase since 2010.
  - The age-standardized prevalence of CKD was highest in Southeast, Central, and South Asia; Central Latin America; and central and southern sub-Saharan Africa (Chart 12-7).
  - There were 1.48 (95% UI, 1.34–1.60) million deaths attributable to CKD in 2020.
  - Central Latin America had the highest age-standardized mortality rates estimated for CKD in 2020. Rates were also higher in the Middle East and North Africa, Andean Latin America, and sub-Saharan Africa. (Chart 12-8).

### 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,<sup>34</sup> although albuminuria tends to be a stronger risk factor for females than for males and for older (>65 years of age) versus younger people.<sup>35</sup>
- The addition of eGFR or albuminuria improves CVD prediction beyond traditional risk factors used in risk equations.<sup>35</sup>
- 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.<sup>36</sup> In the Chronic Renal Insufficiency Cohort of 2399 participants without a history of CVD at baseline, a composite inflammation score (IL-6, tumor necrosis factor- $\alpha$ , 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]).<sup>37</sup>
- In a randomized clinical trial of adults with PAD, CKD was associated with increased 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]).<sup>38</sup>

- In a post hoc analysis of hypertension patients in SPRINT, albuminuria was associated with 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]).<sup>39</sup>

### Prevalence of CVD Among People With CKD

#### (See Charts 12-9 and 12-10)

- 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 12-9 and 12-10).
- In 2018, CVD was present in 37.5% of patients without CKD, but a higher prevalence was noted in the CKD population. CVD was present in 63.4% of patients with CKD stage 1 to 2 CKD, 66.6% in those with stage 3 CKD, and 75.3% in those with stage 4 to 5 CKD.<sup>1</sup>
- The prevalence of CVD in patients with ESRD differs by treatment modality. Approximately 76.5% of patients with ESRD on hemodialysis have any CVD, whereas 65% of patients on peritoneal dialysis and 53.7% of patients receiving transplantation have any CVD (Chart 12-10).
- Among 2257 community-dwelling adults with CKD (ARIC study) monitored with an ECG for 2 weeks, nonsustained VT was the most frequent major arrhythmia, occurring at a rate of 4.2 episodes per person per month.<sup>40</sup> Albuminuria was associated with higher prevalence of AF and percent time in AF and nonsustained VT.

### 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.<sup>41</sup>
- Both eGFR and albuminuria appear to predict HF events more strongly than CHD or stroke events.<sup>35</sup>
- 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  $\chi^2=2.7$ ,  $P=0.45$ ), with moderately good discrimination (C index, 0.71 [95% CI, 0.65–0.77]) for ASCVD events.<sup>42</sup>
- In a meta-analysis of patients with CKD, the prevalence of PH was 23% and was associated with increased risk of CVD (RR, 1.67 [95% CI, 1.07–2.60]) and mortality (RR, 1.44 [95% CI, 1.17–1.76]).<sup>43</sup>

- Females with CKD appear to have a higher risk of incident PAD than males with CKD, particularly at younger ages.<sup>44</sup>
- A patient-level pooled analysis of randomized trials explored the relationship between CKD and prognosis in females who undergo PCI.<sup>45</sup> 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.<sup>46</sup> However, the risk of HF associated with CKD might be greater for Black people and Hispanic people than for White people.<sup>41</sup>
- 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.<sup>47</sup>

### Prevention and Treatment of CVD in People With CKD

- 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]).<sup>48</sup>
- Among veterans with diabetes and CKD, the proportion receiving an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker was 66% (95% CI, 62%–69%) in 2013 to 2014.<sup>49,50</sup>
- In NHANES 1999 to 2014, 34.9% of adults with CKD used an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. The use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers increased in the early 2000s among adults with CKD but plateaued subsequently.<sup>49</sup>
- Among Medicare beneficiaries with CKD, 74.8% of patients with CKD were on  $\beta$ -blockers and 81.8% were on lipid-lowering agents.<sup>1</sup>
- Among 22 739 Medicare beneficiaries with stage 3 to 5 CKD, apixaban compared with warfarin was associated with decreased risk of stroke (HR, 0.70 [95% CI, 0.51–0.96]) and major bleeding (HR, 0.47 [95% CI, 0.37–0.59]), but these risks did not differ with the use of rivaroxaban and dabigatran.<sup>51</sup>
- 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]).<sup>52</sup>

- 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.<sup>53</sup>
- Among patients who underwent TAVR in the PARTNER trial, CKD stage either improved or was unchanged after the procedure.<sup>54</sup>
- For patients with eGFR <60 but >15 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> undergoing TAVR in the TVT registry, approximately one-third will die and 1 in 6 will require dialysis within a year.<sup>55</sup>
- 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.<sup>56</sup> 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.<sup>57</sup>
- 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.<sup>58</sup>
- 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<sup>-1</sup>·1.73 m<sup>-2</sup> 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]).<sup>59</sup>
- In a pooled analysis of data from the ARIC, MESA, and CHS studies, healthy lifestyle behaviors were associated with lower all-cause mortality, major coronary events, ischemic stroke, and HF.<sup>60</sup>
- Sodium/glucose cotransporter-2 inhibitor (dapagliflozin) use reduced the risk of a composite of a sustained decline in eGFR of at least 50%, ESRD, or death attributable to renal and cardiovascular causes among those with diabetes and nondiabetic

CKD.<sup>61</sup> These benefits were independent of the presence of concomitant CVD (HR, 0.61 [95% CI, 0.48–0.78] in the primary prevention group versus HR, 0.61 [95% CI, 0.47–0.79] in the secondary prevention group).

### Cardiovascular Hospitalization and Mortality Attributable to CVD Among People With CKD (See Chart 12-11)

- 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 aRR of all-cause mortality and cardiovascular mortality is highest in those with eGFR of 15 to 30 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> and those with ACR >300 mg/g.
- Data from CARES and the Centers for Medicare & Medicaid 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.<sup>62</sup>
- 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 12-11).<sup>63</sup>
- 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.<sup>64</sup>
  - 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.<sup>65</sup>
  - 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.<sup>66</sup>

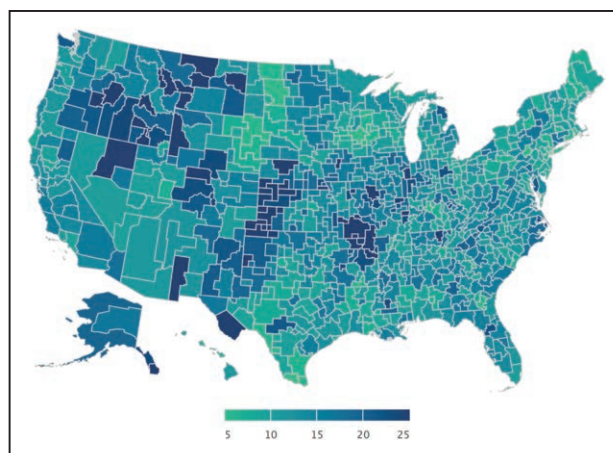
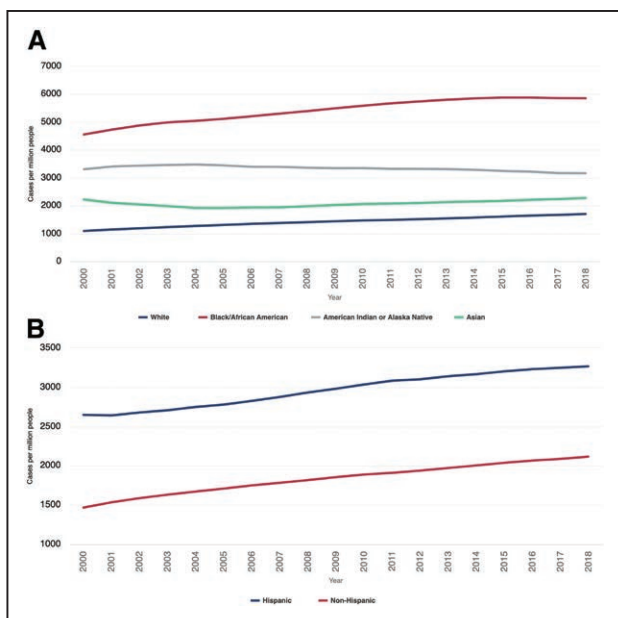
#### FOOTNOTE

A portion of the data reported here has been supplied by the USRDS.<sup>1</sup> 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.

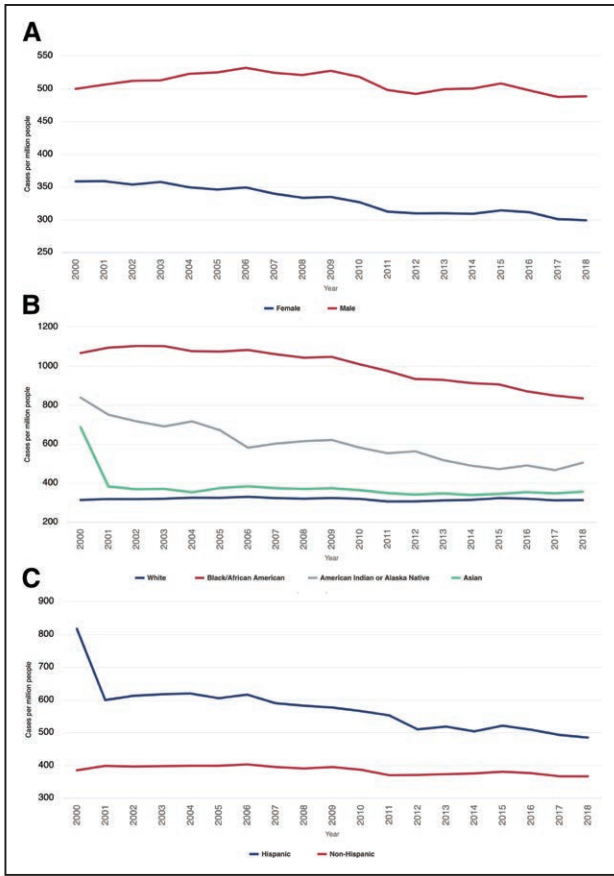
eGFR Categories	A1: Normal to mildly increased (ACR <30 mg/g)	A2: Moderately increased (ACR 30-299 mg/g)	A3: Severely increased (ACR ≥300 mg/g)	Total
<b>G1: Normal or high</b> (eGFR ≥90ml/min/1.73m <sup>2</sup> )	53.5	4.1	0.58	58.3
<b>G2: Mildly decreased</b> (eGFR 60-89 ml/min/1.73m <sup>2</sup> )	31.5	2.9	0.43	34.8
<b>G3a: Mildly to moderately decreased</b> (eGFR 45-59 ml/min/1.73m <sup>2</sup> )	3.9	0.84	0.27	5.0
<b>G3b: Moderately to severely decreased</b> (eGFR 30-44 ml/min/1.73m <sup>2</sup> )	0.88	0.40	0.17	1.5
<b>G4: Severely decreased</b> (eGFR 15-29 ml/min/1.73m <sup>2</sup> )	0.11	0.09	0.17	0.37
<b>G5: Kidney failure</b> (eGFR <15 ml/min/1.73m <sup>2</sup> )	0.01	0.01	0.09	0.11
<b>Total</b>	90.0	8.3	1.7	100

**Chart 12-1. Percentage of NHANES participants within the KDIGO CKD risk categories defined by eGFR and ACR, United States, 2015 to 2018.**

Green=low risk; yellow=moderately high risk; orange=high risk; red=very high risk. ACR indicates urinary albumin to creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; and NHANES, National Health and Nutrition Examination Survey. Source: Reprinted from 2020 United States Renal Data System Annual Data Report, volume 1, Table 1.1,<sup>1</sup> using NHANES 2015 to 2018.

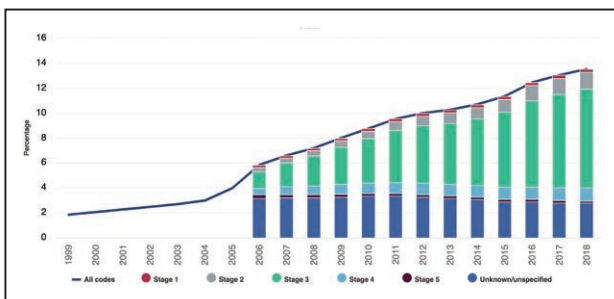


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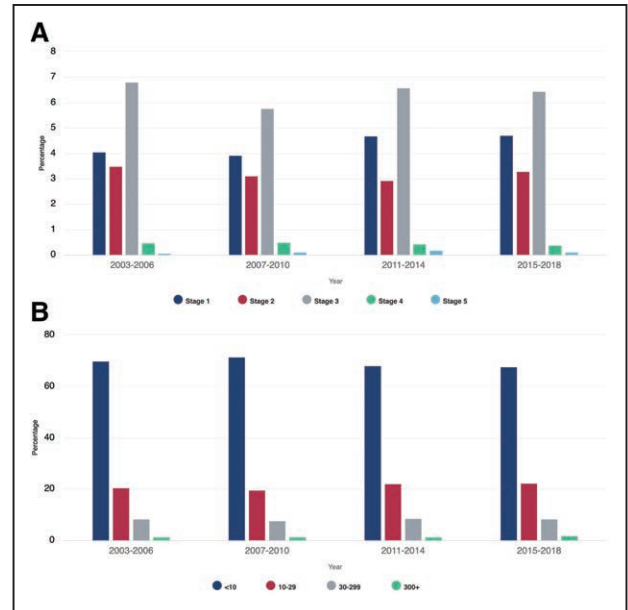
**Chart 12-4. Temporal trends in ESRD incidence, United States, 2000 to 2018.**

**A**, Incidence by sex. **B**, Incidence by race. **C**, Incidence by ethnicity. Incidence estimates are presented as cases per million people and adjusted for age, sex, and ethnicity. ESRD indicates end-stage renal disease. Source: Reprinted from 2020 United States Renal Data System Annual Data Report, volume 2, Figure 1.4.<sup>1</sup>



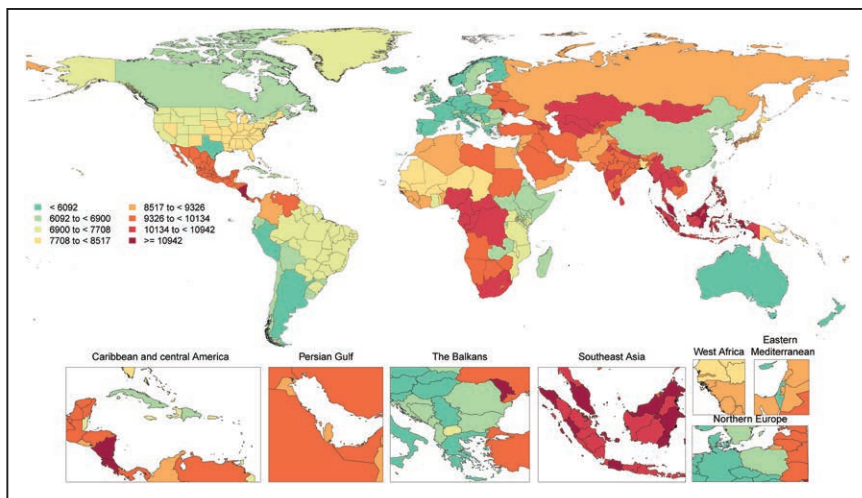
**Chart 12-5. Prevalence of CKD, overall and by CKD category, among Medicare beneficiaries ≥66 years of age, United States, 1999 to 2018.**

CKD indicates chronic kidney disease. Source: Reprinted from 2020 United States Renal Data System Annual Data Report, volume 1, Figure 2.1.<sup>1</sup>



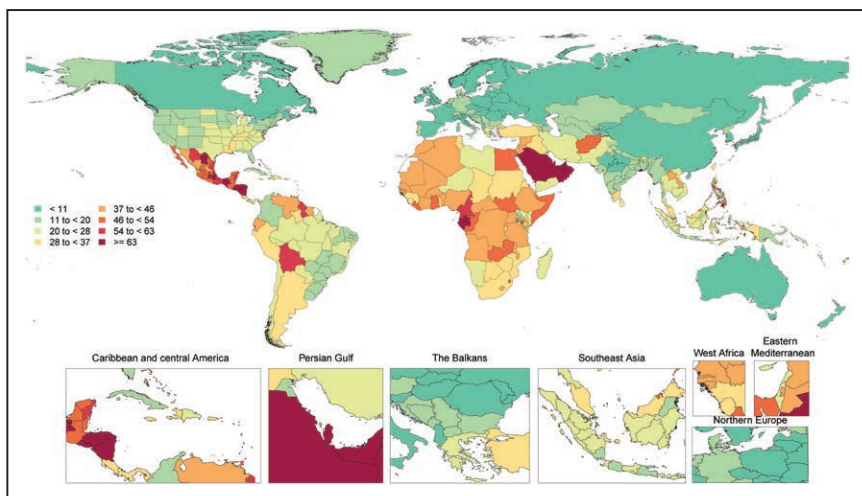
**Chart 12-6. Prevalence of reduced eGFR and ACR in NHANES, United States, 2003 to 2018.**

**A**, Prevalence of eGFR by stage. **B**, Prevalence of ACR by category. eGFR stages 1 through 5. Adjusted for age, sex, and race; single-sample calibrated estimates of ACR; eGFR calculated with the Chronic Kidney Disease Epidemiology Collaboration equation. ACR indicates albumin-to-creatinine ratio; eGFR, glomerular filtration rate; and NHANES, National Health and Nutrition Examination Survey. Source: Reprinted from 2020 United States Renal Data System Annual Data Report, volume 1, Figures 1.1 and 1.3,<sup>1</sup> using NHANES<sup>67</sup> data 2003 to 2006, 2007 to 2010, 2011 to 2014, and 2015 to 2018.



**Chart 12-7. Age-standardized global prevalence rates for CKD per 100 000, both sexes, 2020.**

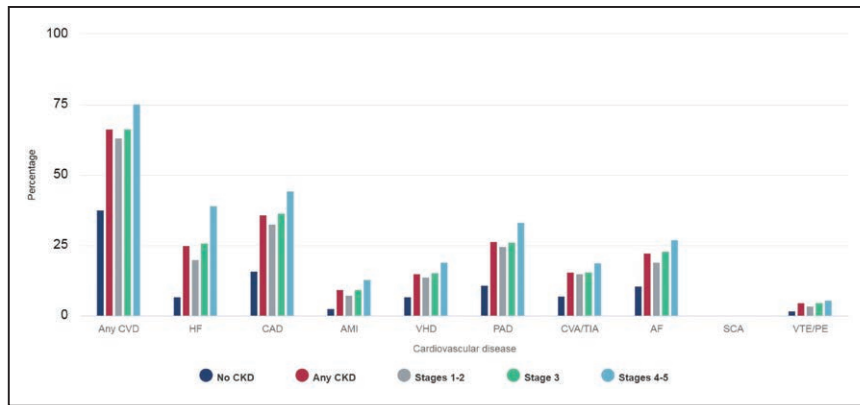
CKD indicates chronic kidney disease. Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. Additional information is available on the Global Burden of Disease Study website.<sup>31</sup>



**Chart 12-8. Age-standardized global mortality rates for CKD per 100 000, both sexes, 2020.**

CKD indicates chronic kidney disease. Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. Additional information is available on the Global Burden of Disease Study website.<sup>31</sup>



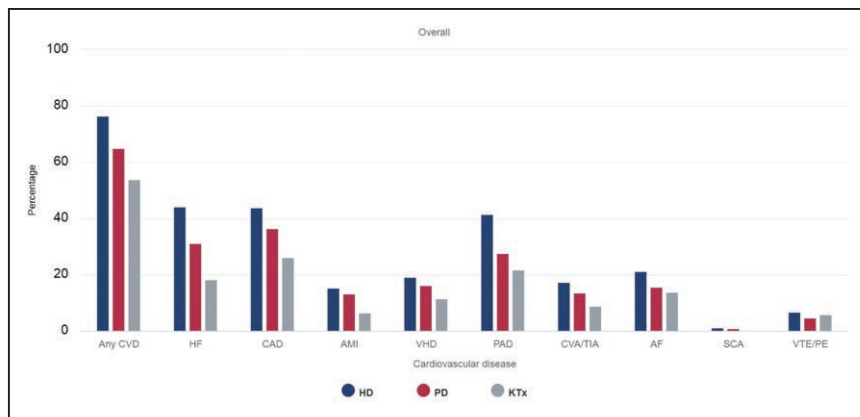


**Chart 12-9. Adjusted prevalence of common CVDs in Medicare beneficiaries ≥66 years of age, by CKD status and stage, United States, 2018.**

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; VHD, valvular heart disease; and VTE, venous thromboembolism.

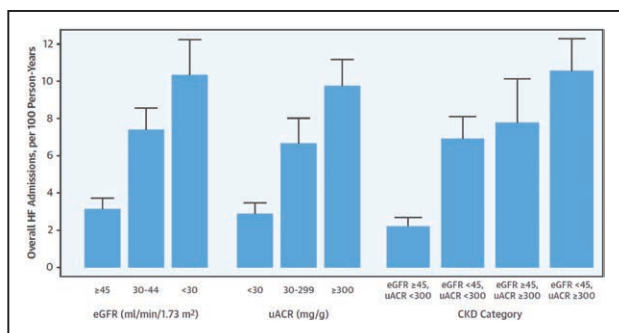
Source: Reprinted from 2020 United States Renal Data System Annual Data Report, volume 1, Figure 4.2.<sup>1</sup>



**Chart 12-10. Unadjusted prevalence of common CVDs in adult patients with ESRD, by treatment modality, United States, 2018.**

AF indicates atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; ESRD, end-stage renal disease; HD, hemodialysis; HF, heart failure; KTx, kidney transplant recipients; PAD, peripheral arterial disease; PD, peritoneal dialysis; PE, pulmonary embolism; SCA, sudden cardiac arrest; TIA, transient ischemic attack; VHD, valvular heart disease; and VTE, venous thromboembolism.

Source: Reprinted from 2020 United States Renal Data System Annual Data Report, volume 2, Figure 8.1.<sup>1</sup>



**Chart 12-11. US HF 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,<sup>63</sup> Central Illustration, with permission from the American College of Cardiology Foundation. Copyright © 2019 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.

### Prevalence

(See *Charts 13-1 and 13-2*)

- The American Academy of Sleep Medicine and the Sleep Research Society recommend that adults obtain  $\geq 7$  hours of sleep per night to promote optimal health. Sleeping  $> 9$  hours may be appropriate for some individuals (eg, younger or ill adults), but for others, it is unclear whether this much sleep is associated with health benefits or health risk.<sup>1</sup>
- The CDC used data from the 2014 BRFSS to determine the age-adjusted prevalence of a healthy sleep duration ( $\geq 7$  hours) in the United States and found that “11.8% of people reported a sleep duration  $\leq 5$  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  $\geq 10$  hours.” Overall, 65.2% met the recommended sleep duration of  $\geq 7$  hours.<sup>2</sup>
- Analysis of 2018 BRFSS data indicates 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 (Chart 13-1).<sup>3</sup>
- The prevalence of inadequate sleep ( $< 7$  hours) varied by state or territory: In 2014, the lowest prevalence was observed 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%).<sup>4</sup>

The 2022 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 2022. 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.

- 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%).<sup>5</sup>
- 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 (unpublished tabulation using BRFSS<sup>3</sup>; Chart 13-2).
- The prevalence of restless legs syndrome was estimated in a population-based study of adults  $\geq 30$  years of age in Iran (N=19 176).<sup>6</sup> The crude prevalence was 8.2% (95% CI, 7.8%–8.6%), and restless legs syndrome was more common in females (8.6%) than in males (7.5%; OR, 1.2 [95% CI, 1.0–1.3]).
- 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 in 26 patients (8.0%).<sup>7</sup>

### 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.<sup>8</sup>

### 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 ( $\geq 7$  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  $\geq 65$  years of age.<sup>2</sup>

### Risk Factors

- On the basis of data from NHANES, risk factors for short sleep duration include smoking (OR, 1.59

[95% CI, 1.27–1.96] compared with previous smoking; OR, 1.47 [95% CI, 1.18–1.89] compared with never smoking), physical inactivity (OR, 1.48 [95% CI, 1.15–1.86] for no PA versus PA), poor diet (OR, 1.07 [95% CI, 1.05–1.10] per 1 point lower on nutrient adequacy scale), obesity (OR, 1.39 [95% CI, 1.17–1.65] for BMI  $\geq 30$  kg/m<sup>2</sup> versus  $< 25$  kg/m<sup>2</sup>), 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 score of  $\geq 10$  versus  $< 10$  on the Patient Health Questionnaire).<sup>9</sup>

- 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, 2.56 [95% CI, 2.33–2.78] compared with never smoking), no alcohol consumption (OR, 2.56 [95% CI, 2.33–2.78] compared with alcohol consumption), obesity (OR, 1.25 [95% CI, 1.02–1.54] for BMI  $\geq 30$  kg/m<sup>2</sup> versus  $< 25$  kg/m<sup>2</sup>), 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  $\geq 10$  versus  $< 10$  on the Patient Health Questionnaire).<sup>9</sup>
- Predictors of moderate to severe OSA (AHI  $\geq 15$  events per hour) among a sample of 852 Black adults were male sex (OR, 2.67 [95% CI, 1.87–3.80]), higher 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]).<sup>10</sup>
- 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  $\geq 65$  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 the 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  $\geq 3$ ), 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.<sup>11</sup> 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.<sup>11</sup>
- Among a random sample of 1936 Sicilian males and females  $\geq 18$  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 adjusted 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.<sup>12</sup>

## Social Determinants

### Race and Ethnicity and Sleep

#### (See Charts 13-3 and 13-4)

- 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%).<sup>2</sup>
- 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.<sup>13</sup> This study also observed lower sleep quality in Black and Hispanic/Latino individuals compared with White individuals.
- In the 2018 BRFSS, NH Black adults had the highest percentage of respondents reporting sleeping  $< 7$  hours per night (45.4%), whereas NH White adults had the lowest percentage (33.2%) of respondents reporting sleeping  $< 7$  hours (Chart 13-3).
- In the 2018 BRFSS, NH American Indian/Alaska Native adults had the highest percentage of respondents indicating sleep problems on  $\geq 7$  of 14 days (54.8%), whereas NH Black adults and Hispanic adults had the lowest percentages (14.9% and 15.2%, respectively; Chart 13-4).
- In a sample of Black adults from the JHS, the prevalence of moderate to severe OSA (AHI  $\geq 15$  events per hour) was 23.6%.<sup>10</sup>

### Other Social Determinants of Sleep

- In addition to race and ethnicity, social characteristics associated with short sleep duration include lower education (OR, 1.47 [95% CI, 1.19–1.79] 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  $\geq 2$ ).<sup>9</sup>
- 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.<sup>14</sup>

## 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.<sup>15</sup>
- Heritability of SDB varies but is estimated to be ≈40%.<sup>16</sup> Genetic studies have identified variants associated with OSA.<sup>17,18</sup> Data suggest genetic control of interindividual variability in circadian rhythms, with variants in clock genes such as *CRY1* and *CRY2* being of particular interest.<sup>19,20</sup> Several variants have been found to be associated with chronotype, insomnia, and sleep duration in >446 000 participants in the UK Biobank, including *PAX8*, *VRK2*, and *FBXL12/UBL5/PIN1*, with evidence for shared genetics between insomnia and cardiometabolic traits.<sup>21–23</sup>
- GWAS of self-reported daytime napping in the UK Biobank (N=452 633) and 23andMe research cohort (N=541 333) identified 61 replicated loci, including missense variants in established drug targets for sleep disorders (*HCRTR1*, *HCRTR2*). Many of the loci colocalized with loci for other sleep phenotypes, and cardiometabolic outcomes. Mendelian randomization suggested a causal link between more frequent daytime napping and higher BP and WC.<sup>24</sup>
- 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]).<sup>25</sup>

## 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.<sup>26</sup>
- 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.<sup>27</sup>

- An RCT enrolled adults 45 to 75 years of age with moderate to severe OSA without excessive daytime sleepiness who also had coronary or cerebrovascular disease to compare CPAP plus usual care with usual care alone.<sup>28</sup> A total of 2687 patients were included in this secondary prevention trial and followed up for an average of 3.7 years. No difference between CPAP intervention and the usual care group 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.
- 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 3.8 years differed between the CPAP group (n=1248) and the control group (n=1235). 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]). Among 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]).<sup>29</sup>
- In Spain, a multicenter RCT of patients with ACS randomized patients with ACS with OSA without excessive daytime sleepiness to either CPAP therapy plus usual care (n=629) or usual care alone (n=626).<sup>30</sup> The mean CPAP adherence was 2.78 hours per night (SD 2.73) in the CPAP group. There were 98 patients (16%) in the CPAP group and 108 (17%) in the usual care group who experienced a cardiovascular event during follow-up, which was not significantly different (HR, 0.89 [95% CI, 0.68–1.17]).

## 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.<sup>31</sup>
- A prospective cohort study found that the association between sleep duration and mortality varied



with age.<sup>32</sup> Among adults <65 years of age, both short sleep duration ( $\leq 5$  hours per night) and long sleep duration ( $\geq 8$  hours per night) were associated with increased mortality risk (HR, 1.37 [95% CI, 1.09–1.71] and 1.27 [95% CI, 1.08–1.48], respectively). Sleep duration was not significantly associated with mortality in adults  $\geq 65$  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]) and 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  $\geq 65$  years of age (HR, 1.80 [95% CI, 1.30–2.50]) but not among those <65 years of age (HR, 1.92 [95% CI, 0.78–4.69]).<sup>9</sup> 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]).<sup>33</sup>
- 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]).<sup>26</sup>

## Complications

### Sleep Duration

- A meta-analysis examined sleep duration and total CVD (26 articles), CHD (22 articles), and stroke (16 articles).<sup>31</sup> 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 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.<sup>34</sup>

- A cross-sectional study in Corinthia, Greece (N=1752) reported associations between self-reported sleep duration and carotid IMT from a carotid duplex ultrasonography examination.<sup>35</sup> Compared with normal sleep duration (7–8 hours), larger mean carotid IMT was associated with sleeping  $<6$  hours ( $b=0.067$  mm [95% CI, 0.003–0.132]) and sleeping  $>8$  hours ( $b=0.054$  mm [95% CI, 0.002–0.106]), but those reporting sleeping 6 to  $<7$  hours did not differ ( $b=0.012$  mm [95% CI, –0.043 to 0.068]). Maximum carotid IMT differed only for those reporting sleeping  $<6$  hours ( $b=0.16$  mm [95% CI, 0.033–0.287]) compared with those with a normal sleep duration, whereas those who reported sleeping 6 to  $<7$  hours ( $b=0.057$  mm [95% CI, –0.052 to 0.166]) or  $>8$  hours ( $b=0.082$  mm [95% CI, –0.019 to 0.184]) did not differ.
- Analysis of the UK Biobank study (N=468 941) found that participants who reported short sleep ( $<7$  h/d) or long sleep ( $>9$  h/d) had an increased risk of incident HF compared with normal sleepers (7–9 h/d).<sup>36</sup> In males, the aHR was 1.24 (95% CI, 1.08–1.42) for short sleep and 2.48 (95% CI, 1.91–3.23) for long sleep. In females, the aHR was 1.39 (95% CI, 1.17–1.65) for short sleep and 1.99 (95% CI, 1.34–2.95) for long sleep.
- A prospective, population-based cohort study in China enrolled 52 599 Chinese adults 18 to 98 years of age and examined self-reported sleep duration trajectories over 4 years.<sup>37</sup> They identified 4 patterns: normal stable (mean range, 7.4–7.5 hours), normal decreasing (mean decrease, 7.0 to 5.5 hours), low increasing (mean increase, 4.9 to 6.9 hours), and low stable (mean range, 4.2–4.9 hours). Compared with the normal stable group, increased risk of incident cardiovascular events was observed for the low increasing group (HR, 1.22 [95% CI, 1.04–1.43]) and the low stable group (HR, 1.47 [95% CI, 1.05–2.05]) but not the normal decreasing group (HR, 1.13 [95% CI, 0.97–1.32]). Similarly, risk of all-cause mortality was higher for the normal decreasing group (HR, 1.34 [95% CI, 1.15–1.57]) and the low stable group (HR, 1.50 [95% CI, 1.07–2.10]) but not the normal decreasing group (HR, 0.95 [95% CI, 0.80–1.13]).

### Restful Sleep and Sleepiness

- Medical records from patients in Japan (N=1 980 476) were examined to determine whether restful sleep (yes/no) was associated with incident CVD over an average of 1 122 days.<sup>38</sup> Restful sleep was associated with lower risk of MI (HR, 0.89 [95% CI, 0.82–0.96]), AP (HR, 0.85 [95% CI, 0.83–0.87]), stroke (HR, 0.86 [95% CI,



0.83–0.90]), HF (HR 0.86 [95% CI, 0.83–0.88]), and AF (HR, 0.93 [95% CI, 0.88–0.98]).

- A meta-analysis combined data from 17 articles with a total of 153 909 participants from cohort studies to examine excessive daytime sleepiness and risk of CVD events.<sup>39</sup> Mean follow-up time was 5.4 years and ranged from 2 to 13.8 years. Excessive daytime sleepiness was associated with increased risk of any CVD event (RR, 1.28 [95% CI, 1.09–1.50]), CHD (RR, 1.28 [95% CI, 1.12–1.46]), stroke (RR, 1.52 [95% CI, 1.10–2.12]), and CVD mortality (RR, 1.47 [95% CI, 1.09–1.98]).

### Obstructive Sleep Apnea

- 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).<sup>40</sup>
- 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]).<sup>41</sup>
- 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 for ≥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).<sup>42</sup>
- 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]).<sup>43</sup>
- 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]).<sup>44</sup>
- Among 607 patients with AMI, the presence of moderate to severe OSA was associated with a greater likelihood of an NSTEMI versus STEMI (OR, 1.59 [95% CI, 1.07–2.37]), and the prevalence of NSTEMI was 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 ( $P<0.001$ ,  $\chi^2$  test).<sup>45</sup>
- 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.<sup>46</sup>
- 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 non-adherent), untreated severe OSA (AHI ≥30 events per hour and no or nonadherent CPAP), and CPAP treated (AHI ≥15 events per hour and CPAP adherence ≥4 h/d). Patients were followed up for ≈71 to 72 months. Compared with the patients with AHI <15 events per hour, the fully aHRs 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 aHRs for the incidence of CHD 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).<sup>47</sup>
- A prospective study in China enrolled 804 consecutive patients admitted for ACS 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 or ≥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, 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]).<sup>48</sup>

- A retrospective cohort study from Mayo Clinic examined adults who underwent cardiac surgery to compare perioperative outcomes between patients with and without OSA.<sup>49</sup> OSA was present in 2636 of 8612 patients (30.6%). In multivariable adjusted analyses, OSA was associated with an increased odds of readmission (OR, 1.53 [95% CI, 1.21–1.92]), prolonged length of stay (OR, 1.29 [95% CI, 1.14–1.46]), and acute kidney injury (OR, 1.34 [95% CI, 1.18–1.52]) but not AF (OR, 0.97 [95% CI, 0.87–1.09]).
- The HCHS/SOL measured SDB and conducted echocardiography in a subset of participants 45 to 74 years of age (n=1506).<sup>50</sup> Higher AHI was associated with impaired diastolic function. Specifically, every additional 10 units of AHI was associated with 0.2 unit lower (95% CI, –0.3 to –0.1) average of the septal and lateral mitral annular descent tissue Doppler velocity (E'), 0.3 larger ratio of early mitral inflow velocity to E' (95% CI, 0.1–0.5), and 1.07 times higher prevalence of LV diastolic dysfunction (95% CI, 1.03–1.11). There were no significant associations between AHI and

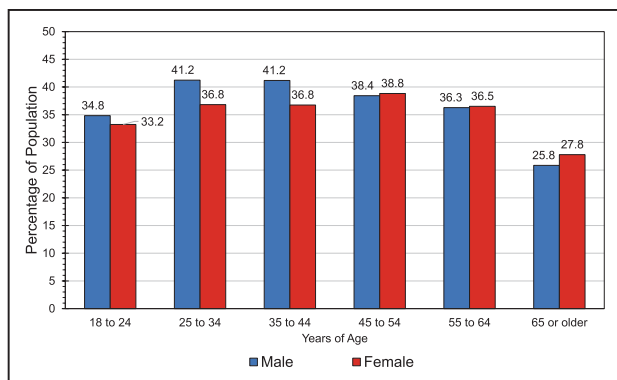
measures of systolic dysfunction. AHI was significantly associated with larger LV mass index (1.3 g/m<sup>2</sup> larger per 10 units of AHI [95% CI, 0.3–2.4]), but there was no association between AHI and left atrial volume index ( $\beta=0.0$  [95% CI, –0.3 to 0.3]).

### Costs

- Analysis of direct and indirect costs related to inadequate sleep in Australia suggested that the approximate cost for a population the size of that of the United States would be more than \$585 billion for the 2016 to 2017 financial year.<sup>51</sup>

### Global Burden

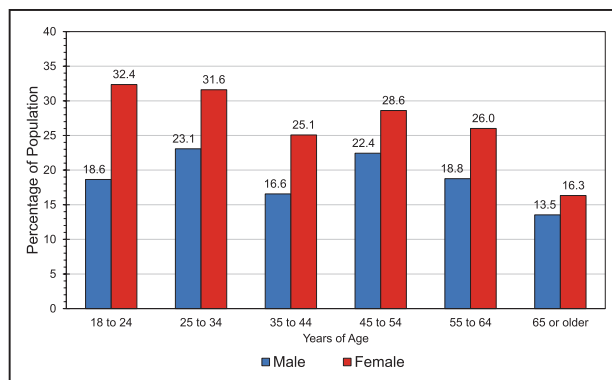
- An analysis of the global prevalence and burden of OSA estimated that 936 million (95% CI, 903–970 million) males and females 30 to 69 years of age have mild to severe OSA (AHI  $\geq 5$  events per hour) and 425 million (95% CI, 399–450 million) have moderate to severe OSA (AHI  $\geq 15$  events per hour) globally. The prevalence was highest in China, followed by the United States, Brazil, and India.<sup>52</sup>



**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?”

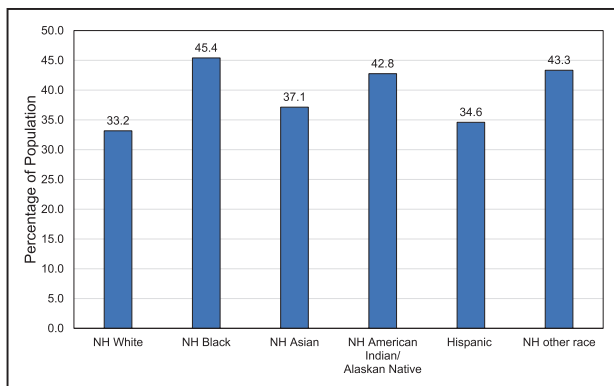
Source: Unpublished tabulation using Behavioral Risk Factor Surveillance Survey.<sup>3</sup>



**Chart 13-2. Prevalence of reporting sleep problems  $\geq 7$  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.<sup>3</sup>

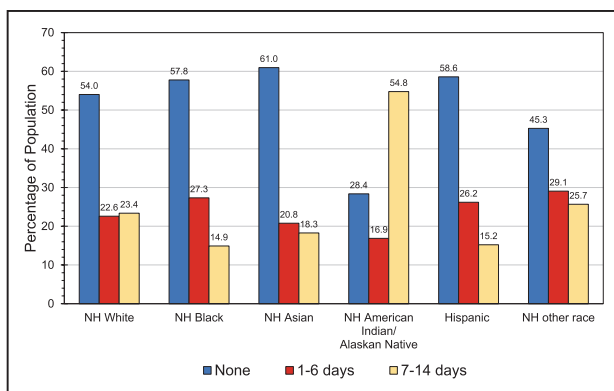


**Chart 13-3. Prevalence of reporting sleep duration <7 hours per night in US adults, by race, 2018.**

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.<sup>3</sup>



**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.<sup>3</sup>

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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,<sup>1</sup> the prevalence of CVD (comprising CHD, HF, stroke, and hypertension) in adults  $\geq 20$  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<sup>2</sup>:
  - 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 and 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).
  - 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).

The 2022 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 2022. 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.

- In a cross-sectional study of 56716 adults  $\geq 40$  years of age in northern China, 22.7% had a high 10-year risk of CVD, measured with the WHO/International Society of Hypertension risk prediction charts.<sup>3</sup> The age-adjusted prevalence of history of CVD was 4.6%. Furthermore, age-adjusted prevalence of hypertension, dyslipidemia, obesity, and diabetes, in all respondents was 54.3%, 36.5%, 24.8%, and 18.2, respectively.

### Incidence

- In a meta-analysis of CVD incidence among 32 studies of Asian participants 18 to 92 years of age who were free of CVD at baseline and had  $>10$  years of follow-up, the incidence of fatal CVD was 3.68 (95% CI, 2.84–4.53) events per 1000 person-years.<sup>4</sup>

### 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  $\geq 7.0$  mmol/L (126 mg/dL) or taking diabetes medication at baseline.<sup>5</sup> 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  $\geq 7.0$  mmol/L or taking diabetes medication at baseline.
- The Cardiovascular Lifetime Risk Pooling Project estimated the long-term risks of CVD among 30447 participants with a mean age of 55.0 years (SD, 13.9 years) from 7 US cohort studies.<sup>6</sup> After 538477 person-years of follow-up, the 40-year risk of CVD for an adult  $<40$  years of age with high CVH was 0.7% (95% CI, 0.0%–1.7%) for White males, 2.1% (95% CI, 0.0%–5.0%) for Black males, 1.7% (95% CI, 0.4%–3.0%) for White females, and 2.0% (95% CI, 0.0%–4.7%) for Black females. For an adult  $<40$  years of age with low CVH, the 40-year risk of CVD was 14.4% (95% CI, 9.1%–19.6%) for White males, 17.6% (95% CI, 9.9%–25.3%) for Black males, 8.6% (95% CI, 2.1%–15.2%) for White females, and 8.4% (95% CI, 5.3%–11.5%) for Black females. White females  $\geq 60$  years of age with high CVH had 35-year risk of CVD of 38.6% (95% CI, 22.6%–54.7%), but this risk was incalculable for these older, high-CVH individuals in other race-sex groups because of insufficient follow-up. Among individuals  $\geq 60$  years of age with low

CVH, the 35-year risk of CVD was highest in White males (65.5% [95% CI, 62.1%–68.9%]), followed by White females (57.1% [95% CI, 54.4%–59.7%]), Black females (51.9% [95% CI, 43.1%–60.8%]), and Black males (48.4% [95% CI, 41.9%–54.9%]). These estimated risks accounted for competing risks of death resulting from non-CVD causes.

## Secular Trends

- According to data from NHANES using 35 416 participants, BMI increased more in females (from mean of 28.1 kg/m<sup>2</sup> in 2001–2004 to 29.6 kg/m<sup>2</sup> in 2013–2016) than males (from mean of 27.9 to 29.0 kg/m<sup>2</sup>; *P*=0.006). 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; *P*=0.002). Secular trends in SBP, smoking status, HDL-C, and HbA1c were not statistically significantly different between males and females.<sup>7</sup>
- 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 at 9.11 (95% CI, 5.87–14.13) in 2000 and 10.01 (95% CI, 7.55–13.27) in 2012.<sup>8</sup>

## Risk Factors

- 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).<sup>9</sup>
- In a registry-based study of 416 709 females hospitalized in Quebec, Canada, from 2006 and 2018, 818 females who were hospitalized for bulimia nervosa were compared with 415 891 females without bulimia nervosa who were hospitalized for pregnancy-related events for a total follow-up period of 2 957 677 person-years.<sup>10</sup> Females hospitalized for bulimia nervosa had a higher incidence of CVD (10.34 [95% CI, 7.77–13.76] per 1000 person-years) than females hospitalized for pregnancy-related events (1.02 [95% CI, 0.99–1.06] per 1000 person-years). Furthermore, the risk of any CVD (4.25 [95% CI, 2.98–6.07]) or death (4.72 [95% CI, 2.05–10.84]) was higher among females hospitalized for bulimia nervosa compared with females hospitalized for pregnancy-related events.
- Among females in the WHS (N=27 858; 629 353 person-years of follow-up), those with a self-reported history of migraine with aura had a higher incidence

rate of major CVD (3.36 [95% CI, 2.72–3.99 per 1000 person-years]) than females with migraine without aura or no migraine (2.11 [95% CI, 1.98–2.24]).<sup>11</sup>

- 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 100 000 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 100 000 person-years.<sup>12</sup>
- 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.<sup>13</sup>
- Among 31 162 adults 35 to 74 years of age in the Henan Rural Cohort Study, each 1-μg/m<sup>3</sup> increase in particulate matter (PM1 [particles with aerodynamic diameter <1 μm], PM2.5, PM10 [particles with aerodynamic diameter <10 μm], and NO<sub>2</sub>) was associated with a 4.4% (OR, 1.04 [95% CI, 1.03–1.06]) higher 10-year ASCVD risk for PM1, 9.1% (OR, 1.09 [95% CI, 1.08–1.10]) higher 10-year ASCVD risk for PM2.5, 4.6% (OR, 1.05 [95% CI, 1.04–1.05]) higher 10-year ASCVD risk for PM10, and 6.4% (OR, 1.06 [95% CI, 1.06–1.07]) higher 10-year ASCVD risk for NO<sub>2</sub> (all *P*<0.001). However, PA attenuated the association between air pollution and 10-year ASCVD risk.<sup>14</sup>
- 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).<sup>15</sup>
- In a meta-analysis of dietary sodium intake and CVD risk (36 studies representing 616 905 participants), those with high sodium intake had a higher adjusted risk of CVD (rate ratio, 1.19 [95% CI, 1.08–1.30]) than individuals with low sodium intake. CVD risk was up to 6% higher for every 1-g increase in dietary sodium intake.<sup>16</sup>
- A prospective analysis of dietary patterns among adults in the NHS (1984–2016), NHS II (1991–2017), and HPFS (1986–2012), with 5 257 190 person-years of follow-up, found that greater adherence to various healthy eating patterns (HEI-2015: HR, 0.83 [95% CI, 0.79–0.86]; AHEI: HR, 0.79 [95% CI, 0.75–0.82]; Alternate Mediterranean Diet Score: HR, 0.83 [95% CI, 0.79–0.86]; and Healthful Plant-Based Diet Index: HR, 0.86 [95% CI, 0.82–0.89]) was inversely and consistently associated with CVD risk.<sup>17</sup>

## Social Determinants

- Among older adults in the NIH-AARP Diet and Health Study, the highest tertile of neighborhood socioeconomic deprivation in 1990 and 2000 compared with the lowest tertile was associated with a higher risk of CVD mortality (aHR for males, 1.47 [95% CI, 1.40–1.54]; aHR for females, 1.78 [95% CI, 1.63–1.95]) after accounting for individual socioeconomic factors and CVD risk factors.<sup>18</sup>
- In a retrospective cohort study of patients (N=2876) receiving care at a large health system in Miami, FL, patients in the highest quartile of weighted social determinants of health score (including foreign-born status, underrepresented race or ethnicity status, social isolation, financial strain, health literacy, education, stress, delayed care, census-based income) had higher CVD risk, measured with the FRS (OR, 1.84 [95% CI, 1.21–2.45]) than those in the lowest quartile.<sup>19</sup>
- Being divorced/separated or widowed or living alone was associated with a higher CVD risk (HR, 1.21 [95% CI, 1.08–1.35]) compared with being married or cohabitating in the Swedish Twin Registry (N=10 058; median follow-up, 9.8 years).<sup>20</sup>

## Risk Prediction

- In a meta-analysis of studies assessing the performance of the FRS, ATP III score, and the PCE 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.<sup>21</sup>
- 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 UK-based QRISK3 score (C statistics were 0.86 and 0.88 in males and females, respectively).<sup>22</sup>
- The addition of walking pace (change in C index: PCE score, +0.0031; SCORE, +0.0130), grip strength (PCE score, +0.0017; SCORE, +0.0047), or both (PCE score, +0.0041; SCORE, +0.0148) improved 10-year CVD risk prediction in the UK Biobank (N=406 834).<sup>23</sup>
- In an analysis of electronic health record data from 56 130 Asian (Asian Indian, Chinese, Filipino, Vietnamese, Japanese, and other Asian) and 19 760 Hispanic (Mexican, Puerto Rican, and other Hispanic) patients who received care in Northern

California between 2006 and 2015, the PCE overestimated ASCVD risk by 20% to 60%.<sup>24</sup>

## 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).<sup>25</sup>
- Among 1005 patients with known CAD who had 2 coronary CT angiography scans in the PARADIGM study, those with a high ASCVD risk score (>20%) had a larger average annual increase in total plaque (1%) compared with those with an intermediate ASCVD risk score (7.5%–20% risk; 0.6% increase of total plaque;  $P<0.001$ ) or low ASCVD risk score (<7.5% risk; 0.5% increase in total plaque;  $P<0.001$ ).<sup>26</sup>
- Among 1849 females participating in the Mexican Teachers' Cohort living in Chiapas, Yucatán, or Nuevo León who were sampled to be included in an ancillary study on CVD, having a family member incarcerated was associated with an OR of 1.41 (95% CI, 1.04–2.00) for carotid atherosclerosis (mean left or right IMT  $\geq 0.8$  mm or plaque). This OR was adjusted for age, site, and demographic variables such as indigenous background, education, and marital status, as well as exposure to violence.<sup>27</sup>

## Genetics and Family History

- Genetic contributors to IHD are well documented. 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.<sup>28</sup> Other GWASs have identified at least 13 additional loci across the genome, implicating pathways in blood vessel morphogenesis, lipid metabolism, nitric oxide signaling, and inflammation.<sup>29</sup>
- Ischemic stroke is a heritable disease. The largest multiethnic GWAS of stroke conducted to date reports 32 genetic loci from an analysis of 520 000 individuals.<sup>30</sup> These 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 cases with PAD 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.<sup>31</sup>

- HCM and familial DCM are the most common mendelian cardiomyopathies, with autosomal dominant or recessive transmission, in addition to X-linked and mitochondrial inheritance. 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.<sup>32</sup> In a sample of >1 million individuals, >100 AF loci were identified.<sup>33</sup> Given the heterogeneous multifactorial nature of common HF, identification of causal genetic loci remains a challenge.
- Among 3259 participants of the CHS, FHS, and WHI with leukocyte telomere collection dates between 1992 and 1998, a participant with a 1-kilobase shorter leukocyte telomere length than average for an individual 50 years of age had an HR of 1.28 (95% CI, 1.08–1.52) for cardiovascular mortality compared with a participant with an average leukocyte telomere length for an individual 50 years of age.<sup>34</sup>

## Prevention

**(See Chapter 2 [Cardiovascular Health] 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 HPFS, regular consumption of peanuts and tree nuts ( $\geq 2$  times weekly) or walnuts ( $\geq 1$  time weekly) versus no or almost no consumption of nuts was associated with an aHR of 0.86 (95% CI, 0.81–0.91) for total CVD.<sup>35</sup>
- 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).<sup>36</sup>
- 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 were decreased by 30%. UIs were generated from the 2.5th and

97.5th percentile estimates from 1000 Monte Carlo simulations.<sup>37</sup>

- Combining estimates from NHANES, REGARDS, and RCTs for BP-lowering treatments yielded estimates that achieving the 2017 ACC/AHA BP goals could prevent 3.0 million (UI, 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 (UI, 2.2–4.4 million).<sup>38</sup> 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 WHS (conducted from 1997–2014), the aHR for CVD mortality in the highest versus lowest quintiles of dietary vitamin B<sub>6</sub> intake was 0.73 (95% CI, 0.63–0.85) in males and 0.80 (95% CI, 0.70–0.92) in females.<sup>39</sup>
- 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  $\approx 230 000$  deaths by 2030 and reduce the socioeconomic disparity in CVD mortality by 6%.<sup>40</sup>

## Awareness, Treatment, and Control

- According to data from NHANES among 35 416 participants in 2013 to 2016, the prevalence of controlled BP (SBP <130 mmHg and DBP <80 mmHg) among participants with hypertension was 30% in females and 22% in males; the prevalence of controlled diabetes (HbA1c <6.5%) among participants with diabetes was 30% in females and 20% in males; and the prevalence of TC <240 mg/dL among participants with dyslipidemia was 51% in females and 63% in males.<sup>7</sup>
- Among 5246 individuals from rural China participating in the MIND-China study, the prevalence of CVD was 35%. CVD was defined as the presence of ischemic HD, HF, AF, or stroke from a combination of self-reported medical history, ECG, and a neurological examination. Among those with prevalent CVD, the most commonly used therapies were calcium channel blockers (17.7%), traditional Chinese medicine products (16.7%), antithrombotic agents (14.0%), and lipid-lowering agents (9.4%). Approximately 50% of participants with prevalent CVD reported taking no medication for secondary prevention of CVD.<sup>41</sup>



- Among 202 072 participants 35 to 70 years of age in the PURE study followed up from 2005 to 2019, which included participants from 27 countries, the ORs for treatment with pharmacotherapy for secondary prevention of CVD in females versus males varied by agent. The OR for treatment in females compared with males was 0.65 (95% CI, 0.69–0.72) for antiplatelet drugs, 0.93 (95% CI, 0.83–1.04) for  $\beta$ -blockers, 0.86 (95% CI, 0.77–0.96) for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and 1.56 (95% CI, 1.37–1.77) for diuretics. These ORs were adjusted for age, education, urban versus rural location, and INTERHEART risk score.<sup>42</sup>
- Among 284 954 privately insured and Medicare Advantage enrollees from the OptumLab Data Warehouse database at least 21 years of age with an incident ASCVD event between 2007 and 2016, the use of statins increased from 50.3% in 2007 to 59.9% in 2016, the use of high-intensity statins increased from 25% to 49.2%, the out-of-pocket costs for a 30-day supply of statins fell from \$20 to \$2, the 1-year cumulative risk for a major cardiac adverse event decreased from 8.9% to 6.5%, and the prevalence of statin intolerance in the first year of therapy increased from 4.0% to 5.1%.<sup>43</sup>

## 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 AD; 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 (41.3%) was the leading cause of CVD death in the United States in 2019, followed by stroke (17.2%), HBP (11.7%), HF (9.9%), diseases of the arteries (2.8%), and other minor CVD causes combined (17.3%) (Chart 14-4).
- The age-adjusted death rate attributable to CVD decreased from 239.7 per 100 000 people in 2009 to 214.6 per 100 000 in 2019, which amounts to a 10.5% decrease (unpublished NHLBI tabulation using CDC WONDER<sup>44</sup>).
- 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 4 years.<sup>45</sup>

- 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<sup>46</sup>:
  - 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 related to CVD.
  - 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 hospitalizations and 73 000 deaths attributable to cardiovascular events.
  - The cardiovascular mortality rate in NH Black people in 2016 was 211.6 per 100 000, which was the highest compared with all other racial and ethnic groups.
  - There is remarkable geographic variation in 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 2019 mortality data (unpublished NHLBI tabulation using the NVSS<sup>47</sup>):
  - HD and stroke currently claim more lives each year than cancer and chronic lower respiratory disease combined. In 2019, 198.5 of 100 000 people died of HD and stroke.
  - In 2019, 2 854 838 resident deaths were registered in the United States, which exceeds the 2018 figure by 15 633 deaths. Of all registered deaths, the 10 leading causes accounted for 73.4%. The 10 leading causes of death in 2019 were the same as in 2018, although 2 causes exchanged ranks: HD (No. 1), cancer (No. 2), unintentional injuries (No. 3), chronic lower respiratory diseases (No. 4), stroke (No. 5), AD (No. 6), diabetes (No. 7), kidney disease (No. 8; No. 9 in 2018), influenza and pneumonia (No. 9; No. 8 in 2018), and suicide (No. 10). From 2018 to 2019, 7 of the 10 leading causes of death had a decrease in age-adjusted death rates. The age-adjusted rate decreased 1.3% for HD, 1.9% for cancer, 2.8% for unintentional injuries, 3.8% for chronic lower respiratory disease, 1.6% for kidney disease, 17.4% for influenza and pneumonia,

2.1% for suicide, and 2.3% for AD. The age-adjusted death rates increased 2.7% for unintentional injury but did not change appreciably for diabetes or stroke.<sup>48</sup>

- HD accounted for 360 900 of the total 874 613 CVD deaths in 2019 (unpublished NHLBI tabulation using NVSS<sup>47</sup>).
- 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 and ethnicity are presented in Charts 14-8 through 14-11.
- The number of CVD deaths per year for all males and females in the United States declined from 1980 to 2010 but increased in recent years from 78 454 in 2010 to 874 613 in 2019 (Chart 14-12). The difference in age-adjusted death rates for HD also narrowed among US racial and ethnic groups between 1999 and 2019. 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 and ethnic groups. In 1999, there were 337.4 deaths per 100 000 individuals among NH Black people compared with 156.5 among NH Asian people or Pacific Islander people. In 2019, the death rates per 100 000 people for these 2 groups were 205.7 and 82.6, respectively, thus preserving the >2-fold difference in death rates observed in 1999 (unpublished NHLBI tabulation using CDC WONDER<sup>44</sup>).
- The age-adjusted death rates per 100 000 people 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 (235.7 versus 119.1 deaths per 100 000 people) and 1.7 for cerebrovascular disease (68.1 versus 40.3 deaths per 100 000 people). For other CVD causes, the ratio ranged from 1.4 (aortic aneurysm: 5.1 versus 3.5 deaths per 100 000 people) to 4.2 (hypertensive HD: 17.9 versus 4.3 deaths per 100 000 people).<sup>49</sup> A region of higher CVD mortality extends from southeastern Oklahoma along the Mississippi River Valley to eastern Kentucky.<sup>49</sup>

## 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 experienced rapid functional decline compared with 16.2% of

those without CVD at baseline. The Short Physical Performance Battery was used to assess physical function.<sup>50</sup>

- In a meta-analysis of 18 studies (N = 4858 patients) in patients with COVID-19 conducted from November 2019 through April 2020, the OR for severe COVID-19 in those with preexisting CVD compared with those without CVD was 3.14 (95% CI, 2.32–4.24). The meta-analysis included both cohort and case-control studies from China (16 studies) and the United States (2 studies).<sup>51</sup>
- In a meta-analysis of 25 studies of individuals diagnosed with COVID-19 (65 484 individuals), the authors investigated associations between preexisting conditions and death attributable to COVID-19. In the 14 studies that investigated CVD, preexisting CVD had a RR of 2.25 (95% CI, 1.60–3.17).<sup>52</sup>

## 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.<sup>45</sup>
- In 2019, 8.3% (95% CI, 7.9%–8.8%) of US adults ≥18 years of age did not obtain needed medical care because of cost within the previous 12 months.<sup>53</sup>
- From 2008 to 2018, the number of inpatient discharges from short-stay hospitals with CVD as the principal diagnosis decreased from ≈5.6 million to 5.0 million (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 (unpublished NHLBI tabulation using HCUP;<sup>54</sup> 2018).
- From 1993 to 2018, 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 2018, there were 69 679 000 physician office visits with a primary diagnosis of CVD (unpublished NHLBI tabulation using NAMCS,<sup>55</sup> 2018). In 2018, there were 7 124 000 ED visits with a primary

diagnosis of CVD (unpublished NHLBI tabulation using HCUP;<sup>54</sup> 2018).

- In 2014, an estimated 7 971 000 inpatient cardiovascular operations and procedures were performed in the United States (unpublished NHLBI tabulation of HCUP<sup>54</sup>).

## Cost

**(See Chapter 28 [Economic Cost of Cardiovascular Disease] for detailed information.)**

- The estimated direct and indirect cost of CVD for 2017 to 2018 was \$378.0 billion (MEPS,<sup>56</sup> unpublished NHLBI tabulation).

## Global Burden

**(See Charts 14-14 through 14-17, 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.
- The GBD 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020. (Data courtesy of the GBD Study.) CVD mortality and prevalence vary widely among world regions:
  - In 2020, 19.05 million (95% UI, 17.53–20.24 million) deaths were estimated for CVD globally, which amounted to an increase of 18.71% (95% UI, 13.03%–24.14%) from 2010. The age-standardized death rate per 100 000 population was 239.80 (95% UI, 219.37–255.12),

which represents a decrease of 12.19% (95% UI, –16.30% to –8.28%) from 2010. Overall, the crude prevalence of CVD was 607.64 million (95% UI, 568.07–644.85 million) cases in 2020, an increase of 29.01% (95% UI, 27.73%–30.38%) compared with 2010. However, the age-standardized prevalence rate was 7354.05 (95% UI, 6887.52–7813.75) per 100 000, an increase of 0.73% (95% UI, –0.08% to 1.60%) from 2010.

- In 2020, the highest age-standardized mortality rates estimated for CVD were in Eastern Europe and Central Asia, with higher levels also seen in Oceania, North Africa and the Middle East, Central Europe, sub-Saharan Africa, and South and Southeast Asia. Rates were lowest for locations in high-income Asia Pacific and North America, Latin America, Western Europe, and Australasia (Chart 14-19).
- In 2020, age-standardized CVD prevalence was estimated as highest in North Africa and the Middle East, followed by parts of southern and western sub-Saharan Africa, Central Asia, Eastern Europe, the Caribbean, and the southern and eastern United States (Chart 14-20).
- CVD represents 37% of deaths in individuals <70 years of age that are attributable to noncommunicable diseases.<sup>58</sup>
- In 2019, 27% of the world's deaths were caused by CVD, making it the predominant cause of death globally.<sup>58</sup>
- According to data from the GBD, the change in CVD age-standardized mortality rate in Brazil, Russia, India, China, and South Africa (–17%) was less than in North America (–39%) between 1992 and 2016.<sup>59</sup>

**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, 2019: all ages‡	Hospital discharges, 2018: all ages	Cost, 2017–2018
Both sexes	126 900 000 (49.2%)	26 100 000 (9.3%)	874 613	5 020 000	\$378.0 Billion
Males	66 100 000 (54.1%)	13 700 000 (10.4%)	453 801 (51.9%)§		\$239.2 Billion
Females	60 800 000 (44.4%)	12 400 000 (8.4%)	420 812 (48.1%)§		\$138.8 Billion
NH White males	53.6%	10.4%	347 087	...	...
NH White females	42.1%	7.8%	324 795	...	...
NH Black males	60.1%	11.0%	57 761	...	...
NH Black females	58.8%	11.5%	54 544	...	...
Hispanic males	52.3%	8.7%	31 864	...	...
Hispanic females	42.7%	8.1%	26 820	...	...
NH Asian males	52.0%	6.8%	12 939	...	...
NH Asian females	42.5%	4.2%	11 862	...	...
NH American Indian/Alaska Native	...	...	4635	...	...

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.<sup>1</sup> Percentages for racial and 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.<sup>47</sup> 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.<sup>54</sup> Cost: Unpublished NHLBI tabulation using Medical Expenditure Panel Survey,<sup>56</sup> average annual 2017 to 2018 (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 People for CVD, CHD, and Stroke, by State, 2017 to 2019**

State	CVD			CHD			Stroke		
	Rank	Death rate	% Change, 2007–2009 to 2017–2019	Rank	Death rate	% Change, 2007–2009 to 2017–2019	Rank	Death rate	% Change, 2007–2009 to 2017–2019
Alabama	51	292.0	−8.8	20	82.4	−26.5	51	51.0	−9.3
Alaska	7	183.6	−12.7	7	67.2	−24.8	26	36.6	−17.5
Arizona	8	185.6	−12.5	24	83.8	−27.6	9	30.7	−9.2
Arkansas	49	283.2	−7.0	52	134.7	−12.2	44	42.0	−24.7
California	16	195.8	−16.9	23	83.4	−31.9	30	37.3	−9.1
Colorado	4	173.0	−12.3	3	62.1	−29.1	20	34.8	−6.9
Connecticut	6	183.1	−13.5	11	74.6	−22.8	4	27.2	−16.5
Delaware	30	216.7	−11.1	25	86.0	−32.4	49	45.9	14.0
District of Columbia	40	240.5	−19.4	40	101.2	−39.5	27	36.8	−1.5
Florida	18	197.6	−10.7	29	88.7	−25.6	36	39.6	13.7
Georgia	38	236.0	−13.9	9	71.7	−25.3	46	42.9	−13.2
Hawaii	5	175.1	−13.6	5	64.8	−18.4	29	37.3	−9.4
Idaho	25	205.5	−5.8	16	79.3	−19.3	25	36.3	−14.9
Illinois	31	217.5	−13.3	17	80.5	−34.0	32	38.3	−9.5
Indiana	39	239.5	−10.3	36	97.8	−21.4	39	40.3	−11.5
Iowa	33	218.8	−9.1	42	101.9	−24.7	14	32.6	−23.2

(Continued)



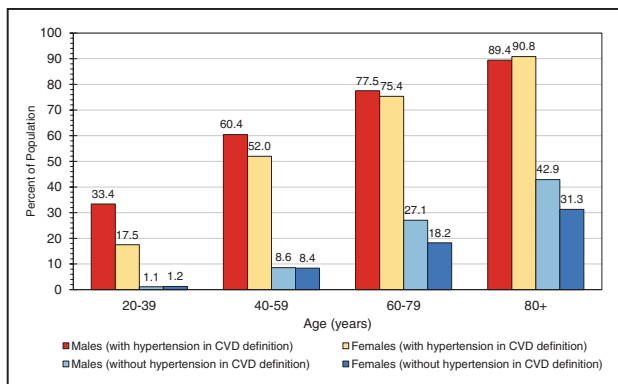
**Table 14-2. Continued**

State	CVD			CHD			Stroke		
	Rank	Death rate	% Change, 2007–2009 to 2017–2019	Rank	Death rate	% Change, 2007–2009 to 2017–2019	Rank	Death rate	% Change, 2007–2009 to 2017–2019
Kansas	32	218.2	−9.9	34	94.9	−7.0	24	36.1	−21.8
Kentucky	45	253.6	−12.3	37	100.9	−27.4	42	41.2	−14.1
Louisiana	48	270.4	−10.8	33	94.7	−27.1	50	46.1	−6.1
Maine	12	192.3	−12.3	13	77.1	−25.4	18	34.1	−13.8
Maryland	34	219.6	−13.6	30	90.0	−32.7	41	40.7	−1.2
Massachusetts	3	171.8	−19.1	6	65.9	−35.5	3	26.8	−22.9
Michigan	43	251.5	−9.7	47	112.0	−23.5	35	39.5	−7.1
Minnesota	2	166.6	−7.5	1	60.4	−17.1	13	32.6	−11.5
Mississippi	52	300.8	−13.0	45	105.6	−23.5	52	51.7	−2.6
Missouri	41	243.6	−13.4	43	102.5	−29.7	33	39.1	−18.3
Montana	23	204.7	−6.4	28	88.2	−5.1	11	31.4	−20.6
Nebraska	17	197.2	−11.4	10	73.4	−17.4	12	31.5	−24.3
Nevada	44	251.8	−3.1	46	107.3	3.1	28	36.8	−5.9
New Hampshire	11	189.8	−11.5	15	78.2	−27.8	6	28.2	−17.7
New Jersey	24	205.2	−13.4	27	87.9	−31.1	8	30.1	−11.2
New Mexico	20	199.0	−7.0	44	102.6	−5.0	16	33.2	−13.0
New York	28	211.6	−21.0	48	115.6	−32.0	2	24.3	−13.4
North Carolina	29	213.3	−16.1	21	82.4	−30.3	43	41.9	−15.5
North Dakota	14	195.5	−10.4	22	82.9	−29.2	17	33.7	−10.7
Ohio	42	248.9	−6.3	41	101.4	−25.3	45	42.5	−3.7
Oklahoma	50	289.7	−8.6	50	120.9	−25.4	40	40.6	−24.0
Oregon	10	189.1	−10.9	2	61.9	−30.5	34	39.1	−10.8
Pennsylvania	36	224.2	−12.8	32	94.2	−26.0	22	35.7	−15.1
Puerto Rico	1	151.4	−22.8	8	68.0	−24.4	1	24.2	−39.3
Rhode Island	21	200.5	−15.5	38	100.9	−32.4	5	28.1	−14.6
South Carolina	37	229.1	−14.0	18	82.2	−26.7	48	44.1	−17.0
South Dakota	27	206.9	−8.2	39	101.1	−19.2	19	34.1	−14.3
Tennessee	47	263.8	−10.9	49	120.5	−25.1	47	43.4	−17.3
Texas	35	222.7	−13.5	31	93.0	−24.2	37	40.2	−17.3
Utah	15	195.6	−4.8	4	63.2	−15.0	23	35.7	−9.6
Vermont	19	198.5	−6.4	35	96.2	−14.4	7	29.3	−16.8
Virginia	22	203.7	−15.3	12	75.5	−27.8	31	38.2	−13.6
Washington	9	188.1	−15.2	14	77.9	−29.6	21	35.3	−13.7
West Virginia	46	257.6	−14.1	51	127.5	−15.6	38	40.2	−16.6
Wisconsin	26	206.7	−8.5	26	86.9	−17.7	15	33.1	−17.4
Wyoming	13	195.3	−16.1	19	82.3	−18.3	10	30.8	−27.7
Total United States		217.0	−13.2		90.5	−27.2		37.2	−10.8

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.

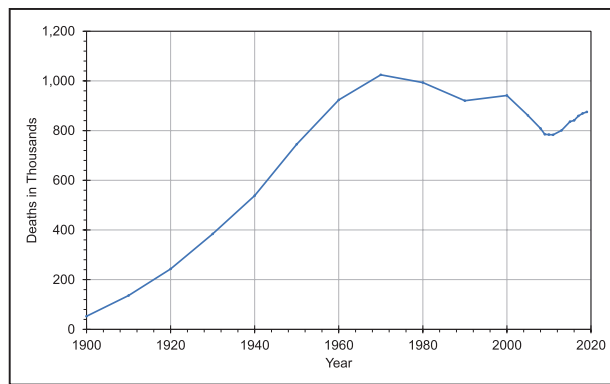
CHD indicates coronary heart disease; and CVD, cardiovascular disease.

Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System data.<sup>47</sup>



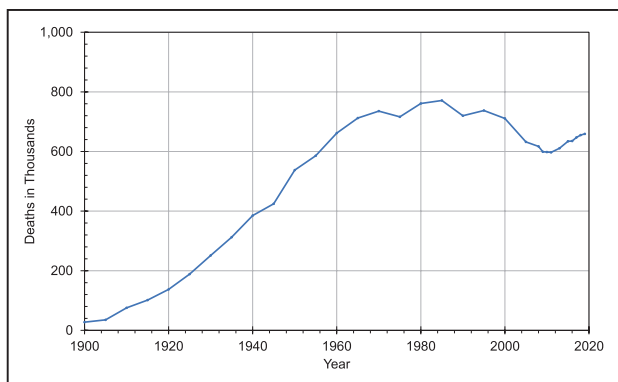
**Chart 14-1. Prevalence of CVD in US adults ≥20 years of age, by age and sex (NHANES, 2015–2018).**

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.<sup>1</sup>



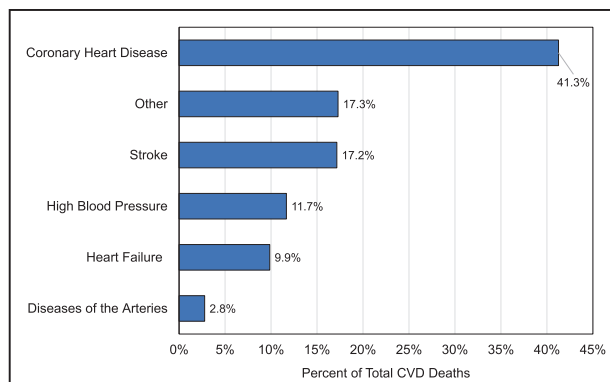
**Chart 14-3. Deaths attributable to CVD, United States, 1900 to 2019.**

CVD (*International Classification of Diseases, 10th Revision codes 100–199*) does not include congenital heart disease. Before 1933, data are for a death registration area, not the entire United States. CVD indicates cardiovascular disease. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.<sup>47</sup>



**Chart 14-2. Deaths attributable to diseases of the heart, United States, 1900 to 2019.**

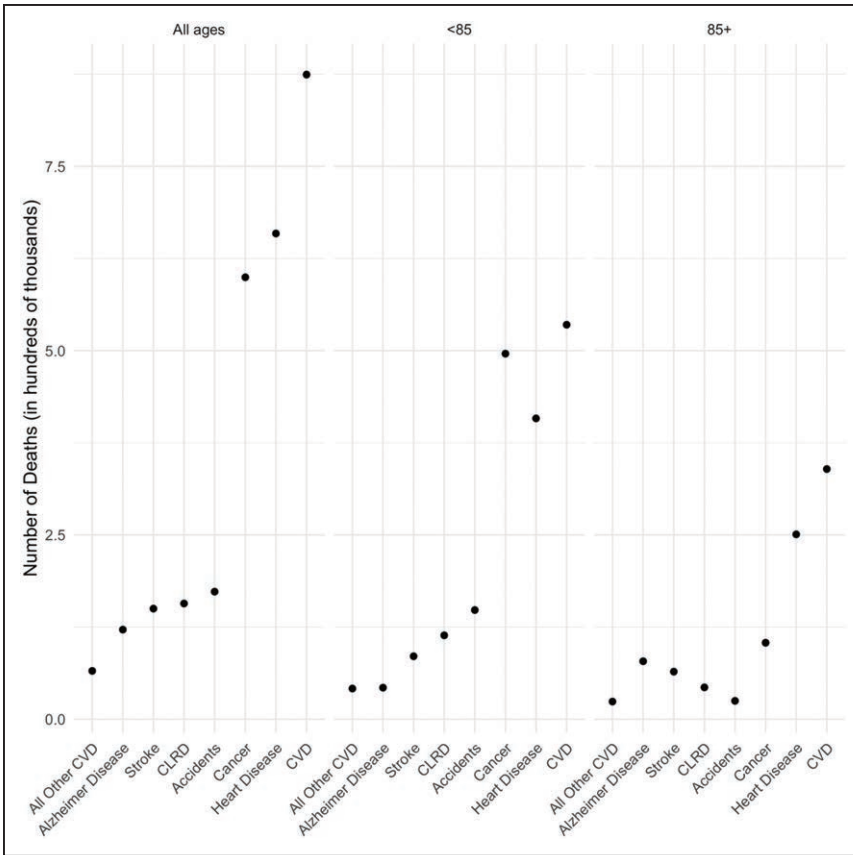
See Glossary (Chapter 30) for an explanation of diseases of the heart. In the years 1900 to 1920, the *International Classification of Diseases* codes were 77 to 80; for 1925, 87 to 90; for 1930 to 1945, 90 to 95; for 1950 to 1960, 402 to 404 and 410 to 443; for 1965, 402 to 404 and 410 to 443; for 1970 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 2019, 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.<sup>47</sup>



**Chart 14-4. Percentage breakdown of deaths attributable to CVD, United States, 2019.**

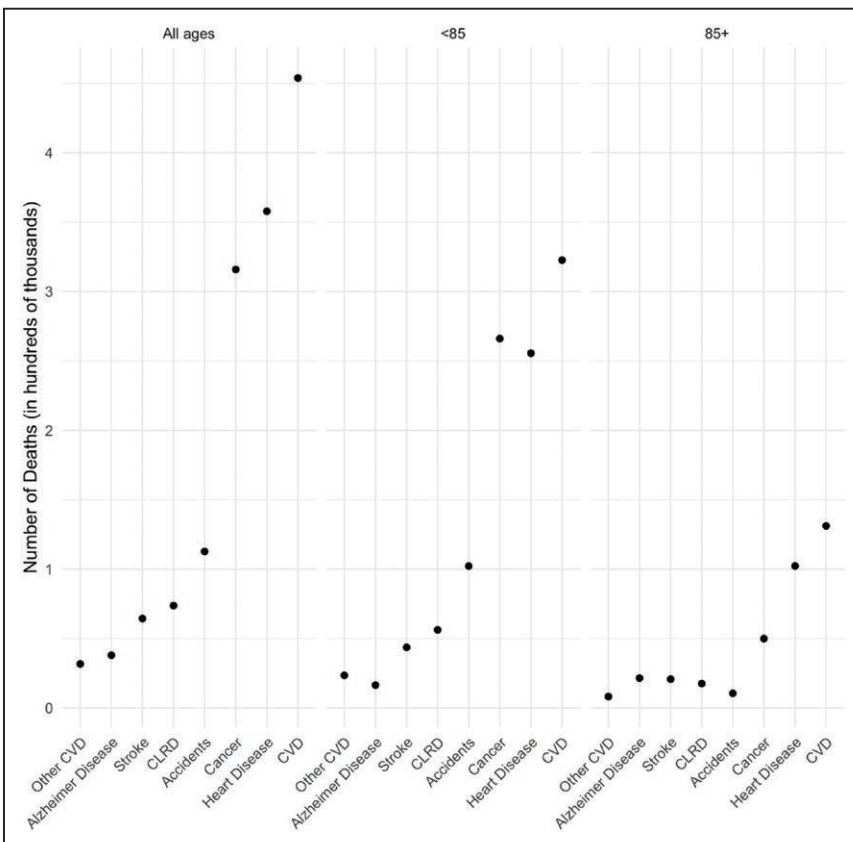
Total may not add to 100 because of rounding. Coronary heart disease includes *International Classification of Diseases, 10th Revision (ICD-10) codes I20 to I25*; stroke, I60 to I69; HF, I50; high blood pressure, I10 to I13 and I15; diseases of the arteries, I70 to I78; and other, all remaining *ICD-10* categories. CVD indicates cardiovascular disease; and HF, heart failure. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.<sup>47</sup>

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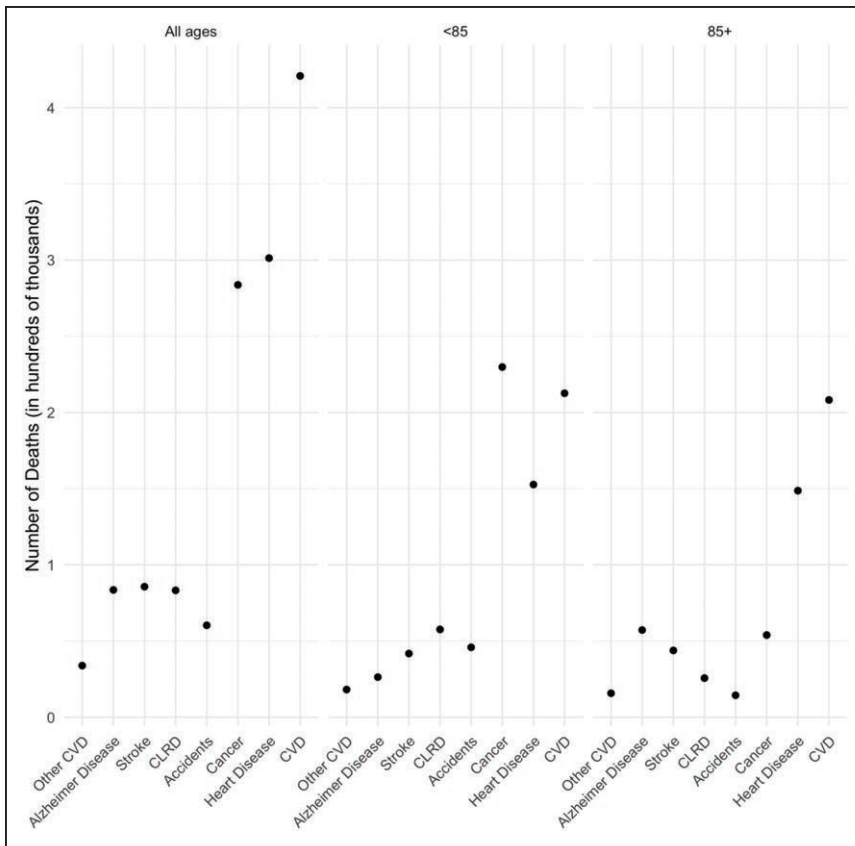
**Chart 14-5. CVD and other major causes of death: all ages, <85 years of age, and ≥85 years of age, United States, 2019.**

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.<sup>47</sup>



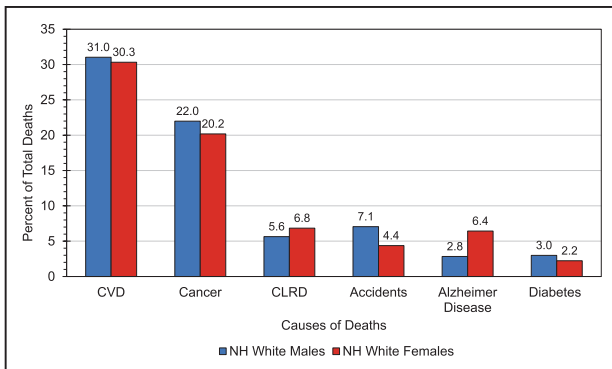
**Chart 14-6. CVD and other major causes of death in US males: all ages, <85 years of age, and ≥85 years of age, 2019.**

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.<sup>47</sup>



**Chart 14-7. CVD and other major causes of death in US females: all ages, <85 years of age, and ≥85 years of age, 2019.**

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.<sup>47</sup>



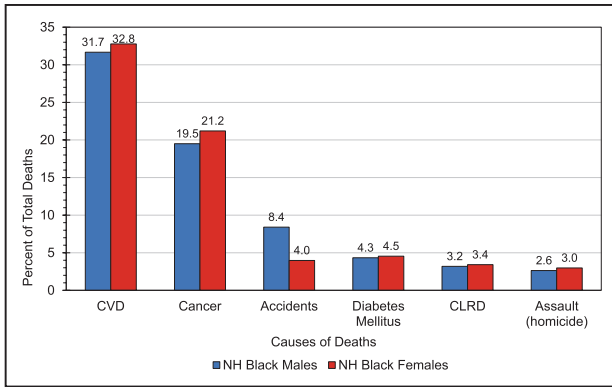
**Chart 14-8. CVD and other major causes of death for NH White males and females, United States, 2019.**

Diseases included CVD (*International Classification of Diseases, 10th Revision* codes I00–I99); cancer (C00–C97); chronic lower respiratory disease (J40–J47); accidents (V01–X59 and Y85–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.<sup>47</sup>



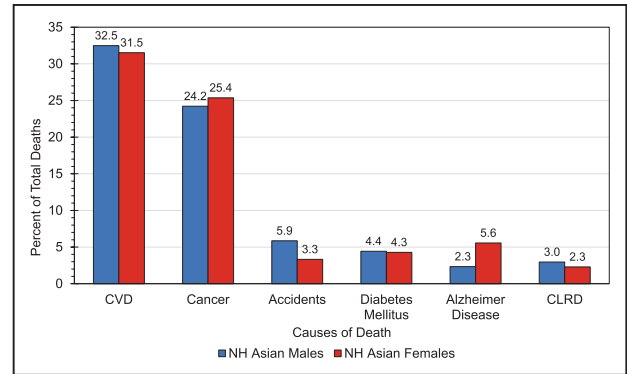


**Chart 14-9. CVD and other major causes of death for NH Black males and females, United States, 2019.**

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, U02, X85–Y09, and 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.<sup>47</sup>

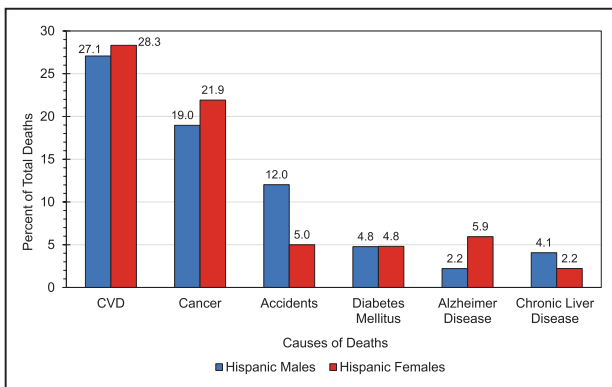


**Chart 14-11. CVD and other major causes of death for NH Asian or Pacific Islander males and females, United States, 2019.**

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).

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.<sup>47</sup>

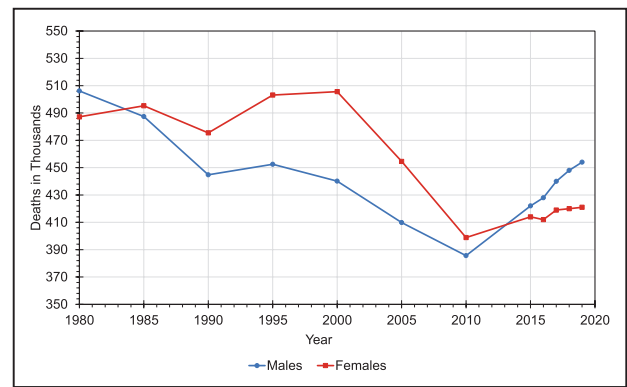


**Chart 14-10. CVD and other major causes of death for Hispanic or Latino males and females, United States, 2019.**

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.

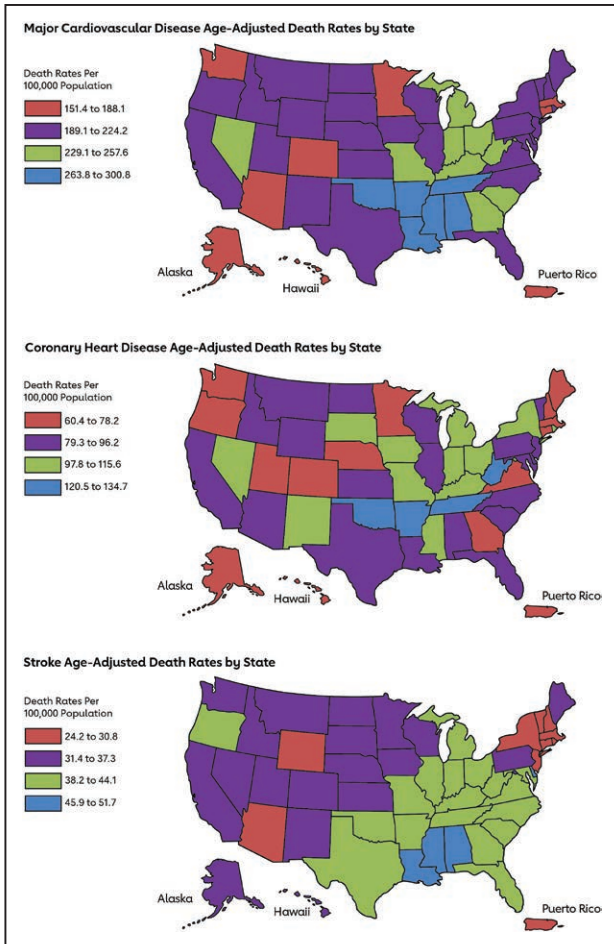
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.<sup>47</sup>



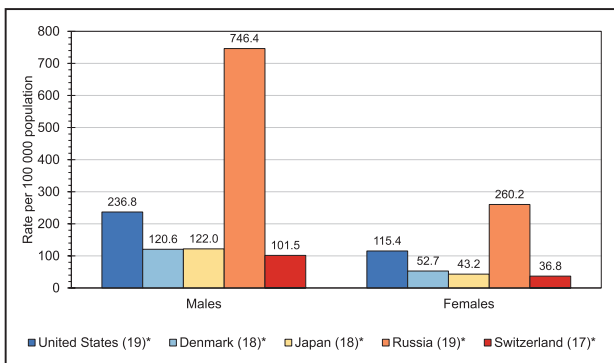
**Chart 14-12. CVD mortality trends for US males and females, 1980 to 2019.**

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. CVD indicates cardiovascular disease.

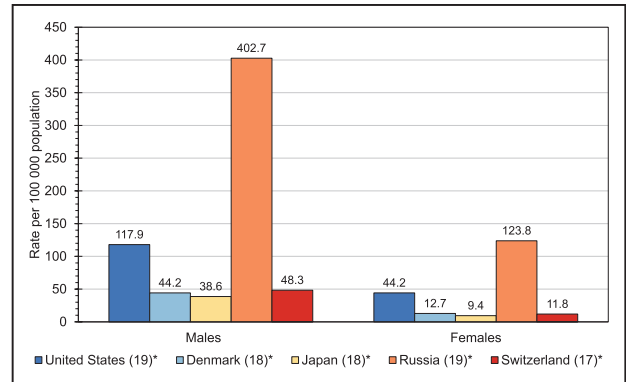
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.<sup>47</sup>



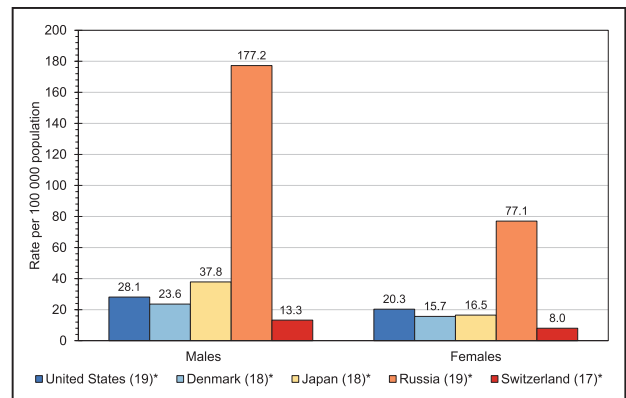
**Chart 14-13. US maps corresponding to the state age-adjusted death rates per 100 000 people for CVD, CHD, and stroke (including the District of Columbia), 2019.** CHD indicates coronary heart disease; and CVD, cardiovascular disease. Source: American Heart Association maps from unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.<sup>47</sup>



**Chart 14-14. Death rates for CVD in selected countries for adults 35 to 74 years of age, 2017 to 2019.** Rates are adjusted to the European Standard Population. *International Classification of Diseases, 10th Revision* codes are I00 to I99 for CVD. CVD indicates cardiovascular disease. \*Number in parentheses indicates year of most recent data available (17 is 2017, 18 is 2018, and 19 is 2019). Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.<sup>60</sup>

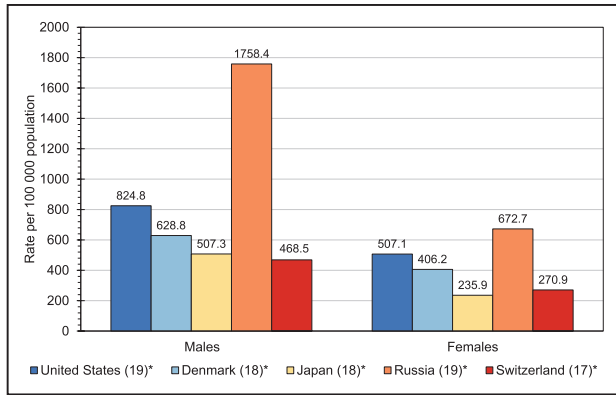


**Chart 14-15. Death rates for CHD in selected countries for adults 35 to 74 years of age, 2017 to 2019.** Rates are adjusted to the European Standard Population. *International Classification of Diseases, 10th Revision* codes are I20 to I25 for CHD. CHD indicates coronary heart disease. \*Number in parentheses indicates year of most recent data available (17 is 2017, 18 is 2018, and 19 is 2019). Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.<sup>60</sup>



**Chart 14-16. Death rates for stroke in selected countries for adults 35 to 74 years of age, 2017 to 2019.** 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, 18 is 2018, and 19 is 2019). Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.<sup>60</sup>

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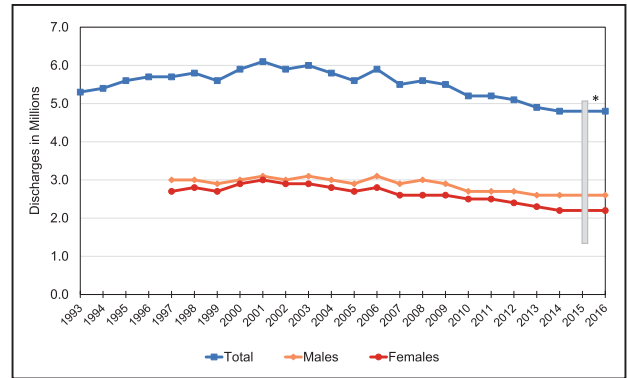


**Chart 14-17. Death rates for all causes in selected countries for adults 35 to 74 years of age, 2017 to 2019.**

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, 18 is 2018, and 19 is 2019).

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.<sup>60</sup>

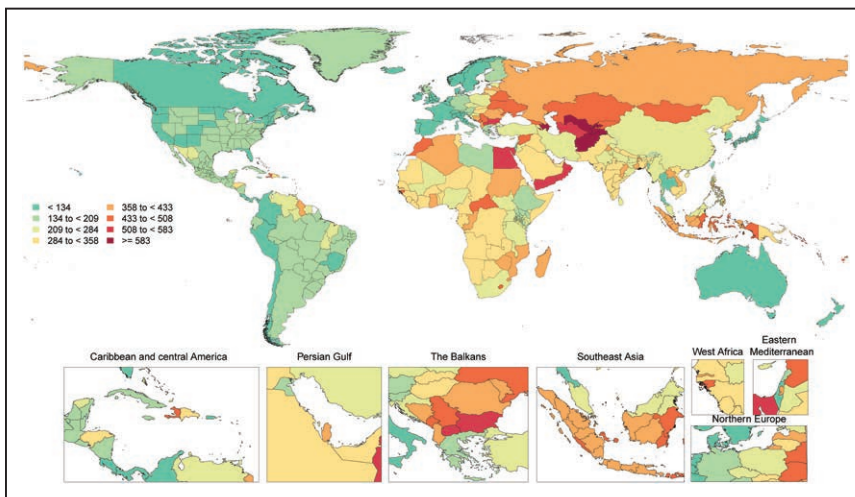


**Chart 14-18. Hospital discharges for CVD, United States males and females, 1993 to 2016.**

Hospital discharges include people discharged alive, dead, and status unknown.

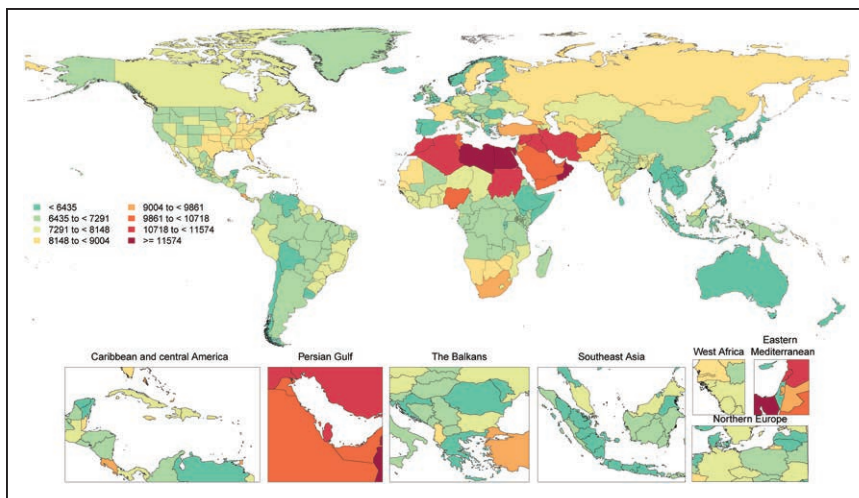
CVD indicates cardiovascular disease.

\*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.<sup>54</sup>



**Chart 14-19. Age-standardized global mortality rates of CVDs per 100 000, both sexes, 2020.**

CVD indicates cardiovascular disease. Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. Additional information is available on the Global Burden of Disease Study website.<sup>61</sup>



**Chart 14-20. Age-standardized global prevalence rates of CVDs per 100 000, both sexes, 2020.**

CVD indicates cardiovascular disease.  
Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission.  
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## 15. STROKE (CEREBROVASCULAR DISEASES)

*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).
- An estimated 7.6 million Americans  $\geq 20$  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 2019 BRFSS<sup>1</sup> (unpublished NHLBI tabulation), stroke prevalence in adults is 3.2% (median) in the United States, with the lowest prevalence in Colorado and Puerto Rico (2.0%) and the highest prevalence in Alabama (4.6%).
- 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 18 462 participants enrolled in a national cohort study, 17.8% of the population  $>45$  years of age reported at least 1 symptom.<sup>2</sup> 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  $\geq 18$  years of age, representing

The 2022 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 2022. 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.

3.9% of the adult population, will have had a stroke, a 20.5% increase in prevalence from 2012.<sup>3</sup> The highest increase (29%) is projected to be in White Hispanic males.

### Stroke Incidence

(See Table 15-1)

- Each year,  $\approx 795\,000$  people experience a new or recurrent stroke (Table 15-1). Approximately 610 000 of these are first attacks, and 185 000 are recurrent attacks (GCNKSS, NINDS, and NHLBI; GCNKSS and NINDS data for 1999 provided July 9, 2008; unpublished estimates compiled by the 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  $\geq 65$  years of age. The decreases varied across age groups but were similar across sex and race.<sup>4</sup>
- 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  $\geq 55$  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.<sup>5</sup> Comparing data from 1962 to 1967 and 1998 to 2005 shows that the relative incidence in older adults  $\geq 55$  years of age declined by more than half (HR, 0.47 [95% CI, 0.36–0.60]).<sup>6</sup>
- 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  $\geq 30$  years of age for the time period of 1995 to 2012.<sup>7</sup>
- According to 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.<sup>8</sup>
- 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%]).<sup>9</sup>

### Race and Ethnicity

- The BASIC Project demonstrated an increased incidence of ischemic stroke among Mexican American people compared with NH White people.<sup>10</sup> According to population-based surveillance data from 2000 to 2010, the age- and sex-adjusted IRR in Mexican American individuals/White individuals was the following:
  - Overall: 1.34 (95% CI, 1.23–1.46);
  - 45 to 59 years of age: 1.94 (95% CI, 1.67–2.25);
  - 60 to 74 years of age: 1.50 (95% CI, 1.35–1.67); and
  - ≥75 years of age: 1.00 (95% CI, 0.90–1.11).
- Mexican American people have a higher incidence of ICH and SAH than NH White people.<sup>11,12</sup> 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 national REGARDS cohort, in 27 744 participants followed up for 4.4 years (2003–2007), the overall age- and sex-adjusted IRR for Black participants/White participants 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).<sup>13</sup>
- 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 a greater risk of total stroke than White females after adjustment for age (HR, 1.47 [95% CI, 1.33–1.63]).<sup>14</sup> Adjustment for socioeconomic factors and stroke risk factors attenuated this association, although the higher risk for Black females remained statistically significant in those 50 to <60 years of age (HR, 1.76 [95% CI, 1.09–2.83]).
- 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); of extracranial atherosclerotic stroke, 3.18 (95% CI, 1.42–7.13); of lacunar stroke, 3.09 (95% CI, 1.86–5.11); and of 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); of extracranial atherosclerotic stroke, 1.71 (95% CI, 0.80–3.63); of lacunar stroke, 2.32 (95% CI, 1.48–3.63); and of cardioembolic stroke, 1.42 (95% CI, 0.97–2.09).<sup>15</sup>

- 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).<sup>16</sup>
- 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).<sup>4</sup>
- 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.<sup>17</sup>

### Sex

- Each year, ≈55 000 more females than males have a stroke (GCNKSS, NINDS).<sup>18</sup>
- 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%).<sup>19</sup>
- 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.<sup>20</sup>
- 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.<sup>20,21</sup>
- Racial and ethnic disparities in stroke risk may persist or even increase in elderly females from underrepresented races and ethnicities.<sup>21</sup> In NOMAS, among 3298 stroke-free participants followed up through 2019, Black and Hispanic females ≥70 years of age



had a higher risk of stroke compared with White females after adjustment 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]).<sup>22</sup> This increased risk was not present among elderly Black or Hispanic males compared with White males.

### TIA: Prevalence, Incidence, Racial and Ethnic Disparities, 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.<sup>23</sup> 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 professional.
- In the GCNKSS, the incidence rate of TIA was higher for males (101.4 [95% CI, 92.4–110.4] per 100 000) than for females (69.8 [95% CI, 64.0–75.8] per 100 000;  $P < 0.0001$ ).<sup>24</sup> The incidence rate of TIA was also higher for Black (98.0 [95% CI, 82.1–113.9]) than White (81.3 [95% CI, 76.0–86.6]) individuals ( $P = 0.025$ ).
- In the BASIC study, Mexican American individuals 45 to 59 years of age were almost twice as likely to experience a TIA as NH White individuals (risk ratio, 1.95 [95% CI, 1.30–2.92]). However, at older ages, there were no significant differences.<sup>11</sup>
- TIAs confer a substantial short-term risk of stroke, hospitalization for CVD events, and death. There is a 1.2% risk of stroke at 2 days and 7.4% risk of stroke at 90 days after TIA.<sup>25</sup>
- In a large multicenter TIA registry study, the 1-year stroke risk was 5.1% and 5-year stroke risk was 9.5%.<sup>26</sup> The combined risk of stroke, ACS, or death attributable to cardiovascular causes was 6.2% at 1 year and 12.9% at 5 years.<sup>27</sup>
- Among Medicare beneficiaries >65 years of age in the US nationwide GWTG–Stroke Registry linked to Medicare claims data (2011–2014), in those with an NIHSS score  $\leq 5$  or high-risk TIA ( $n = 6518$  patients from 1471 hospitals), the cumulative incidence of stroke was 2.4% at 30 days, 4.0% at 90 days, and 7.3% at 1 year.<sup>28</sup>
- In a meta-analysis of 47 studies,<sup>29</sup> 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.<sup>30</sup> In the Oxford Vascular Study, acute lesions on MRI were identified in 13% of participants with TIA.<sup>31</sup> In age- and sex-adjusted analyses, these participants had a higher risk of recurrent ischemic stroke compared

with individuals with TIA and negative MRI (HR, 2.54 [95% CI, 1.21–5.34];  $P = 0.014$ ).

- Among patients with TIA enrolled in the POINT trial, 188 of 1964 patients (9.6%) enrolled with TIA had a modified Rankin Scale score  $< 1$  (some disability) at 90 days.<sup>32</sup> In multivariable analysis, age, subsequent ischemic stroke, serious adverse events, and major bleeding were significantly associated with disability in TIA.

### Recurrent Stroke: Incidence, Race and Ethnicity, and Risk

- 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.<sup>33</sup> 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.
- 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]).<sup>34</sup>
- 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.<sup>35</sup> 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 (aHR, 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]).<sup>36</sup>

- 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]).<sup>37</sup>
- 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).<sup>38</sup>
- In a nationwide cohort study of Danish patients with first ischemic stroke treated with intravenous tPA, time from symptom onset to treatment was associated with long-term recurrent stroke risk.<sup>39</sup> Compared with those treated within 90 minutes, the risk was increased for those treated at 91 to 180 minutes (HR, 1.25 [95% CI, 1.06–1.48]) and for those treated at 181 to 270 minutes (HR, 1.35 [95% CI, 1.12–1.61]).
- In a study in China (N=9022), adherence to guideline-based secondary stroke prevention conferred a lower risk of recurrent stroke (HR, 0.85 [95% CI, 0.74–0.99]) at 12 months compared with those with low or no adherence.<sup>40</sup>

## 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.<sup>41,42</sup>

### High BP

(See Chapter 8 [High Blood Pressure] for more information.)

- 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 mmHg, which suggests that stroke risks in patients with hypertension do not increase with extremely low mean arterial pressure or pulse pressure values.<sup>43</sup>

- A scientific statement from the AHA identified resistant hypertension, defined as above-goal elevated BP of 130/80 mmHg 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.<sup>44</sup>
- In a meta-analysis (11 studies), hypertension was associated with risk of recurrent stroke (OR, 1.67 [95% CI, 1.45–1.92]).<sup>45</sup>
- Among adults treated for hypertension in an ambulatory setting in the United States, tight BP control (<130 mmHg) was associated with 42% lower incidence of stroke (95% CI, 9%–63% lower) compared with standard BP control (130–139 mmHg).<sup>46</sup>
- Higher pulse pressure was associated with first ischemic stroke (aHR per SD, 1.17 [95% CI, 1.05–1.40]) in a study of hypertensive adults ≥60 years of age who annually attended physical examination in the community health care center in Guangdong, China.<sup>47</sup>
- Among adults in the United Kingdom, genetically predicted pulse pressure was associated with ischemic stroke in those ≥55 years of age (aOR per SD, 1.23 [95% CI, 1.13–1.34]) independently of genetically predicted mean arterial pressure.<sup>48</sup>
- Among adults ≥35 years of age recruited from rural areas of Fuxin County, Liaoning Province, China, ideal BP for stroke prevention varied by BMI: At BMI <24 kg/m<sup>2</sup>, stroke risk was lowest in those with BP <130/80 mmHg, whereas at BMI ≥24 kg/m<sup>2</sup>, stroke risk was lowest in those with BP <120/80 mmHg.<sup>49</sup> A 20-mmHg increment in SBP was associated with 1.28 times the risk for stroke (95% CI, 1.22–1.34), and a 10-mmHg increment in DBP was associated with 1.14 times the risk for stroke (95% CI, 1.09–1.19).
- In a secondary analysis of 17 916 patients in the PROFESS trial, BP variability, defined as the SD across repeated measurements, was associated with an increased risk of recurrent stroke.<sup>50</sup> 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.<sup>51</sup>
- 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.<sup>52</sup> 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 [Diabetes] for more information.)

- 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 aRR 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.<sup>53</sup> 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 aRR for stroke was 1.21 (95% CI, 1.02–1.44).<sup>54</sup>
- 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 diabetes (HR, 1.45 [95% CI, 1.32–1.59]).<sup>55</sup>
- 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]).<sup>56</sup>
- In a meta-analysis of 11 RCTs that included 56 161 patients with type 2 diabetes and 1835 cases of stroke, 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];  $P=0.33$ ).<sup>57</sup>
- A meta-analysis of 28 RCTs involving 96 765 participants with diabetes revealed that a decrease in SBP by 10 mmHg 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  $\geq 140$  mmHg and no significant associations among trials with baseline SBP  $< 140$  mmHg (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  $< 130$  mmHg and the  $\geq 130$  mmHg groups.<sup>58</sup>

## Disorders of Heart Rhythm

(See Chapter 18 [Disorders of Heart Rhythm] for more information.)

### Atrial Fibrillation

- Because AF is often asymptomatic<sup>59</sup> and frequently undetected clinically,<sup>60</sup> the stroke risk attributed to AF is likely substantially underestimated. In a meta-analysis of 50 studies, AF was detected in  $\approx 24\%$  (95% CI, 17%–31%) of patients with embolic stroke of undetermined source, depending on duration and type of monitoring used.<sup>61</sup>
- 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.<sup>62</sup>
- 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.<sup>63</sup>
- Important risk factors for stroke in the setting of AF include older age, hypertension, HF, diabetes, previous stroke or TIA, vascular disease, renal dysfunction, low BMI, and female sex.<sup>64–68</sup> Biomarkers such as high levels of troponin and BNP are associated with an increased risk of stroke in AF after adjustment for traditional vascular risk factors.<sup>69</sup>
- In patients with AF who are being treated with anticoagulation, presence of persistent AF versus paroxysmal AF is associated with higher risk of stroke.<sup>70,71</sup> In a meta-analysis of 26 studies of patients with AF and prior stroke (N= 23 054 patients), nonparoxysmal AF compared with paroxysmal AF was associated with a higher risk of recurrent stroke (OR, 1.47 [95% CI, 1.08–1.99]).<sup>72</sup>
- In a meta-analysis of 35 studies (N=2458010 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]).<sup>73</sup>

- In a meta-analysis of 28 studies (N = 2612816 patients), AF after noncardiac surgery was associated with a  $\approx 3$  fold increased risk of stroke at 1 month (OR, 2.82 [95% CI, 2.15–3.70]) and  $\approx 4$  fold increase in long-term risk of stroke (OR, 4.12 [95% CI, 3.32–35.11]).<sup>74</sup>
- In an analysis of 2046 patients admitted with acute ischemic stroke who had AF, mean heart rate during the acute ischemic stroke period was not associated with stroke recurrence but was associated with higher mortality.<sup>75</sup>

### Other Arrhythmias

- In an analysis of inpatient and outpatient claims data from a 5% sample of all Medicare beneficiaries  $\geq 66$  years of age (2008–2014), atrial flutter was associated with a lower risk of stroke than AF.<sup>76</sup>
- Paroxysmal SVT<sup>77</sup> and excessive supraventricular ectopic activity<sup>78</sup> have been associated with a doubling of stroke risk in the absence of known AF. In a meta-analysis of 5 studies (N=7545 patients), excessive supraventricular ectopic activity, defined as the presence of either  $\geq 30$  premature atrial contractions per hour or any runs of  $\geq 20$  premature atrial contractions, was associated with an increased risk of stroke (HR, 2.19 [95% CI, 1.24–4.02]).<sup>79</sup>
- In a French longitudinal cohort study of 1692 157 patients who underwent 1:1 propensity score matching, isolated sinus node disease was associated with a lower risk of ischemic stroke compared with AF (HR, 0.77 [95% CI, 0.73–0.82]) but a higher risk compared with a control population (HR, 1.27 [95% CI, 1.19–1.35]).<sup>80</sup>

### High Blood Cholesterol and Other Lipids

(See Chapter 7 [High Blood Cholesterol and Other Lipids] for more information.)

- The relationships between the distinct serum lipid fractions (TC, LDL-C, HDL-C, and triglycerides) and stroke risk and outcomes vary; associations differ for ischemic stroke, its subtypes, and ICH.<sup>81–84</sup>

### Total Cholesterol

- An association between TC and ischemic stroke has been found in most, but not all, prospective observational studies.<sup>81,84–86</sup> An association between elevated TC and ischemic and total stroke mortality was noted to be present in those 40 to 59 years of age but not in other age groups in the Prospective Studies Collaboration.<sup>83</sup>
- In a meta-analysis of data from 61 cohorts, TC was weakly associated with risk of total stroke.<sup>87</sup>
- Elevated TC is inversely associated with hemorrhagic stroke. In a meta-analysis of 23 prospective cohort and case-control studies, a 1-mmol higher TC concentration was associated with a 15% lower

risk of hemorrhagic stroke (HR, 0.85 [95% CI, 0.80–0.91]).<sup>88</sup>

### LDL Cholesterol

- Evidence from RCTs, mendelian randomization analyses, and population-based cohort studies supports a direct and causal relationship between serum LDL-C and atherosclerotic ischemic stroke risk.<sup>89</sup>
  - A meta-analysis of LDL-C-lowering drug treatment trials has demonstrated that every 1-mmol/L ( $\approx 39$  mg/dL) reduction in LDL-C is associated with a 20% lower risk of ischemic stroke (RR, 0.80 [95% CI, 0.76–0.84]) and 17% increased risk of ICH (RR, 1.17 [95% CI, 1.03–1.32]).<sup>90</sup>
  - In an RCT that enrolled individuals with prior ischemic stroke/TIA and evident atherosclerosis, achieving an LDL-C  $< 70$  mg/dL (versus an LDL-C target range of 90–110 mg/dL) was associated with a lower risk of subsequent cardiovascular events (HR, 0.78 [95% CI, 0.61–0.98]) without increased risk of ICH.<sup>91</sup>
  - In a nested case-control analysis using data from the Chinese Kadoorie Biobank prospective study of 489762 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.<sup>90</sup> 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.
  - Another mendelian randomization study of lipid genetics also suggested an increased risk of large-artery ischemic stroke with increased LDL.<sup>92</sup>

### HDL Cholesterol

- HDL-C has been inversely associated with ischemic stroke risk in most, but not all, observational studies.<sup>84,93,94</sup>
- A meta-analysis of prospective cohort and case-control studies demonstrated an association between elevated HDL-C and reduced risk of total stroke.<sup>84</sup> In the cohort studies, a 10-mg/dL increase in HDL-C was associated with an 11% to 15% reduced risk of total stroke.<sup>84</sup>
  - Genetic predisposition to higher HDL-C has been associated with lower risk of small-vessel ischemic stroke in mendelian randomization analyses.<sup>92,95</sup>
- In a meta-analysis, a direct association was observed between increased HDL-C levels and

risk of hemorrhagic stroke (RR, 1.17 [95% CI, 1.02–1.35]).<sup>88</sup>

### Triglycerides

- Serum triglyceride levels have been associated with increased risk of ischemic stroke in some, but not all, prospective population-based cohort studies.<sup>94,96–99</sup>
- Low triglyceride levels have been associated with an increased risk of hemorrhagic stroke. In the WHS, compared with females in the highest quartile of triglyceride levels, those in the lowest quartile had an increased risk of hemorrhagic stroke (RR, 2.00 [95% CI, 1.18–3.39]).<sup>100</sup>

### Smoking/Tobacco Use

(See Chapter 3 [Smoking/Tobacco Use] for more information.)

- Current smoking is associated with an increased prevalence of MRI-defined subclinical brain infarcts.<sup>101</sup>
- A meta-analysis of 141 cohort studies showed that low cigarette consumption ( $\approx$ 1 cigarette per day) carries a risk of developing stroke up to 50% of the risk associated with high cigarette consumption ( $\approx$ 20 cigarettes per day).<sup>102</sup> This is much higher than what would be predicted from a linear or log-linear dose-response relationship between smoking and risk of stroke.<sup>102</sup>
- 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.<sup>103,104</sup>
  - Data from a 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  $\geq$ 80 years of age (HR, 1.24 [95% CI, 1.05–1.46]).<sup>105</sup> 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,  $96.4 \pm 20.8$  versus  $56.7 \pm 4.8$  per 100 person-years;  $P=0.026$ ).<sup>106</sup>
- 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]).<sup>107</sup>
- 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.<sup>108</sup>
- Smoking is perhaps the most important modifiable risk factor in preventing SAH, with the highest PAR (38%–43%) of any SAH risk factor.<sup>109</sup>
- 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.<sup>110</sup>
- In a systematic review of efficacy of smoking-cessation pharmacotherapy after stroke ( $n=2$  trials and  $n=6$  observational studies), cessation rates ranged from 33% to 66% with pharmacological therapy combined with behavioral interventions versus 15% to 46% without behavioral interventions, but no individual study demonstrated a statistically significant benefit.<sup>111</sup>

### Physical Inactivity

(See Chapter 4 [Physical Activity and Sedentary Behavior] for more information.)

- The GBD 2019 study demonstrated that the burden of stroke attributable to physical inactivity was  $\approx$ 1.68% globally and 2.75% in high-income countries.<sup>41,42</sup>
- Physical inactivity is a significant risk factor for stroke in middle-aged and elderly populations.<sup>112,113</sup>
- A prospective study among 437 318 participants in China found that physical inactivity was associated with increased risk of incident stroke and its subtypes (HR, 1.74 [95% CI, 1.61–1.89]; aHR, 1.52 [95% CI, 1.37–1.70]).<sup>114</sup>
- 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 min/d versus 38 min/d) than controls ( $n=23$ ).<sup>115</sup>
- A case-control study ( $>60$  years of age) found that subjects with stroke ( $n=97$ ) were physically inactive more often than controls ( $n=97$ ; 74.2% versus 63.9%) and showed that lack of PA was associated with increased odds of stroke (OR 3.34 [95% CI, 1.34–8.41]).<sup>116</sup> 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]).<sup>117</sup>



- In the CHS, both a greater amount of leisure-time PA (across quintiles,  $P_{\text{trend}}=0.001$ ) and exercise intensity (categories: high, moderate, and low versus none,  $P_{\text{trend}}<0.001$ ) were associated with lower risk of stroke among individuals  $>65$  years of age. The relationship between greater PA and lower risk of stroke was observed even in individuals  $\geq 75$  years of age.<sup>118</sup>
- In the Cooper Center Longitudinal Study, 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.<sup>119</sup>
- 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.<sup>120</sup>

### Cardiorespiratory Fitness

- The REGARDS study ( $\geq 45$  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 White participants 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]).<sup>121</sup>
- The Oslo Ischemia Cohort Study assessed change in cardiorespiratory fitness levels, assessed by a bicycle electrocardiographic test, between baseline and over 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 (above median) from unfit (below median) 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.<sup>122</sup>
- 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]).<sup>123</sup>
- Studies have also demonstrated a significant association between sedentary time and risk of CVD, including stroke, that was independent of

PA levels. In the WHI, those who sat  $\geq 10$  h/d compared with those who sat  $< 5$  h/d were at increased risk of stroke after multivariable adjustment, including BMI and PA (aHR, 1.18 [95% CI, 1.04–1.34]).<sup>124</sup>

- 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.<sup>125</sup>

### Nutrition

#### (See Chapter 5 [Nutrition] for more information.)

- Overall dietary pattern: In a 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 consumption of 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.<sup>126</sup>
- Fruits and vegetables: In a study based on 2017 GBD data for China, the association of low fruit intake with stroke mortality was stronger for men than for women and stronger for older adults than for younger adults.<sup>127</sup> Compared with 1992, in 2017, the age-standardized stroke mortality attributed to fruit intake was 0.94 for men and 0.59 for females.
- Fiber: 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 fiber per day had the greatest health benefits.<sup>128</sup>
- Coffee: In a meta-analysis of 21 studies (N $> 2.4$  million individuals), the highest category of coffee consumption was associated with 13% (95% CI, 6%–20%) lower stroke risk compared with the lowest category of coffee consumption.<sup>129</sup>
- Milk: In the Japan Collaborative Cohort, daily milk consumption was associated with 20% (95% credible interval, 7%–31%) lower stroke risk among males but not among females (RR, 0.95 [95% CI, 0.80–1.17]).<sup>130</sup>
- ASBs: The FHS (N=2888,  $> 45$  years of age) showed that those who consumed  $\geq 1$  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.<sup>131</sup>
- Omega-3 fatty acids:
  - 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.<sup>132</sup>
- In the VITAL RCT in the United States (N=25 871), those participants (males ≥50 years of age; females ≥55 years of age) who consumed an omega-3 fatty acid supplement 1 g/d (EPA 460 mg plus DHA 380 mg) for an average of 5.3 years had a stroke risk similar to those not taking omega-3 supplements (RR, 1.04 [95% CI, 0.83–1.31]).<sup>133</sup>
  - However, in the US Million Veteran Program, omega-3 fatty acid supplement use was associated with 12% (95% CI, 5%–19%) lower risk of nonfatal ischemic stroke over 3.3 years of follow-up, although fish intake was not associated with stroke risk.<sup>134</sup>
  - Vitamin D: In a meta-analysis of 20 observational cohort studies (n = 217 235), the highest category of vitamin D intake was associated with 25% (95% CI, 2%–43%) lower stroke risk than the lowest category of vitamin D intake; optimal vitamin D intake for low stroke risk was ≈12 μg/d.<sup>135</sup> However, in a meta-analysis of 22 RCTs (N=83 200), vitamin D supplementation did not affect stroke risk (RR, 0.97 [95% CI, 0.90–1.03]).<sup>136</sup>
  - Saturated fats: In a meta-analysis of 12 studies (N=462 268), each 10-g/d increment in saturated fat intake was associated with 6% (95% CI, 2%–11%) lower stroke risk.<sup>137</sup>

### Kidney and Liver Disease

(See Chapter 12 [Kidney Disease] 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<sup>-1</sup>·1.73 m<sup>-2</sup>.<sup>138</sup>
- A meta-analysis of 38 studies comprising 1 735 390 participants (n=26 405 stroke events) showed that any level of proteinuria was associated with greater stroke risk even after adjustment for cardiovascular risk factors (aRR, 1.72 [95% CI, 1.51–1.95]).<sup>139</sup> The association did not substantially attenuate with further adjustment for hypertension.
- A meta-analysis showed that stroke risk increases linearly and additively with declining GFR (RR per 10-mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> 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]).<sup>140</sup>
- 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]).<sup>141</sup>
- Among 232 236 patients in the GWTC-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<sup>-1</sup>·1.73 m<sup>-2</sup> without dialysis (OR, 2.52 [95% CI, 2.07–3.07]) compared with eGFR ≥60 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>. Lower eGFR was also associated with decreased likelihood of being discharged home.<sup>142</sup>

- In a Chinese stroke registry, low eGFR (<60 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>) compared with eGFR ≥90 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> 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.<sup>143</sup> 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).
- In a retrospective observational cohort study (N=85 116 patients with incident nonvalvular AF), stroke rates increased from 1.04 events per 100 person-years in stage 1 CKD to 3.72 in stages 4 to 5 CKD.<sup>144</sup> Major bleeding rates increased from 0.89 per 100 person-years in stage 1 CKD to 4.91 events per 100 person-years in stages 4 to 5 CKD.
- In the ARIC study cohort (N=12 588 participants; median follow-up time, 24.2 years), those in the top quartile of concentration of the liver enzyme γ-glutamyl transpeptidase compared with those in the lowest were at increased risk of stroke after adjustment for age, sex, and race (aHR, 1.94 [95% CI, 1.64–2.30] for all incident stroke; aHR, 2.01 [95% CI, 1.68–2.41] for ischemic stroke).<sup>145</sup> There was a dose-response association (*P* for linear trend <0.001).

### Stroke After Procedures and Surgeries

- In-hospital stroke rates after TAVR declined from 2.2% in 2012 to 1.6% in 2019.<sup>146</sup>
- In a registry of 123 186 patients, the use of embolic protection devices for TAVR increased over time, reaching 13% of TAVR procedures in 2019.<sup>147</sup> However, embolic protection device use was not associated with a lower risk of in-hospital stroke in the primary instrumental variable analysis (aRR, 0.90 [95% CI, 0.58–1.13]).
- In a study from the STS National Adult Cardiac Surgery Database, the incidence of postoperative stroke after type A aortic dissection repair was 13%.<sup>148</sup> Axillary cannulation and retrograde

cerebral perfusion were associated with lower risk of postoperative stroke.

- In a nationwide prospective cohort study from Denmark (N=78096 elderly patients undergoing hip fracture surgery), patients with a higher CHA<sub>2</sub>DS<sub>2</sub>-VASc score had a higher risk of ischemic stroke among patients with and without AF.<sup>149</sup>
- In the PRECOMBAT trial evaluating the long-term outcomes of PCI with drug-eluting stents compared with CABG for unprotected left main CAD, the 10-year incidence of ischemic stroke was not significantly different (HR, 0.71 [95% CI, 0.22–2.23]; incidence rate, 1.9% in the PCI arm [n=300] and 2.2% in the CABG arm [n=300]).<sup>150</sup>

### 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 100000 pregnancies (95% CI, 18.8–47.9). The crude rates per 100000 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.<sup>151</sup>
- Among 80191 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]).<sup>152</sup>
- 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 (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.<sup>153</sup>
- In the UK Million Women Study, there was a U-shaped relationship between age at menarche and risk of incident stroke.<sup>154</sup> 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 1.13 [95% CI, 1.03–1.24], respectively).

- In a prospective cohort study in Japan (N=74928 adults), weight gain during midlife was associated with an increased risk of stroke in females (aHR, 1.61 [95% CI, 1.36–1.92] for weight gain ≥5 kg) but not in males.<sup>155</sup>
- In a population-based matched cohort study in the United Kingdom (n=56090 females with endometriosis and 223669 matched control subjects without endometriosis), females with endometriosis had a 19% increased risk of cerebrovascular disease (aHR, 1.19 [95% CI, 1.04–1.36]) compared with females without endometriosis.<sup>156</sup>
- In a study among females in Beijing, China (N=2104), compared with females who experienced menopause at 50 to 51 years of age, the risk of ischemic stroke was higher in females with menopause at <45 years of age (HR, 2.16 [95% CI, 1.04–4.51]) and at 45 to 49 years of age (HR, 2.05 [95% CI, 1.15–3.63]).<sup>157</sup> Females who had menopause before 50 years of age and at least 1 risk factor had a higher risk of stroke (HR, 2.92 [95% CI, 1.03–8.29]) than those with menopause at 50 to 51 years of age and optimal levels of all risk factors. 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]).<sup>158</sup>
- Overall, randomized clinical trial data indicate that the initiation 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<sup>159–162</sup> and recent stroke or TIA.<sup>163</sup>
- In a nested case-control study of the UK 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.<sup>164</sup>
- 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.<sup>165,166</sup>
- Among people living with HIV, females had a higher incidence of stroke or TIA than males, especially at younger ages.<sup>167</sup> Compared with females without HIV, females living with HIV had a 2-fold higher incidence of ischemic stroke.<sup>168</sup>
- In the setting of AF, females have a significantly higher risk of stroke than males.<sup>169–173</sup>

## SDB and Sleep Duration

(See Chapter 13 [Sleep] 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.<sup>174</sup>
- 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]).<sup>175</sup>
- OSA is also common after stroke.<sup>176</sup> 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%.<sup>177</sup> 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 after stroke of SDB with AHI >5 episodes per hour was 71% (95% CI, 66.6%–74.8%) and with AHI >30 episodes per hour was 30% (95% CI, 24.4%–35.5%).<sup>178</sup> 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 (PR, 1.21 [95% CI, 1.01–1.46]).<sup>176</sup>
- 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 aOR 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.<sup>179</sup>
- OSA is associated with higher poststroke mortality.<sup>180–182</sup>
- Sleep duration also may be 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 (aHR, 1.46 [95% CI, 1.26–1.69]) after adjustment for demographics, vascular risk factors, and comorbidities.<sup>183</sup>
- 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).<sup>184</sup>

- In a mendelian randomization analysis using the UK Biobank data (N=446 118 participants), short sleep was associated with an increased risk of cardioembolic stroke (OR, 1.33 [95% CI, 1.11–1.60]), and long sleep increased the risk of large-artery stroke (OR, 1.41 [95% CI, 1.02–1.95]), but associations were not significant after correction for multiple comparisons.<sup>185</sup>

## Psychosocial Factors

- A meta-analysis of 28 prospective cohort studies (317 540 participants; follow-up, 2–29 years) found that depression was associated with an increased risk of total stroke (HR, 1.45 [95% CI, 1.29–1.63]), fatal stroke (HR, 1.55 [95% CI, 1.25–1.93]), and ischemic stroke (HR, 1.25 [95% CI, 1.11–1.40]).<sup>186</sup>
- In the INTERSTROKE case-control study of 26 919 participants from 32 countries, participants with psychological distress had a >2-fold (OR, 2.20 [95% CI, 1.78–2.72]) greater odds of having a stroke than control participants.<sup>187</sup>
- In a prospective cohort study in New South Wales (N=221 677 participants; average follow-up, 4.7 years), high psychological distress was associated with increased risk of fatal and nonfatal stroke in females (HR 1.56 [95% CI, 1.26–1.93]) and males (HR, 1.19 [95% CI, 0.96–1.48]) compared with those with a low level of psychological distress.<sup>188</sup>
- 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]).<sup>189</sup>
- The presence of depressive symptoms, assessed by the 4-item Center for Epidemiological Studies Depression scale, was associated with incident stroke in both Black and White participants in the population-based REGARDS cohort study.<sup>190</sup> Participants with scores of 1 to 3 (aHR, 1.27 [95% CI, 1.11–1.43]) and scores ≥4 (aHR, 1.25 [95% CI, 1.03–1.51]) had increased stroke risk compared with participants without depressive symptoms, with no differential effect by race.



- 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]).<sup>191</sup>
- Among 13930 patients with ischemic stroke and 28026 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.<sup>192</sup> The risk score was associated with increased odds of small-artery occlusion in both ancestry samples, cardioembolic stroke in those of European ancestry, and large-artery atherosclerosis in those of African ancestry.
- In the UK Biobank cohort study (N=479 054; mean follow-up, 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 a 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]).<sup>193</sup>

## 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.<sup>194</sup>
- Long work hours have also been linked to stroke. A meta-analysis of 24 cohort studies from the United States, Europe, and Australia revealed a dose-response relationship between working >40 h/wk and incident stroke.<sup>195</sup>
- 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.<sup>196</sup>

- In a nationwide Danish registry study of individuals after stroke from 2003 to 2012 (n=60 503 strokes), income was inversely related to long-term, but not short-term, mortality for all causes of death.<sup>197</sup> There was a 5.7% absolute difference ( $P<0.05$ ) 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).<sup>198</sup>

## Family History and Genetics

- The largest multiethnic GWAS of stroke conducted to date reports 32 genetic loci.<sup>199</sup> These 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.
- 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.<sup>200,201</sup>
- A multiethnic GWAS of SAH in 10 754 cases and 306 882 controls of European and East Asian ancestry identified 17 risk loci, 11 of which were not previously reported.<sup>202</sup>
- Genetic correlation analyses suggest genetic overlaps between ischemic stroke and PA, cardiometabolic factors, smoking, and lung function. Genetic predisposition to higher concentration of small LDL particles was associated with risk of large-artery stroke (OR, 1.31 [95% CI, 1.09–1.56];  $P=0.003$ ).<sup>203</sup>
- A GWAS focused on small-vessel stroke from the International Stroke Consortium identified a novel association with a region on chromosome 16q24.2.<sup>204</sup>

- 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.<sup>205</sup>
- Low-frequency genetic variants (ie, allele frequency <5%) also may 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.<sup>206</sup> The gene encodes the  $\alpha$ 1-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.<sup>207</sup>
  - 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.<sup>208</sup>
- ICH also appears to have a genetic component, with heritability estimates of 34% to 74%, depending on the subtype.<sup>209</sup> 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.<sup>209</sup>
- Other genes strongly associated with ICH are *PMF1* and *SLC25A44*, which have been linked to ICH with small-vessel disease.<sup>210,211</sup>
- Genetic predisposition to higher monocyte chemoattractant protein-1/chemokine (C-C motif) ligand 2 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.<sup>212</sup>
- Genetic determinants of coagulation factors, including factor XI and factor VII, have been implicated in the pathogenesis of ischemic stroke.<sup>213,214</sup>

### Awareness

- Awareness of stroke symptoms and signs among US adults remains suboptimal but improved in NHIS from 2009 to 2014. In 2014, 68.3% of 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.<sup>215</sup>
- In the 2009 BRFSS (N=132604), 25% of males versus 21% of females had low stroke symptom

knowledge scores (correct response to 0–4 of the 7 survey questions).<sup>216</sup> 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 (79.2% versus 91.5%).<sup>217</sup> 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.<sup>218</sup> 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 seniors from underrepresented races and ethnicities 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.<sup>219</sup>
- 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.<sup>220</sup>

### Stroke Mortality

(See Table 15-1 and Charts 15-2 through 15-7)

- In 2019 (unpublished NHLBI tabulations using CDC WONDER<sup>221</sup> and the NVSS<sup>222</sup>):
  - On average, every 3 minutes 30 seconds, someone died of a stroke.
  - Stroke accounted for  $\approx$ 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, unintentional injuries/accidents, and chronic lower respiratory disease.
  - The number of deaths with stroke as an underlying cause was 150 005 (Table 15-1); the age-adjusted death rate for stroke as an underlying cause of death was 37.0 per 100 000, whereas the age-adjusted rate for any mention of stroke as a cause of death was 63.1 per 100 000.
  - Approximately 64% of stroke deaths occurred outside of an acute care hospital.

- More females than males die of stroke each year because of the higher prevalence of elderly females compared with males. Females accounted for 57.1% of US stroke deaths in 2019.
- Conclusions about changes in stroke death rates from 2009 to 2019 are as follows<sup>221</sup>:
  - The age-adjusted stroke death rate decreased 6.6% (from 39.6 per 100 000 to 37.0 per 100 000), whereas the actual number of stroke deaths increased 16.4% (from 128 842 to 150 005 deaths).
  - The decline in age-adjusted stroke death rates for males and females was similar (–5.8% and –7.7%, respectively).
  - Crude stroke death rates declined most among people 35 to 44 years of age (–8.7%; from 4.6 to 4.2 per 100 000), 45 to 54 years of age (–8.0%; from 13.7 to 12.6), 65 to 74 years of age (–7.7%; from 82.8 to 76.4 per 100 000), and 75 to 84 years of age (–13.8%; from 294.9 to 254.2 per 100 000). In comparison, the crude stroke death rates declined more modestly among those >85 years of age (–1.5%; 992.2 to 977.3 per 100 000). Crude stroke death rates increased slightly among those 55 to 64 years of age (2.7%; from 29.7 to 30.5 per 100 000). There was no change among those 25 to 34 years of age (1.3 per 100 000 in 2009 and 2019). Despite the improvements noted since 2009, there has been a recent flattening of or increase in death rates among all age groups (Charts 15-2 and 15-3).
- There are substantial geographic disparities in stroke mortality, with higher rates in the southeastern United States, known as the Stroke Belt (Chart 15-4). 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).<sup>223</sup>
- On the basis of pooled data from several large studies, the probability of death within 1 or 5 years after a stroke was highest in individuals ≥75 years of age (Charts 15-5 and 15-6).

### **Racial and Ethnic Disparities**

- In 2019, 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 (Charts 15-7).
- Age-adjusted stroke death rates declined by ≈7% or more among all racial and ethnic groups; however,

in 2019, rates remained higher among NH Black people (52.5 per 100 000; change since 2009, –4.9%) than among NH White people (35.6 per 100 000; –7.0%), NH Asian/Pacific Islander people (29.9 per 100 000; –9.9%), NH American Indian/Alaska Native people (30.6 per 100 000; –15.0%), and Hispanic people (32.8 per 100 000; 1.9%).<sup>221</sup>

- The probability of death within 1 year of a stroke was lowest in Black males 45 to 64 years of age (Chart 15-5). The probability of death within 5 years of a stroke was lowest for White males 45 to 64 years of age (Chart 15-6).
- On the basis of US national death statistics for the time period of 1990 to 2009, stroke mortality rates among American Indian and Alaska Native people were higher than among White people. In federally recognized tribal reservations, off-reservation trust land, and adjacent areas, the stroke mortality rate ratios for American Indian and Alaska Native males compared with White males was 1.20 (95% CI, 1.14–1.25). In those same areas, the rate ratios for American Indian and Alaska Native females was 1.19 (95% CI, 1.15–1.24). Stroke mortality rate ratios for American Indian/Alaska Native people versus White people varied by region, with the lowest in the Southwest (0.93 for both sexes combined) and the highest in Alaska (1.51 for both sexes combined). Starting in 2001, rates among American Indian/Alaska Native people decreased in all regions.<sup>224</sup>
- 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, 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).<sup>225</sup>
- Projections of stroke mortality from 2012 to 2030 differ on the basis of what factors are included in the forecasting.<sup>226</sup> 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.<sup>226</sup>

## Complications and Recovery

### (See Chart 15-8)

- Recurrent stroke is common (Chart 15-8).

### Rehabilitation and Readmission

- 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.<sup>227</sup>
- 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.<sup>228</sup>

### Disability

- 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).<sup>229</sup> Approximately 3% of males and 2% of females reported that they were disabled because of stroke.
- In 125 548 Medicare fee-for-service beneficiaries discharged from inpatient rehabilitation facilities after stroke, individuals who had a paid caregiver before their stroke had a lower odds of being discharged with potential to recover to full independence after discharge than those who lived with a caregiver or family (OR for walking, 0.59 [95% CI, 0.51–0.69]).<sup>230</sup>
- In the Swedish Stroke Register (Riksstroke) of 11 775 patients with first ischemic stroke who were functionally independent before stroke, the number of chronic comorbidities was associated with a poor outcome (dead or dependent; modified Rankin Scale score  $\geq 3$ ) at 12 months<sup>231</sup>: no comorbidity, 24.8%, 1 comorbidity, 34.7%, 2 to 3 comorbid conditions, 45.2%, and  $\geq 4$  comorbid conditions, 59.4%. At 5 years, these proportions were 37.7%, 50.3%, 64.3%, and 81.7%, respectively. There were substantial negative effects of dementia, kidney disease, and HF.
- 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 the 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.<sup>232</sup>
- 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).<sup>233</sup> 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% (95% CI, 48.3%–65.1%) at 1 year and 66.7% (95% CI, 60.2%–73.2%) at 2 years in population-based studies.<sup>234</sup>

### Comorbid Complications

- Among 1075 patients undergoing rehabilitation after stroke in a Polish cohort, at least 1 complication was reported by 77% of patients, and 20% experienced  $\geq 3$  complications.<sup>235</sup> 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%).<sup>236</sup>
- In a meta-analysis that included 7 studies from multiple continents, 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.<sup>237</sup>
- In the PROFESS trial, among 15 754 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.<sup>238</sup> Long-standing pain was associated with greater dependence (OR, 2.16 [95% CI, 1.82–2.56]).
- In a meta-analysis of 9 studies (7 countries), reduced motor function in the upper limb (OR, 2.81 [95% CI, 1.40–5.61]), diabetes (OR, 2.09 [95% CI, 1.16–3.78]), and a history of shoulder pain (OR, 2.78 [95% CI, 1.29–5.97]) were identified as significant risk factors for the development of poststroke shoulder pain within the first year after stroke.<sup>239</sup>
- Patients with stroke are at increased risk of fractures compared with those with TIA or no stroke history. In the Ontario Stroke Registry of 23 751 patients with stroke and 11 240 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.<sup>240</sup> 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]).

- In 1262 general practices in Germany, both stroke (HR, 1.26 [95% CI, 1.15–1.39]) and TIA (HR, 1.14 [95% CI, 1.03–1.25]) were associated with an increased risk of fractures compared with no stroke or TIA.<sup>241</sup> Dementia and nonopioid analgesic therapy were associated with fracture risk after both stroke and TIA. 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.<sup>242</sup>
- 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.<sup>243</sup>
- 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.<sup>244</sup> 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.

### 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.<sup>245</sup> Suicidality is also increased after stroke.<sup>246</sup>
- 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.<sup>247</sup>
- 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]).<sup>248</sup>
- 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.<sup>249</sup>
- 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%).<sup>250</sup>

### Functional Impairment

Functional and cognitive impairment and dementia are common after stroke, with the incidence increasing with duration of follow-up.

- Hospital characteristics 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.<sup>251</sup>
- 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.<sup>252–255</sup> In NOMAS, 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.<sup>253</sup>
- Stroke accelerates natural age-related functional decline. In the CHS, 382 of 5888 participants (6.5%) had ischemic stroke during follow-up with  $\geq 1$  disability assessment afterward. The annual increase in disability more than tripled after stroke (0.15 additional Barthel index points per year [95% CI, 0.004–0.30]). Notably, the disability index did not change significantly after MI (0.02 additional points per year [95% CI, –0.07 to 0.11]).<sup>256</sup>
- 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.<sup>257</sup> Racial differences were noted in toileting (Black individuals, 66%; White individuals, 87%;  $P<0.05$ ), walking (Black individuals, 41%; White individuals, 65%;  $P<0.05$ ), transportation (Black individuals, 39%; White individuals, 65%;  $P<0.05$ ), laundry (Black individuals, 45%; White individuals, 76%;  $P<0.01$ ), and shopping (Black individuals, 36%; White individuals, 70%;  $P<0.01$ ).

### Cognitive Impairment and Dementia

- In the REGARDS prospective cohort, 515 of 23 572 participants  $\geq 45$  years of age without baseline cognitive impairment underwent repeat cognitive

testing.<sup>254</sup> Incident stroke was associated with short-term decline in cognitive function and accelerated cognitive decline over 6 years. Participants with stroke had faster declines in global cognition (0.06 points per year faster [95% CI, 0.03–0.08]) and executive function (0.63 points per year faster [95% CI, 0.12–1.15]) 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]).

- 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 score threshold of <27 and in 61% with a Montreal Cognitive Assessment score threshold of <25.<sup>258</sup>
- Among 109 patients with ischemic stroke, NIHSS score ( $\beta = -0.54$  [95% CI,  $-0.99$  to  $-0.89$ ]) and preexisting leukoariosis severity ( $\beta = -1.45$  [95% CI,  $-2.86$  to  $-0.03$ ]) independently predicted functional independence, primarily through an effect on cognitive rather than motor scores.<sup>259</sup>
- 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 AD to HR, 1.95 for vascular dementia).<sup>260</sup>
- In a study of 90-day poststroke outcomes among patients with ischemic stroke in the BASIC Project, Mexican American people scored worse on cognitive outcomes (3.39 points [95% CI, 0.35–6.43] worse on the Modified Mini-Mental State Examination) than NH White people after multivariable adjustment.<sup>261</sup>
- In a retrospective analysis of the 2016 BRFSS, Black (OR, 1.58 [95% CI, 1.54–1.63]) and Hispanic (OR, 2.30 [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.<sup>262</sup>

## Stroke in Children

- On the basis of pathogenic differences, pediatric strokes are typically classified as either perinatal (occurring at  $\leq 28$  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 was 29 per 100 000 live births, or 1 per 3500 live births, in

the 1997 to 2003 Kaiser Permanente of Northern California population.<sup>263</sup>

### Risk Factors

- 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.<sup>264</sup>
- In an analysis of data from the International Pediatric Stroke Study from 2003 to 2014 ( $N = 2127$  children with AIS), 725 (34%) had arteriopathy.<sup>265</sup> Subtypes of arteriopathy were dissection (27%), moyamoya (25%), focal cerebral arteriopathy inflammatory subtype (15%), diffuse cerebral vasculitis (15%), and nonspecific arteriopathy (19%).
- In a separate analysis of the International Pediatric Stroke Study, among 2768 cases of AIS, 1931 (70%) were located in the anterior circulation, 507 (18%) in the posterior circulation, and 330 (12%) in both territories.<sup>266</sup> Cervicocephalic arterial dissections were significantly more frequent in posterior circulation strokes (20%) than in anterior circulation strokes (8.5%), whereas cardioembolism was less frequent in posterior circulation strokes (19% versus 32%;  $P < 0.001$ ). Case fatality was equal in both groups (2.9%), but survivors of posterior circulation childhood stroke were more likely to have a normal neurological examination at hospital discharge (29% versus 21%;  $P = 0.002$ ).
- 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.<sup>267</sup> 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%).<sup>268</sup>
- 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.<sup>269</sup>
- 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];  $P = 0.007$ ).<sup>270</sup> 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.<sup>271</sup> In contrast, a population-based controlled study suggested a minimal association between perinatal stroke and thrombophilia<sup>272</sup>; therefore, routine testing is not recommended in very young children.

### Complications

- Despite current treatment, at least 1 of 10 children with ischemic or hemorrhagic stroke will have a recurrence within 5 years.<sup>273,274</sup> 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.<sup>33</sup> 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 of patients with childhood stroke with a cerebral arteriopathy, the 5-year recurrence risk was as high as 60% among children with abnormal arteries on vascular imaging.<sup>275</sup> 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.<sup>276</sup> The cumulative risk of delayed seizures after later childhood stroke is 13% at 5 years and 30% at 10 years.<sup>277</sup> Children with seizures within 7 days of their stroke have the highest risk for delayed seizures, >70% by 5 years after the stroke.<sup>278</sup>
- Among survivors of ICH in childhood, 13% developed delayed seizures and epilepsy within 2 years.<sup>279</sup>
- Pediatric stroke teams and stroke centers<sup>280</sup> are developing worldwide. In a study of 124 children presenting to a children's hospital ED with stroke symptoms for whom 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.<sup>281</sup>

### Cost

- 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.<sup>282</sup>

- 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.<sup>283</sup>

### Stroke in Young Adults and in Midlife

- Approximately 10% of all strokes occur in individuals 18 to 50 years of age.<sup>284</sup>
- In the NIS, hospitalizations for AIS increased significantly for both males and females and for certain racial and ethnic groups among younger adults 18 to 54 years of age.<sup>285</sup> From 1995 to 2011 through 2012, hospitalization rates almost doubled for males 18 to 34 years of age (from 11.2 to 18.0 per 10 000 hospitalizations) and 35 to 44 (from 37.7 to 68.2 per 10 000 hospitalizations) years of age. Hospitalization rates for ICH and SAH remained stable, however, with the exception of declines among males and NH Black people 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.<sup>286</sup>
- 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 of 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]).<sup>287</sup> 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 ( $P>0.05$ ).<sup>20</sup> 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]).<sup>21</sup>

### Risk Factors

- In the NIS, the prevalence of stroke risk factors also increased from 2003 to 2004 through 2011 to 2012 among those hospitalized for stroke.<sup>285</sup> 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 also increased from 2003 to 2004 through 2011 to 2012.<sup>285</sup> Among males, the prevalence of  $\geq 3$  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  $\geq 3$  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  $< 0.001$ ).

### Long-Term Outcomes

- 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.<sup>288</sup> Rates decreased among older adults  $\geq 65$  years of age from 299.3 per 100 000 in 2010 to 271.4 per 100 000 in 2016.
- 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).<sup>289</sup>

### 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.<sup>290</sup>
- 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.<sup>117</sup>
- The proportion of ischemic strokes attributable to AF increases with age and may reach  $\geq 40\%$  in very elderly patients with stroke.<sup>291</sup>
- Very elderly patients have a higher risk-adjusted mortality,<sup>292</sup> have greater disability,<sup>292</sup> have longer

hospitalizations,<sup>293</sup> receive less evidence-based care,<sup>216,218</sup> and are less likely to be discharged to their original place of residence.<sup>293</sup>

- Over the period of 2010 to 2050, the number of incident strokes is expected to more than double, with the majority of the increase among the elderly ( $\geq 75$  years of age) and people from underrepresented races and ethnicities.<sup>294</sup>
- A study of 1346 patients treated with endovascular therapy for AIS with large-vessel occlusion found that being  $\geq 80$  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  $\geq 80$  years of age was an independent predictor of higher rates of postprocedural hemorrhage.<sup>295</sup>
- Based on large-scale cohort studies and meta-analyses, a Markov model suggested that for individuals  $\geq 80$  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.<sup>296</sup>

### Organization of Stroke Care

- 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.<sup>297</sup>
- In a multinational survey of neurointerventionalists, general anesthesia was the most frequently used anesthesia protocol for endovascular therapy (42%), and 52% used a preprepared endovascular therapy kit.<sup>298</sup>
- 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  $\leq 60$  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]).<sup>299</sup>

- 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.<sup>300</sup> 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 2008 to 2018, the number of inpatient discharges from short-stay hospitals with stroke as the principal diagnosis decreased slightly, from 924 000 in 2008 to 904 000 in 2018 (Table 15-1).
- In 2017, the average length of stay for discharges with stroke as the principal diagnosis was 6.1 days (HCUP,<sup>301</sup> unpublished NHLBI tabulation).
- In 2018, there were 802 000 ED visits with stroke as the principal diagnosis (HCUP,<sup>301</sup> unpublished NHLBI tabulation), and in 2011, there were 209 000 outpatient visits with stroke as the first-listed diagnosis (NHAMCS,<sup>302</sup> unpublished NHLBI tabulation). In 2018, physician office visits for a first-listed diagnosis of stroke totaled 1 942 000 (NAMCS,<sup>303</sup> 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).<sup>304</sup>
- An analysis of the 2011 to 2012 NIS for AIS found that after risk adjustment, all racial and ethnic minorities except Native American people had a significantly higher likelihood of length of stay ≥4 days than White people.<sup>305</sup>

## Operations and Procedures

- In the 2013 to 2016 HCUP Nationwide Readmissions Database (n=925 363 AIS admissions before the endovascular era [January

2013–January 2015] and n=857 347 during the endovascular era [February 2015–December 2016]), the proportion of patients receiving intravenous thrombolysis increased from 7.8% to 8.4% and the proportion receiving endovascular therapy doubled from 1.3% to 2.6%.<sup>306</sup> Length of stay declined from 6.8 to 5.7 days in the endovascular era, but total charges increased (\$56 691 versus \$53 878).

- 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,<sup>301</sup> unpublished NHLBI tabulation).
- Although rates of CEA decreased between 1997 and 2014, the use of CAS increased dramatically from an estimated 2000 procedures in 2004 to 14 000 procedures in 2014 (HCUP,<sup>301</sup> unpublished NHLBI tabulation).

### CEA Compared With CAS for Stroke Prevention

- In a study from the Nationwide Readmissions Database (n=378 354 patients undergoing CEA and 57 273 patients undergoing CAS between 2010 and 2015), rates of CEA declined and rates of CAS remained stable.<sup>307</sup> After matching, patients who underwent CEA had a higher risk of periprocedural stroke compared with those undergoing CAS (OR, 1.41 [95% CI, 1.25–1.59]).
- 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.<sup>308</sup>
- 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]).<sup>309</sup>
- In a study from the NCDR Carotid Artery Revascularization and Endarterectomy and

Peripheral Vascular Intervention registries (N=58 423 patients undergoing CEA or CAS), presence of contralateral carotid occlusion was associated with an increased risk of the composite outcome of death, stroke, and MI after CEA (aOR, 1.69 [95% CI, 1.27–2.30]) and no increase after CAS (aOR, 0.94 [95% CI, 0.72–1.22]).<sup>310</sup>

- Transcarotid artery revascularization with cerebral flow reversal is an emerging treatment option for carotid artery stenosis in patients at high risk for traditional endarterectomy. In a propensity-matched analysis of 342 CEAs and 109 transcarotid artery revascularizations performed between January 2011 and July 2018, transcarotid artery revascularization was associated with an increased incidence of intraoperative hypertension (adjusted coefficient, 1.41 [95% CI, 0.53–2.29]) and decreased reverse flow/clamp time and estimated blood loss. In the perioperative period, there were no differences between transcarotid artery revascularization and CEA with respect to MI, stroke, and all-cause mortality.<sup>311</sup>

## Cost

### (See Table 15-1)

- In 2017 to 2018 (average annual; MEPS,<sup>312</sup> unpublished NHLBI tabulation):
  - The direct and indirect cost of stroke in the United States was \$52.8 billion (Table 15-1).
  - The estimated direct medical cost of stroke was \$33.4 billion. This includes hospital outpatient or office-based health care professional 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 \$8242.
- Among Medicare beneficiaries >65 years of age in the US nationwide GWTG-Stroke Registry linked to Medicare claims data (2011–2014), in those with minor stroke (NIHSS score ≤5) or high-risk TIA (n=62 518 patients from 1471 hospitals), the mean Medicare payment for the index hospitalization was \$7951, and the cumulative all-cause inpatient Medicare spending per patient (with or without any subsequent admission) was \$1451 at 30 days and \$8105 at 1 year.<sup>28</sup>
- 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.<sup>313</sup>
- 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.<sup>313</sup>

## Global Burden of Stroke

The GBD 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020. (Data courtesy of the Global Burden of Disease Study 2020.)

### Prevalence

#### (See Charts 15-9 through 15-12)

In 2020 (Data courtesy of the Global Burden of Disease Study 2020.):

- The global prevalence of all stroke subtypes was 89.13 million (95% UI, 81.38–97.07 million) cases. There was an increase of 0.77% (95% UI, –0.78% to 2.17%) in the age-standardized prevalence rate from 2010 to 2020.
- Age-standardized stroke prevalence rates were highest in sub-Saharan Africa and parts of the southeastern United States and East and Southeast Asia (Chart 15-9).
- The global prevalence of ischemic stroke was 68.16 million (95% UI, 60.30–76.37 million) cases. There was an increase of 2.08% (95% UI, 0.11%–3.93%) in the age-standardized prevalence rate from 2010 to 2020.
- Age-standardized prevalence of ischemic stroke was highest in eastern United States and sub-Saharan Africa (Chart 15-10).
- The global prevalence of ICH was 18.88 million (95% UI, 16.54–21.31 million) cases. There was a decrease of 3.33% (95% UI, –4.75% to –1.96%) in the age-standardized prevalence rate from 2010 to 2020.
- Age-standardized prevalence of ICH was highest in Oceania, western sub-Saharan Africa, and Southeast Asia (Chart 15-11).
- The global prevalence of SAH was 8.09 million (95% UI, 7.02–9.27 million) cases. There was a decrease of 0.81% (95% UI, –1.91% to 0.26%) in the age-standardized prevalence rate from 2010 to 2020.
- Age-standardized prevalence of SAH was highest in Japan and Andean Latin America (Chart 15-12).

### Incidence

In 2020 (Data courtesy of the Global Burden of Disease Study 2020.):

- Global incidence of stroke was 11.71 million people (95% UI, 10.40–13.21 million), whereas that of ischemic stroke was 7.59 million (95% UI, 6.44–8.94 million), that of ICH was 3.41 million (95% UI, 2.94–3.93 million), and that of SAH was 0.71 million (95% UI, 0.62–0.83 million).
- Age-standardized incidence rates for total stroke are highest in East Asia (206.63 per 100 000 [95% UI,

180.43–239.88]), Central Asia (200.48 per 100 000 [95% UI, 183.99–219.51]), and Southeast Asia (190.98 per 100 000 [95% UI, 172.59–211.21]).

### Mortality

#### (See Charts 15-13 through 15-16)

In 2020 (Data courtesy of the Global Burden of Disease Study 2020.):

- Globally, the number of deaths attributable to stroke was 7.08 million (95% UI, 6.48–7.60 million). However, the age-standardized mortality rate decreased 15.27% (95% UI, –20.17% to –10.12%) from 2010.
- Age-standardized mortality attributable to stroke was highest in Central, Southeast, and East Asia, Oceania, and sub-Saharan Africa (Chart 15-13).
- Globally, the number of deaths attributable to ischemic stroke was 3.48 million (95% UI, 3.13–3.73 million). However, the age-standardized mortality rate decreased 13.31% (95% UI, –17.73% to –8.70%) from 2010.
- Age-standardized mortality attributable to ischemic stroke was highest in Eastern Europe and Central Asia (Chart 15-14).
- Globally, the number of deaths attributable to ICH in 2020 was 3.25 million (95% UI, 2.99–3.53 million). However, the age-standardized mortality rate decreased 17.64% (95% UI, –23.24% to –11.67%) from 2010.
- Age-standardized ICH mortality was highest in Oceania, followed by western, central, and eastern sub-Saharan Africa and Southeast Asia (Chart 15-15).
- Globally, the number of deaths attributable to SAH in 2020 was 0.35 million (95% UI, 0.31–0.39 million). However, the age-standardized mortality rate decreased 12.66% (95% UI, –19.85% to –2.12%) from 2010.
- Age-standardized mortality estimated for SAH was highest in Oceania, Andean Latin America, and Central Asia in 2020 (Chart 15-16).

**Table 15-1. Stroke in the United States**

Population group	Prevalence, 2015–2018, age ≥20 y	New and recurrent attacks, 1999, all ages	Mortality, 2019, all ages*	Hospital discharges, 2018, all ages	Cost, 2017–2018
Both sexes	7 600 000 (2.7% [95% CI, 2.4%–3.1%])	795 000	150 005	904 000	\$52.8 Billion
Males	3 500 000 (2.6%)	370 000 (46.5%)†	64 347 (42.9%)†		...
Females	4 100 000 (2.8%)	425 000 (53.5%)†	85 658 (57.1%)†		...
NH White males	2.3%	325 000‡	46 589	...	...
NH White females	2.5%	365 000‡	64 471	...	...
NH Black males	4.1%	45 000‡	8986	...	...
NH Black females	4.9%	60 000‡	11 089	...	...
Hispanic males	2.4%	...	5649	...	...
Hispanic females	1.7%	...	6310	...	...
NH Asian males	1.4%	...	2653§	...	...
NH Asian females	1.0%	...	3282§	...	...
NH American Indian or Alaska Native	...	...	741	...	...

CI, confidence interval. Ellipses (...) indicate data not available; and NH, non-Hispanic.

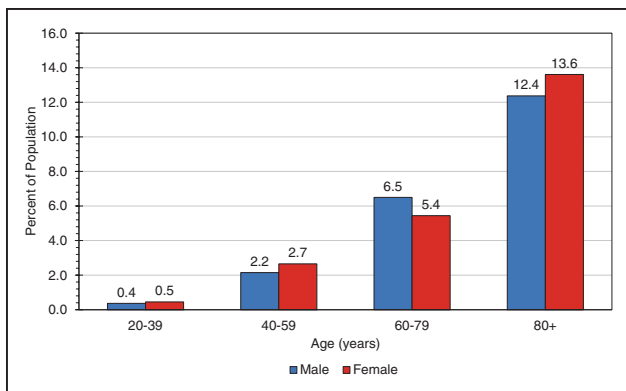
\*Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting 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 NH people. Estimates for White people include other non-Black races.

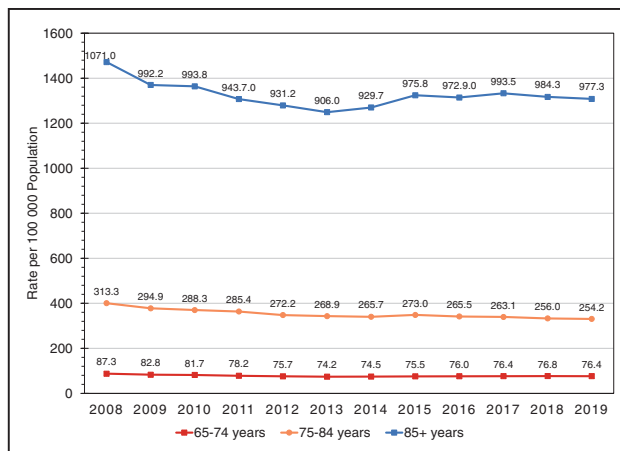
§Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander people.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey.<sup>315</sup> Percentages for racial and ethnic groups are age adjusted for Americans ≥120 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.<sup>316</sup> Data include children. Mortality: Unpublished NHLBI tabulation using National Vital Statistics System.<sup>222</sup> 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.<sup>301</sup> Data include those inpatients discharged alive, dead, or status unknown. Cost: Unpublished NHLBI tabulation using Medical Expenditure Panel Survey.<sup>312</sup> Data include estimated direct and indirect costs for 2017 to 2018 (average annual).



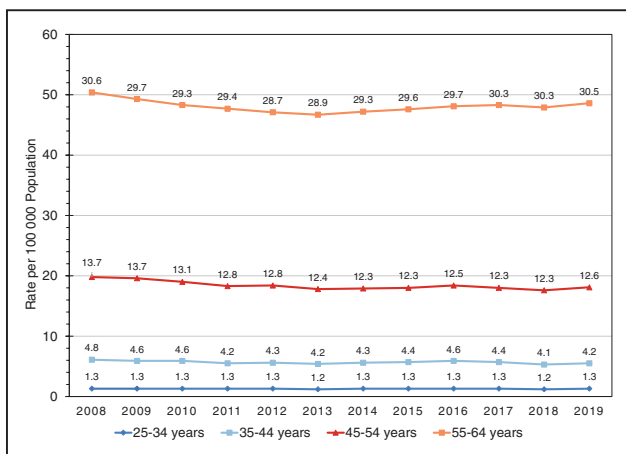
**Chart 15-1. Prevalence of stroke, by age and sex, United States (NHANES, 2015-2018).**

NHANES indicates National Health and Nutrition Examination Survey. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>315</sup>



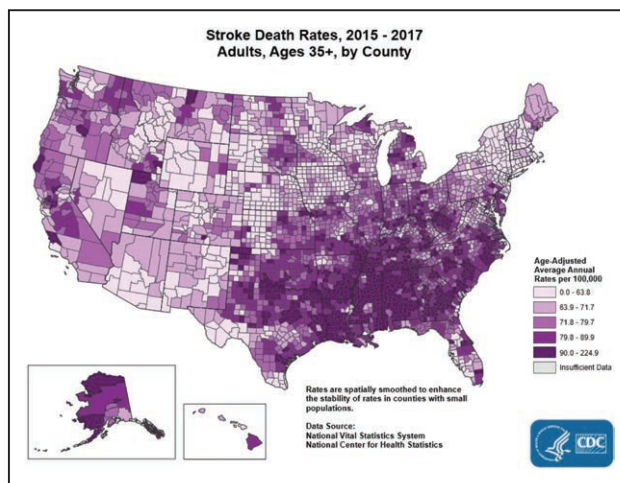
**Chart 15-3. Crude stroke mortality rates among older US adults (≥65 years of age), 2008 to 2019.**

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>221</sup>



**Chart 15-2. Crude stroke mortality rates among young US adults (25-64 years of age), 2008 to 2019.**

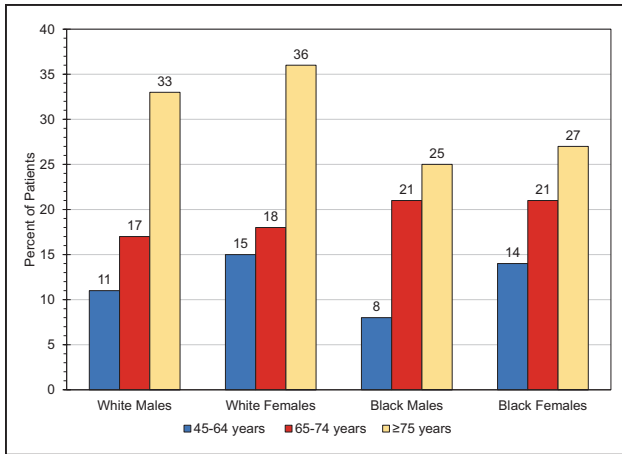
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>221</sup>



**Chart 15-4. Stroke death rates, 2015 through 2017, among adults ≥35 years of age, by US county.**

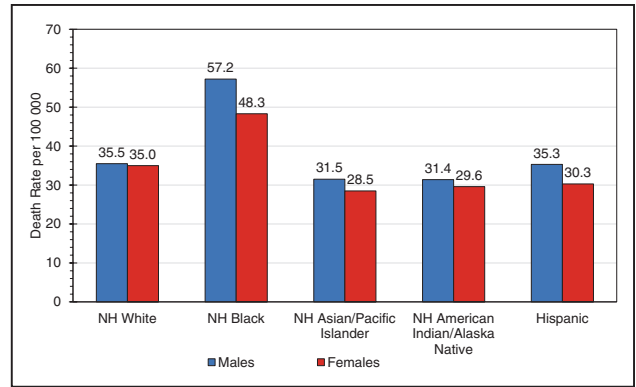
Rates are spatially smoothed to enhance the stability of rates in counties with small populations. *International Classification of Diseases, 10th Revision* codes for stroke: I60 through I69. Source: Reprinted from National Vital Statistics System.<sup>317</sup>





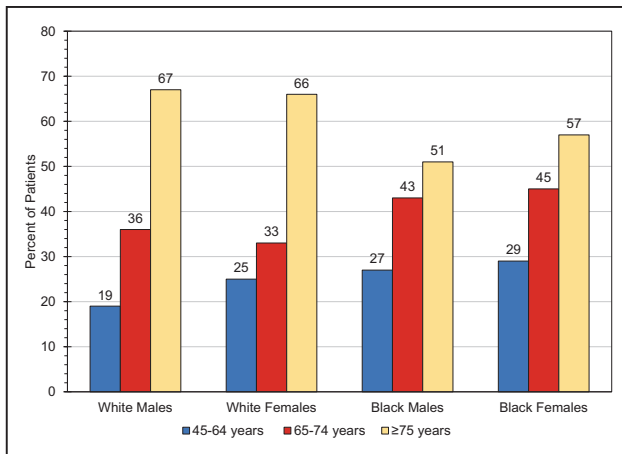
**Chart 15-5. Probability of death within 1 year after first stroke, United States, 1995 to 2011.\***

\*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.



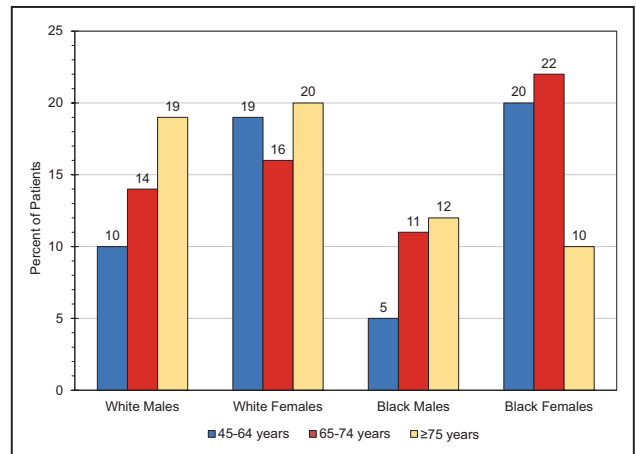
**Chart 15-7. Age-adjusted death rates for stroke, by sex and race and ethnicity, United States, 2019.**

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.<sup>221</sup>



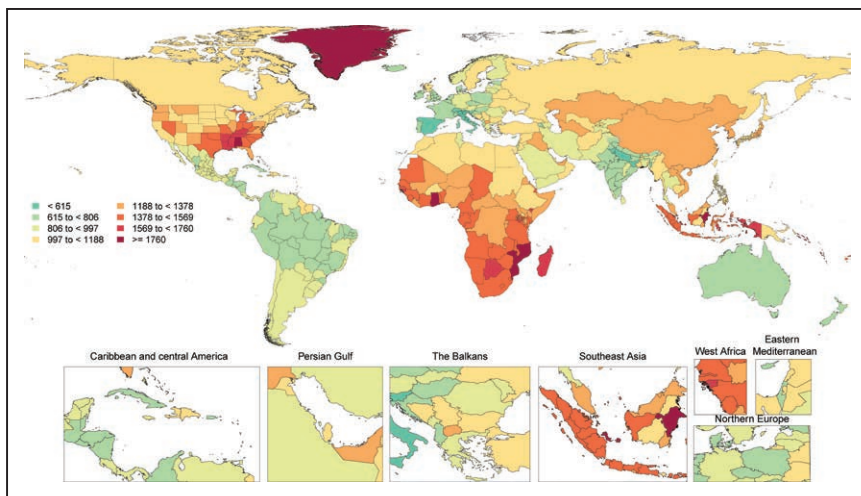
**Chart 15-6. Probability of death within 5 years after first stroke, United States, 1995 to 2011.\***

\*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.



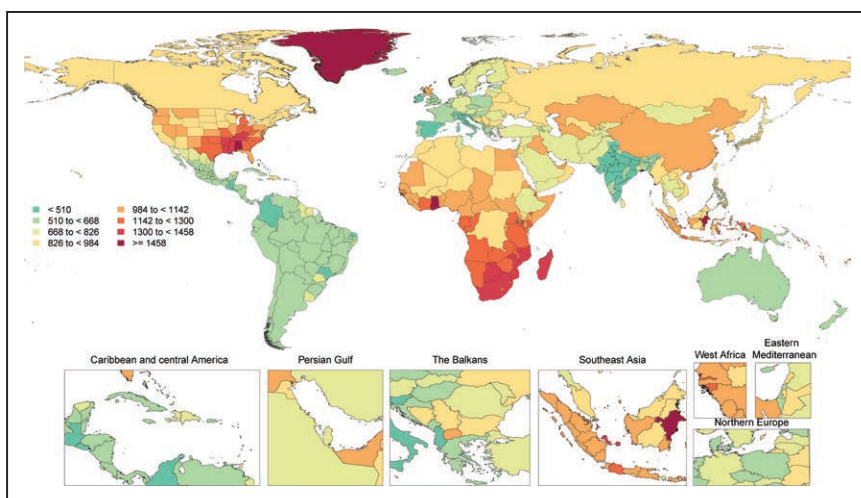
**Chart 15-8. Probability of recurrent stroke in 5 years after first stroke, United States, 1995 to 2011.\***

\*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.



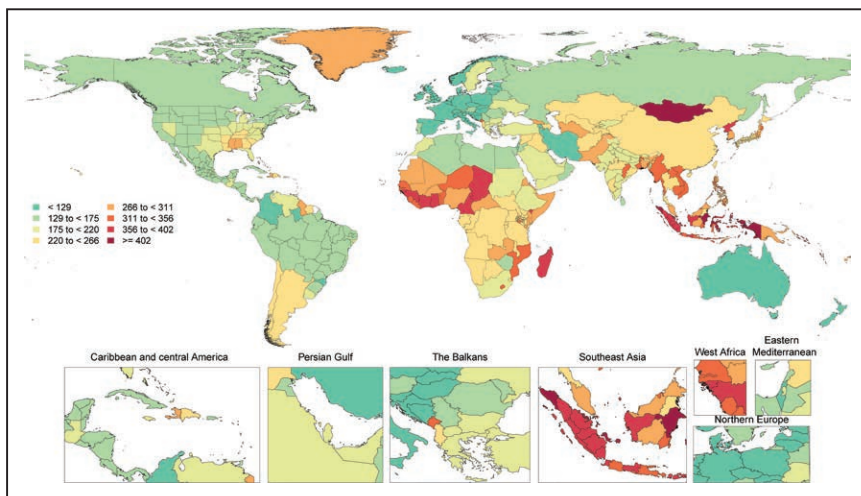
**Chart 15-9. Age-standardized global prevalence rates of total stroke (all subtypes) per 100 000, both sexes, 2020.**

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>318</sup>



**Chart 15-10. Age-standardized global prevalence rates of ischemic stroke per 100 000, both sexes, 2020.**

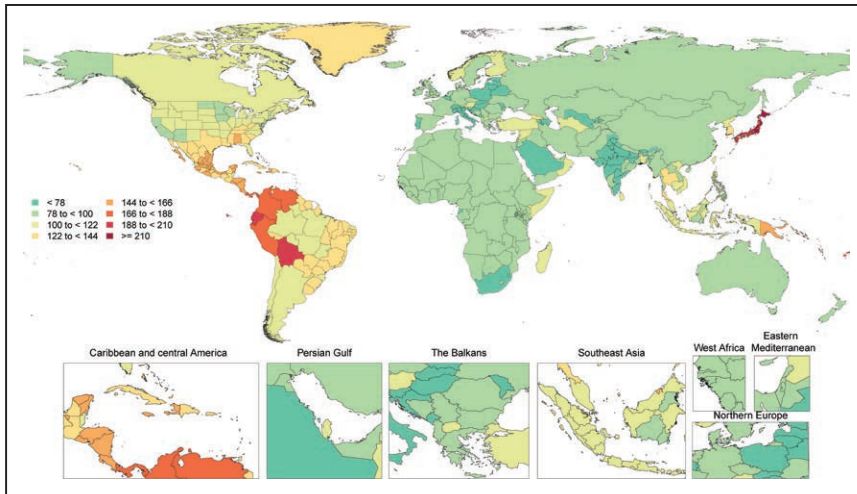
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**Chart 15-11. Age-standardized global prevalence rates of ICH per 100 000, both sexes, 2020.**

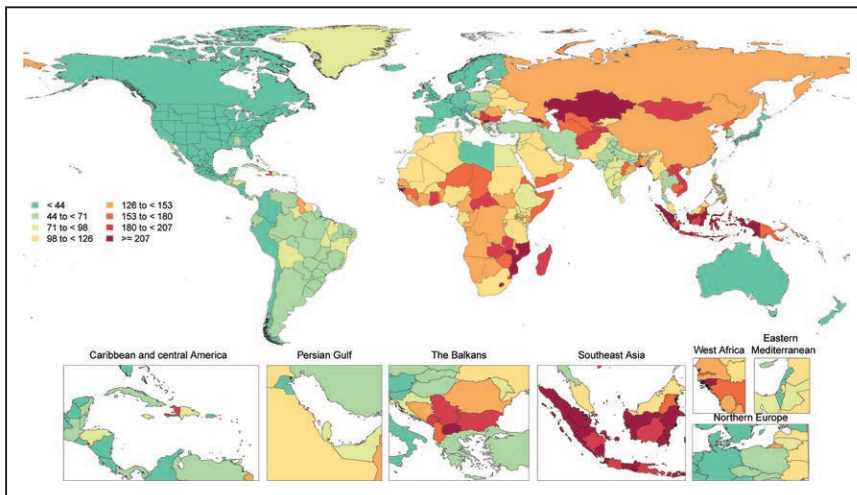
ICH indicates intracerebral hemorrhage. Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>318</sup>

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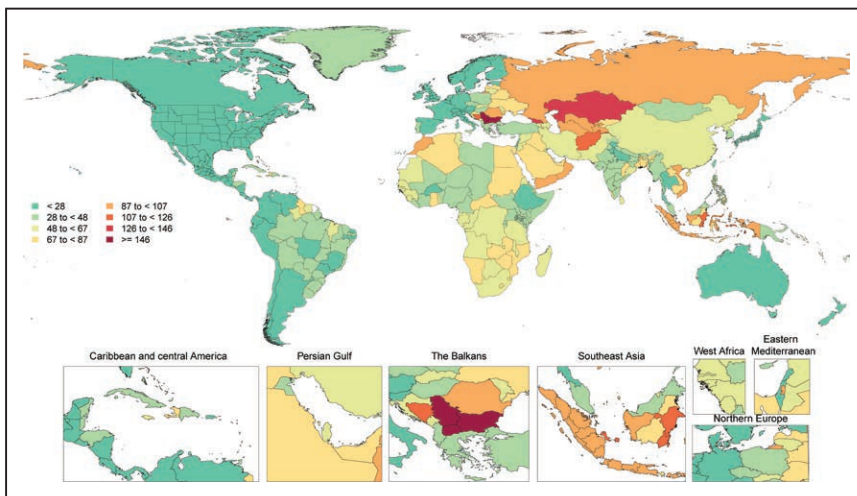
**Chart 15-12. Age-standardized global prevalence rates of SAH per 100 000, both sexes, 2020.**

SAH indicates subarachnoid hemorrhage. Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>318</sup>



**Chart 15-13. Age-standardized global mortality rates of total stroke (all subtypes) per 100 000, both sexes, 2020.**

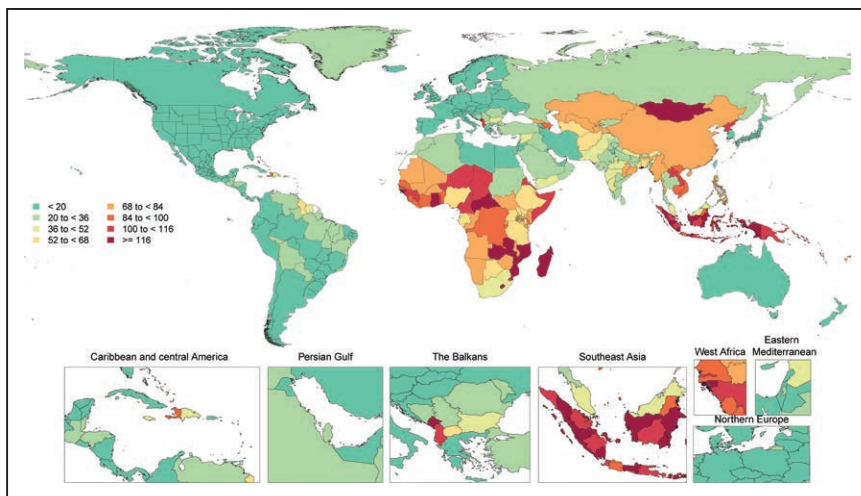
Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021, University of Washington. More information is available on the Global Burden of Disease Study website.<sup>318</sup>



**Chart 15-14. Age-standardized global mortality rates of ischemic stroke per 100 000, both sexes, 2020.**

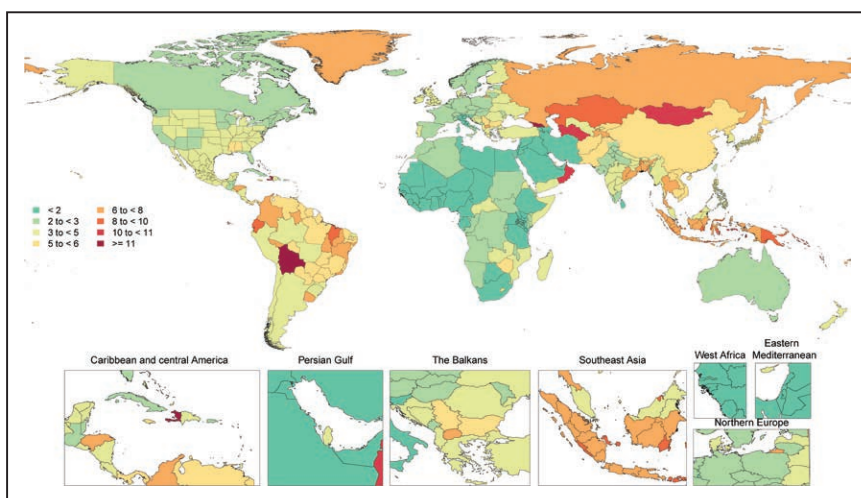
Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>318</sup>





**Chart 15-15. Age-standardized global mortality rates of ICH per 100 000, both sexes, 2020.**

ICH indicates intracerebral hemorrhage. Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>318</sup>



**Chart 15-16. Age-standardized global mortality rates of SAH per 100 000, both sexes, 2020.**

SAH indicates subarachnoid hemorrhage. Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>318</sup>

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## 16. BRAIN HEALTH

**ICD-9 290, 294.2, 331; ICD-10 F01, F03, G30-G31.**  
See Table 16-1 and Charts 16-1 through 16-2

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### Definition

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.”<sup>1</sup> 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.

Although this chapter provides prevalence and incidence estimates separately for dementia, AD, and vascular dementia based on the literature, the chapter authors acknowledge that most dementia is mixed, with contributions of both AD and vascular dementia. Up to one-third of clinical diagnoses of dementia type, made when patients are alive, are wrong. Vascular dementia prevalence and incidence are likely underestimated because most dementia cases have multiple pathologies and vascular disease is common.<sup>2</sup>

### Prevalence

#### Dementia

- The estimated prevalence of dementia in US adults  $\geq 65$  years of age was 10.5% (SE, 0.49%) in 2012 according to data from the nationally representative HRS and its dementia substudy, ADAMS.<sup>3</sup> Dementia prevalence was 7.3% (SE, 0.47%) in males and 12.9% (SE, 0.64%) in females.
- In a systematic review of racial disparities in dementia prevalence and incidence in the United States

that included 114 studies, the prevalence of dementia in adults  $\geq 65$  years of age ranged from 7.2% to 20.9% across multiple studies of Black individuals. Dementia prevalence was 6.3% in Japanese American individuals, 12.9% in Caribbean Hispanic American individuals, and 12.2% in Guamanian Chamorro individuals.<sup>4</sup>

#### Alzheimer Disease

- A systematic analysis of data from the GBD study showed that in 2017 AD/ADRD was the fourth most prevalent neurological disorder in the United States (2.9 million people [95% UI, 2.6–3.2 million]).<sup>5</sup> Among neurological disorders, AD/ADRD was the leading cause of mortality in the United States (38 deaths per 100 000 population per year [95% UI, 38–39]), ahead of stroke.
- Results of a multistate model using biomarker data and US population predictions show that  $\approx 3.7$  million Americans  $\geq 30$  years of age had clinical AD in 2017, and this number is projected to increase to 9.3 million by 2060.<sup>6</sup>
- According to administrative claims data of US Medicare fee-for-service beneficiaries  $\geq 65$  years of age in 2014, AD/ADRD prevalence was 11.5%, with a higher prevalence in females (12.2%) compared with males (8.6%).<sup>7</sup> AD/ADRD prevalence increased with age (65–74 years of age, 3.6%; 75–84 years of age, 13.6%; and  $\geq 85$  years of age, 34.6%). The prevalence of AD/ADRD was 13.8% in Black individuals, 12.2% in Hispanic individuals, 10.3% in NH White individuals, 9.1% in American Indian and Alaska Native individuals, and 8.4% in Asian and Pacific Islander individuals.
- Estimates of AD prevalence in the United States vary widely across population studies. Estimated US prevalence of AD in individuals  $\geq 71$  years of age was 2.3 million in 2002 on the basis of data from ADAMS<sup>8</sup> but 4.5 million in individuals  $\geq 65$  years of age in 2000 derived from CHAP.<sup>9</sup> Two factors primarily explained the lower AD prevalence estimates in ADAMS compared with CHAP: (1) ADAMS required an informant report of functional limitations for a dementia diagnosis, but CHAP did not; and (2) ADAMS assigned dementia cases to vascular disease or undetermined origin, but CHAP assigned most dementia cases, including mixed dementia cases, to AD.<sup>10</sup>
- More than 95% of those with probable AD had multiple or mixed pathologies, and only 3.1% of those with probable AD had only AD pathology on the basis of updated data from 1078 consecutive deceased individuals with autopsy (mean age of death, 89 years; 32% male) from the ROS and the MAP.<sup>11</sup>

#### Vascular Dementia

- In 2002,  $\approx 17\%$  of individuals  $\geq 71$  years of age,  $>577\,000$  (95% CI, 319 000–834 000) Americans,

The 2022 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 2022. 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.

had vascular dementia on the basis of estimates from the ADAMS data.<sup>8</sup>

- More than 80% of those with probable AD had vascular pathology (defined as microinfarcts, moderate to severe atherosclerosis, arteriolosclerosis, and cerebral amyloid angiopathy), and only 4.9% of those with probable AD had vascular pathology only according to data from the ROS and the MAP.<sup>11</sup>
- In a clinical-pathological study of 98 individuals  $\geq 90$  years of age with dementia from the 90+ Study (Irvine, CA), 48% had vascular pathology (defined as  $\geq 3$  microinfarcts,  $\geq 2$  macroinfarcts, and subcortical arteriolosclerotic leukoencephalopathy) or cerebral amyloid angiopathy pathology present, with only 15% having either vascular pathology or cerebral amyloid angiopathy pathology alone.<sup>12</sup>

## Incidence

### Dementia

- In 2017, AD/ADRD had the fifth leading incidence rate of neurological disorders in the United States on the basis of the GBD study data.<sup>5</sup> The US age-standardized incidence rate of AD/ADRD was 85 cases per 100 000 people (95% UI, 78–93).
- In a systematic review of racial disparities in dementia prevalence and incidence in the United States that included 114 studies, estimates of the annual incidence of dementia ranged from 1.4% to 5.5% for Black individuals (12 studies), 2.3% to 5.3% for Caribbean Hispanic individuals (4 studies), 1.4% to 2.7% for Japanese American individuals in Hawaii (3 studies), and 0.8% to 2.5% for non-Latino White individuals (10 studies) and was 0.8% for Mexican American individuals (1 study).<sup>4</sup>

### Alzheimer Disease

- Among 2794 individuals from CHAP, the annual incidence of clinically diagnosed AD dementia was 3.6% (95% CI, 3.3%–3.9%).<sup>13</sup> Black individuals had higher annual incidence of clinically diagnosed AD dementia (4.1% [95% CI, 3.7%–4.6%]) than White individuals (2.6% [95% CI, 2.3%–3.0%]). The annual incidence of clinically diagnosed AD dementia increased with age in Black and White individuals.
- Among 3605 members of Group Health (Seattle, WA)  $\geq 65$  years of age, dementia incidence rates through 80 to 84 years of age were similar in females (44.7 per 1000 person-years from 80–84 years of age [95% CI, 38.2–52.1]) and males (49.2 per 1000 person-years from 80–84 years of age [95% CI, 40.9–59.2]).<sup>14</sup> Among individuals  $\geq 85$  years of age, dementia incidence rates were higher in females (80.3 per 1000 person-years from 85–89 years of age [95% CI, 68.6–94.0]) than males (63.2 per 1000 person-years from 85–89

years of age [95% CI, 49.9–80.1]), with a larger sex difference for AD than for non-AD dementia.

### Vascular Dementia

- Estimates of vascular dementia incidence in the United States are lacking.

## Lifetime Risk and Cumulative Incidence

### Dementia

- In the FHS, the lifetime risk of overall dementia at 45 years of age was  $\approx 1$  in 5 (22.7% [95% CI, 20.9%–24.5%]) for females and  $\approx 1$  in 10 (13.8% [95% CI, 12.2%–15.3%]) for males.<sup>15</sup> The cumulative incidence of dementia, corrected for competing causes of death, was significantly higher among females than among males after 85 years of age.
- In a population-based Japanese cohort of individuals  $\geq 60$  years of age, the lifetime risk of dementia was 54.8% (95% CI, 49.4%–60.1%); elderly females had a greater lifetime risk (64.8% [95% CI, 57.4%–72.1%]) than elderly males (40.8% [95% CI, 33.0%–48.5%]).<sup>16</sup>
- Among participants in the Monzino 80-plus population-based cohort study from Italy, the lifetime risk of dementia at 80 years of age was 55.9% (95% CI, 51.6%–59.8%) and was higher for females (63.0% [95% CI, 58.4%–67.3%]) than for males (42.9% [95% CI, 34.6%–51.0%]).<sup>17</sup>
- According to nationwide individually linked cause-of-death and health register data in the Netherlands, the lifetime risk of dementia (estimated by the proportion of deaths in the presence of dementia) was  $\approx 24.0\%$ , higher for females (29.4%) than males (18.3%).<sup>18</sup>

### Alzheimer Disease

- In the FHS, the lifetime risk of AD at 45 years of age was 19.5% (95% CI, 17.8%–21.2%) for females and 10.3% (95% CI, 8.9%–11.8%) for males.<sup>15</sup>
- In a population-based Japanese cohort of individuals  $\geq 60$  years of age, the lifetime risk of AD was  $\approx 2$ -fold higher for females (42.4% [95% CI, 35.1%–49.7%]) than for males (20.4% [95% CI, 6.6%–34.2%]).<sup>16</sup>

### Vascular Dementia

- In a population-based Japanese cohort of individuals  $\geq 60$  years of age, the estimated lifetime risk of vascular dementia was similar among females (16.3% [95% CI, 11.5%–21.1%]) and males (17.8% [95% CI, 12.9%–22.7%]).<sup>16</sup>

## Secular Trends

### Dementia

- On the basis of an analysis of the GBD study data, from 1990 to 2017, age-standardized incidence

rates of AD/ADRD in the United States decreased from 97.2 per 100 000 to 85.2 per 100 000 (12.4% decrease [95% UI, 5.2%–19.2%]) and age-standardized prevalence decreased from 542.7 per 100 000 to 470.0 per 100 000 (13.4% decrease [95% UI, 5.1%–20.6%]), but mortality rates increased from 35.0 per 100 000 to 38.5 per 100 000 (9.8% increase [95% UI, 7.3%–12.2%]) and DALY rates increased from 413.6 per 100 000 to 418.8 per 100 000 (1.2% increase [95% UI, 1.9% decrease–4.2% increase]).<sup>5</sup> The increase in the burden of AD/ADRD in the United States from 1990 to 2017 was attributed mostly to population aging.

- Data from the nationally representative HRS provide evidence that the prevalence of dementia among individuals  $\geq 65$  years of age declined significantly in the United States from 11.6% in 2000 to 8.8% in 2012 ( $P < 0.001$ ).<sup>19</sup>
- Incidence of all-cause dementia decreased in successive birth cohorts in a population-based sample of community-residing adults  $\geq 70$  years of age in Bronx County, New York. Incidence per 100 person-years was 5.09 in birth cohorts before 1920, 3.11 in the 1920 through 1924 birth cohorts, 1.73 in the 1925 through 1929 birth cohorts, and 0.23 in cohorts born after 1929.<sup>20</sup>
- An analysis of Medicare data estimates that the AD/ADRD burden in the US population will double to 3.3% and affect 13.9 million Americans by 2060.<sup>7</sup>
- For FHS participants  $\geq 60$  years of age, the 5-year age- and sex-adjusted hazard rates for dementia progressively declined over 4 epochs of time from 3.6 per 100 individuals (95% CI, 2.9–4.4) in the late 1970s and early 1980s to 2.0 per 100 individuals (95% CI, 1.5–2.6) in the late 2000s and early 2010s.<sup>21</sup> Relative to the first epoch, the incidence of dementia declined by 22%, 38%, and 44% during the second, third, and fourth epochs, respectively.
- In an analysis of 2 population-based cohort studies from Sweden, the incidence rate of dementia declined  $\approx 30\%$  (HR, 0.70 [95% CI, 0.61–0.80]) from the late 1980s to the early 2010s in adults  $\geq 75$  years of age.<sup>22</sup> The decline in dementia incidence was present even after adjustment for education, psychosocial working conditions, lifestyle factors, and vascular disease (HR, 0.77 [95% CI, 0.65–0.90]).
- A meta-analysis of 53 cohorts demonstrated a decrease in the dementia incidence across 3 older age groups (65–74, 75–84, and  $\geq 85$  years of age).<sup>23</sup> Each 10-year increase in birth year was associated with a reduction in the odds of incident dementia for individuals reaching each of the older age groups (OR, 0.20 [95% CI, 0.18–0.22] for individuals

reaching 65–74 years of age; OR, 0.20 [95% CI, 0.19–0.21] for 75–84 years of age; and OR, 0.72 [95% CI, 0.58–0.90] for  $\geq 85$  years of age).

- In the HRS, a nationally representative study of adults  $\geq 50$  years of age in the United States, dementia prevalence estimates obtained every 2 years from 2000 to 2016 ranged between 1.5 and 1.9 times as high in NH Black individuals as in NH White individuals, standardized for age and sex.<sup>24</sup> Dementia incidence estimates obtained every 2 years from 2000 to 2016 ranged between 1.4 and 1.8 times as high in NH Black individuals as in NH White individuals, standardized for age and sex. There was no evidence of a significant decrease in the racial disparity over time ( $P$  values ranging from 0.55–0.98 for tests of trend over time).
- In NOMAS, there was a 41% reduction in the incidence of dementia among participants recruited in the 1999 cohort compared with those in the 1992 cohort (HR, 0.59 [95% CI, 0.49–0.70], adjusted for demographics and baseline memory complaints).<sup>25</sup> The reduction in incidence was greatest among NH White participants and Black participants and lowest among Hispanic participants.

### Alzheimer Disease

- For FHS participants  $\geq 60$  years of age, the 5-year age- and sex-adjusted hazard rate of AD demonstrated a (statistically nonsignificant) decline over 4 epochs of time from 2.0 per 100 individuals (95% CI, 1.5–2.6) in the late 1970s and early 1980s to 1.4 per 100 individuals (95% CI, 1.0–1.9) in the late 2000s and early 2010s ( $P = 0.052$  for trend analysis).<sup>21</sup>
- A meta-analysis of 35 cohorts demonstrated no significant decrease in the incidence of AD across 3 older age groups (65–74, 75–84, and  $\geq 85$  years of age).<sup>23</sup> Although AD incidence rates were stable in Western countries, studies from non-Western countries demonstrated a significant increase in incidence rates for the age group of 65 to 74 years (OR, 2.78 [95% CI, 1.33–5.79];  $P = 0.04$ ). No significant sex differences in AD incidence were found.

### Vascular Dementia

- For FHS participants  $\geq 60$  years of age, the 5-year age- and sex-adjusted hazard rate of vascular dementia declined over 4 epochs of time from 0.8 per 100 individuals (95% CI, 0.6–1.3) in the late 1970s and early 1980s to 0.4 per 100 individuals (95% CI, 0.2–0.7) in the late 2000s and early 2010s ( $P = 0.004$  for trend analysis).<sup>21</sup>

### Risk Factors

Vascular risk factors are increasingly recognized as the most important cluster of risk factors for brain health,



particularly because of their high prevalence and potential for modification.

### Blood Pressure

- There is consistent and substantial evidence for the role of BP, including hypertension, as a risk factor for cognitive decline and dementia. In a meta-analysis of 139 studies, midlife hypertension was associated with impairment in global cognition (RR, 1.55 [95% CI, 1.19–2.03]; 4 studies) and executive function (RR, 1.22 [95% CI, 1.06–1.41]; 2 studies), in addition to dementia (RR, 1.20 [95% CI, 1.06–1.35]; 9 studies) and AD (RR, 1.19 [95% CI, 1.08–1.32]; 4 studies).<sup>26</sup>
- In the Whitehall II cohort study (N=8639; 33% females), elevated blood pressure, defined as SBP  $\geq$ 130 mmHg at 50 years of age, was associated with increased risk of dementia (HR, 1.38 [95% CI, 1.11–1.70]). Although elevated BP in late life was not associated with greater risk of dementia, longer duration of elevated BP (exposure between 45 and 61 years of age [mean]) was also associated with risk of dementia (HR, 1.29 [95% CI, 1.00–1.66]).<sup>27</sup>
- BP in early adulthood may also be associated with worse cognitive health. In a study that pooled data from 4 observational cohorts of adults between 18 and 95 years of age at enrollment (N=15 001; 34% Black participants; 55% females), early adult vascular risk factors were associated with late-life cognitive decline.<sup>28</sup> Vascular risk factors were imputed across the life course in early adulthood, midlife, and late life for older adults. Early adult elevated SBP was associated with an approximate doubling of mean 10-year decline in late life, even after adjustment for SBP exposure at midlife and late life.
- Elevated and increasing BP from early adulthood to midlife (36–53 years of age) was associated with greater WMH volume (but not amyloid deposition) in late life in the Insight 46 cohort (N=499; 49% females).<sup>29</sup>
- In studies of late-life hypertension, there is often no association or a protective association between hypertension and cognitive outcomes, particularly among the oldest old.<sup>28,30,31</sup>
- Older adults randomized to intensive BP control in SPRINT (a subset with MRI at baseline and follow-up, N=454) had greater declines in hippocampal volume over 4 years compared with those on standard treatment ( $\beta$ =−0.033 cm<sup>3</sup> [95% CI, −0.062 to −0.003];  $P$ =0.03).<sup>32</sup>
- Among 3319 older adults in the Sujets AGÉES—Aged Subjects cohort in France (mean age, 78 years; 57% females), BP variability may also be a marker of risk for poor brain health outcomes. Greater visit-to-visit SBP, DBP, and mean arterial BP variability, measured every 6 months over 3 years, was associated with worse global cognition (for each 1-SD increase of coefficient of variation:  $\beta$  [SE], −0.12 [0.06], −0.20 [0.06], and −0.20 [0.06], respectively;  $P$ <0.05 for all) and risk of dementia (for each 1-SD increase of coefficient of variation: HR, 1.23 [95% CI, 1.01–1.50], 1.28 [95% CI, 1.05–1.56], and 1.35 [95% CI, 1.12–1.63], respectively).<sup>33</sup>
- BP variability over 25 years from early adulthood to midlife was associated with worse midlife cognition in CARDIA (N=2326; mean age, 25 years; 40% Black participants; 57% females). Higher average real variability for both SBP and DBP and higher DBP SD were associated with worse processing speed ( $\beta$  [SE], −0.025 [0.006], −0.029 [0.007], and −0.029 [0.007], respectively; all  $P$ <0.001) and verbal memory ( $\beta$  [SE], −0.016 [0.006], −0.021 [0.007], and −0.019 [0.007], respectively; all  $P$ <0.05) at a mean of 50 years of age.<sup>34</sup>
- Hypotension, particularly in late life, is associated with increased risk of dementia. In ARIC (N=4761; 21% Black participants; 59% females), hypertension (both mid and late life) was associated with increased risk of dementia compared with normal BP at both time periods (HR, 1.49 [95% CI, 1.06–2.08]).<sup>35</sup> A pattern of hypertension in midlife with hypotension in late life was also associated with increased risk of dementia (HR, 1.62 [95% CI, 1.11–2.37]).
- Orthostatic hypotension (a decrease of  $\geq$ 15 mmHg in systolic or  $\geq$ 7 mmHg in diastolic pressure after 2 minutes standing from a sitting position) in the HYVET cohort was associated with greater cognitive decline (HR, 1.39 [95% CI, 1.1–1.62]) and dementia (HR, 1.34 [95% CI, 1.05–1.73]) over 2 years. In a meta-analysis, HYVET results were pooled with 4 other studies of orthostatic hypotension, with a pooled risk ratio of dementia of 1.21 (95% CI, 1.09–1.35).<sup>36</sup>
- Greater arterial stiffness, measured as PWV, is another vascular risk factor consistently associated with worse measures of brain health. In a meta-analysis of 9 longitudinal studies, greater arterial stiffness was associated with worse global cognition (effect size, −0.21 [95% CI, −0.36 to −0.06]), executive function (effect size, −0.12 [95% CI, −0.22 to −0.02]), and memory (effect size, −0.05 [95% CI, −0.12 to 0.03]).<sup>37</sup>
- Aortic stiffness, measured by carotid-femoral PWV, was also associated with increased risk of dementia (HR, 1.60 [95% CI, 1.02–2.51]) over 15 years in the CHS Cognition Study (N=356; mean age, 78 years; 22% Black participants; 59% females).<sup>38</sup>
- In a cross-sectional study (ARIC-PET; N=321; mean age, 76 years; 45% Black participants; 43% females), central arterial stiffness was associated with greater amyloid burden (OR, 1.31 [95% CI,

1.01–1.71]) and WMH burden (OR, 1.6 [95% CI, 1.2–2.1]), as well as lower brain volume in regions vulnerable to AD (in cubic millimeters;  $\beta$  = -1.5 [SD, 0.7];  $P$  = 0.03), including the precuneus.<sup>39</sup>

- PWV was also associated cross-sectionally with other brain health outcomes, including cognition, ventricular volume, and WMH burden, in the slightly younger FHS Third Generation (N = 3207; mean age, 46 years; 47% males).<sup>40</sup>

## Cardiac Dysfunction

### Heart Failure

- 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]).<sup>41</sup> The effect did not vary significantly by HFrEF versus HFpEF.
- In a meta-analysis of 4 longitudinal studies, the pooled risk ratio for dementia associated with HF was 1.80 (95% CI, 1.41–2.31).<sup>42</sup>

### Atrial Fibrillation

- AF is a potential risk factor associated with both cognitive decline and dementia. In ARIC-NCS (N = 12515; mean age, 57 years; 24% Black participants; 56% females), AF was associated with greater cognitive decline over 20 years (global cognitive z score, 0.115 [95% CI, 0.014–0.215]). Risk of dementia was also elevated in participants with AF compared with those without (HR, 1.23 [95% CI, 1.04–1.45]).<sup>43</sup>
- Evidence on the possible benefits of anticoagulant therapy to mitigate this risk relationship is conflicting, with some studies reporting benefits and others not.<sup>44,45</sup> In the SNAC-K, AF was associated with increased risk of all-cause as well as vascular and mixed dementia (HR, 1.40 [95% CI, 1.11–1.77] and 1.88 [95% CI, 1.09–3.23], respectively); however, anticoagulant users with AF were less likely to develop dementia (HR, 0.40 [95% CI, 0.18–0.92]) compared with nonusers with AF.<sup>44</sup>
- In a study of 407 871 older adults enrolled in the US Veterans Health Administration, AF was associated with increased risk of dementia (OR, 1.14 [95% CI, 1.07–1.22]); anticoagulant use among those with AF also was associated with increased risk of dementia (OR, 1.44 [95% CI, 1.27–1.63]).<sup>45</sup>

### Coronary Disease

- A meta-analysis of 10 prospective studies (N = 24 801) found that CHD, including MI, AP, and IHD, was associated with increased risk of poor cognitive outcomes (dementia, cognitive

impairment, or cognitive decline; OR, 1.45 [95% CI, 1.21–1.74]).<sup>46</sup>

## Subclinical Cardiac Disease

- Subclinical measures of cardiac dysfunction also may be associated with brain health outcomes. In particular, LV hypertrophy, measured by LV mass index, has been associated with increased risk of cognitive decline and dementia and worse white matter structure in late life.<sup>47–49</sup>
- In MESA (N = 4999; mean age, 61 years; 47% males; 26% Black participants, 22% Hispanic participants, and 13% Chinese participants; median follow-up, 12 years), both LV mass index and ratio of LV mass to volume were associated with increased risk of dementia (HR, 1.01 [95% CI, 1.00–1.02] and 2.37 [95% CI, 1.25–4.43], respectively).<sup>48</sup> LV hypertrophy and remodeling also were associated with worse global cognition, processing speed, and executive function. Studies suggest that this association is also significant for cognitive and brain MRI outcomes in middle-aged adults.<sup>50,51</sup>
- Heart rate variability in CARDIA (N = 2118; mean age, 45 years; 42% Black; 58% females) was associated with worse midlife executive function 5 years later (quartile 3:  $\beta$  = 1.21 points better than quartile 1, the lowest quartile of SD of normal-to-normal intervals,  $P$  = 0.04; quartile 2:  $\beta$  = 1.72 points better than quartile 1,  $P$  < 0.01).<sup>52</sup>

## Poststroke

See Chapter 15 (Stroke [Cerebrovascular Diseases]).

## Diabetes

- Diabetes is associated with risk of both vascular dementia and AD. In a meta-analysis of 14 studies (N = 2310330, 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]).<sup>53</sup> 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 mendelian randomization study of 115 875 adults, the risk ratio for 1-mmol/L (18 mg/dL) higher plasma glucose level and risk of dementia was 2.40 (95% CI, 1.18–4.89). The results were not significant for vascular dementia or AD.<sup>54</sup>
- Other studies also have demonstrated an association between elevated glucose levels in early adulthood to midlife and worse midlife cognitive outcomes among nondiabetic participants.<sup>55–57</sup>
- HbA1c variability may be an indicator of increased risk for worse cognitive outcomes. In a study

that pooled cohort data from the HRS and ELSA (N=6237; mean age, 63 years; 58% females; median follow-up, 11 years), greater HbA1c variability was associated with greater decline in memory ( $\beta$  [highest quartile of HbA1c variability compared with the lowest quartile],  $-0.094$  SD/y [95% CI,  $-0.185$  to  $-0.003$ ]) and executive function ( $-0.083$  SD/y [95% CI,  $-0.125$  to  $-0.041$ ]). This association was significant even among those without diabetes.<sup>58</sup>

- A history of hypoglycemia is also associated with worse brain health outcomes. In ARIC (N=580), there was a significant cross-sectional association between hypoglycemia and reduced total brain volume ( $\beta=-0.308$  [95% CI,  $-0.612$  to  $-0.004$ ]). In a prospective analysis (N=1263; median follow-up, 14 years), hypoglycemia was associated with increased risk of developing dementia (RR, 2.54 [95% CI, 1.78–3.63]).<sup>59</sup>
- Investigators have observed associations between lower fasting insulin and risk of dementia. In the PPSW (N=1212 nondiabetic females; mean age, 48 years), fasting serum insulin at baseline was categorized into tertiles. Among those in the lowest tertile of fasting insulin, there was an increased risk of dementia over 34 years (HR, 2.34 [95% CI, 1.52–3.58]) compared with those with fasting insulin in the middle tertile.<sup>60</sup>
- Late-life diabetes, poor glycemic control among those with diabetes, and diabetes duration ( $\geq 5$  years) were also associated with greater risk of MCI/dementia in ARIC (HR, 1.14 [95% CI, 1.00–1.31], 1.31 [95% CI, 1.05–1.63], and 1.59 [95% CI, 1.23–2.07], respectively). Late-life higher HbA1c ( $>7.5\%$ , 58 mmol/mol) and lower HbA1c ( $<5.8\%$ , 40 mmol/mol) were also associated with increased risk of MCI/dementia compared with HbA1c in the midrange.<sup>61</sup>

### Chronic Kidney Disease

- Kidney dysfunction has more recent evidence as a risk factor for poor cognitive outcomes. Albuminuria and eGFR, defined by cystatin C and  $\beta$ -2-microglobulin, were associated with increased risk of dementia on average 12 years later in ARIC (N=9967 without dementia, ESRD, or stroke; mean age, 63 years; 20% Black participants; 57% female).<sup>62</sup>
- A meta-analysis for dementia based on a small number of studies showed a significant association with albuminuria but no association with eGFR  $<60$  mL $\cdot$ min $^{-1}$  $\cdot$ 1.73 m $^{-2}$ .<sup>63</sup> Another meta-analysis for cognition<sup>64</sup> found associations for eGFR  $<60$  mL $\cdot$ min $^{-1}$  $\cdot$ 1.73 m $^{-2}$  but was based on studies with methodological limitations in the selection of comparison groups.

### Obesity

- Midlife obesity is associated with increased risk of dementia. In a meta-analysis of longitudinal studies with up to 42 years of follow-up, the risk ratio for dementia associated with midlife obesity was 1.33 (95% CI, 1.08–1.63).<sup>65</sup>
- In NOMAS, abdominal adiposity measured as waist-hip ratio in middle-aged adults was associated with cognitive decline over 6 years. For each increase in SD for waist-hip ratio, the associated decline in global cognition was equivalent to a 2.6-year increase in age. There was also a significant association with decline on processing speed and executive function.<sup>66</sup> In a separate analysis of NOMAS cohort data, BMI and WC were associated with reduced cortical thickness on brain MRI at follow-up.<sup>67</sup>
- In 9652 participants from the UK BioBank (mean age, 55 years; 48% males), BMI, waist-hip ratio, and fat mass were cross-sectionally associated with worse gray matter volume ( $\beta$  per 1 SD of measure,  $-4113$  [95% CI,  $-4862$  to  $-3364$ ],  $-4272$  [95% CI,  $-5280$  to  $-3264$ ], and  $-4590$  [95% CI,  $-5386$  to  $-3793$ ], respectively).<sup>68</sup>
- The evidence for obesity and BMI in late life is less clear,<sup>69</sup> with some studies suggesting that obesity is protective or that weight loss may be a prodrome of late-life dementia.<sup>70,71</sup>
- In the Whitehall II Study (N=10308; age, 35–55 years at baseline; 33% females), obesity at 50 years of age, but not at 60 or 70 years of age, was associated with increased risk of dementia (HR, 1.93 [95% CI, 1.35–2.75]).<sup>70</sup> In a subanalysis, the trajectory of BMI among those with dementia was higher than in participants without dementia 28 and 16 years before dementia diagnosis, whereas BMI was lower among those with dementia 8 years before diagnosis.
- In an analysis combining data from 39 cohort studies (N=1 349 857 dementia-free participants; mean follow-up, 16 years [range, 4–38 years]), the HR for each 5-unit increase in BMI increased as the time between BMI assessment and dementia diagnosis increased (BMI assessed  $<10$  years before dementia diagnosis: HR, 0.71 [95% CI, 0.66–0.77]; BMI assessed 10 to 20 years before dementia diagnosis: HR, 0.94 [95% CI, 0.89–0.99]; BMI assessed  $>20$  years before dementia diagnosis: HR, 1.16 [95% CI, 1.05–1.27]).<sup>72</sup>
- In a prospective cohort study (MARS and MAP; N=2134; mean age, 78 years; 33% Black participants; 75% females), lower BMI in late life was associated with greater decline in global cognition, semantic memory, and episodic memory ( $P<0.01$  for all) over a mean of 6 years of follow-up. There was no association with decline in working memory, perceptual speed, or visuospatial function.<sup>73</sup>

**SDB/Sleep Apnea**

- In a meta-analysis of 18 longitudinal studies (N=246786 participants), SDB was associated with all-cause dementia (pooled RR, 1.18 [95% CI, 1.02–1.36]), AD (pooled RR, 1.20 [95% CI, 1.03–1.41]), and vascular dementia (pooled RR, 1.23 [95% CI, 1.04–1.46]).<sup>74</sup>
- In a second meta-analysis of 6 longitudinal studies, SDB was associated with increased risk of cognitive decline and dementia (RR, 1.26 [95% CI, 1.05–1.50]). The study also reported cross-sectional associations (7 studies) between SDB and worse global cognition and executive function.<sup>75</sup>
- In the SOF (N= 298 females; mean age, 82 years), SDB was associated with increased risk of MCI and dementia over a median follow-up of 5 years (OR, 1.85 [95% CI, 1.11–3.08]).<sup>76</sup> The association with increased risk of MCI and dementia was also significant for those with oxygen desaturation index  $\geq 15$  and those with a total sleep time  $> 7\%$  in apnea or hypopnea (OR, 1.67 [95% CI, 1.03–2.69] and 1.79 [95% CI, 1.01–3.20], respectively), suggesting that hypoxia is the primary mechanism linking SDB to risk of worse cognitive outcomes.
- Greater OSA severity was associated with decreased cerebrospinal fluid  $\beta$ -amyloid<sub>42</sub> over 2 years in a community-based sample of adults with normal cognition (N=208; 62% females).<sup>77</sup> There was also a trend, although nonsignificant, between OSA severity and cortical Pittsburgh compound B-positron emission tomography uptake.
- In a cross-sectional study (AgeWell Trial [France, secondary analysis]; N=127; mean age, 69 years; 63% females), SDB was also associated with greater amyloid burden in addition to greater gray matter volume, perfusion, and metabolism in the cingulate cortex and precuneus.<sup>78</sup>
- Sleep apnea was also cross-sectionally associated with greater predicted brain age, a calculated score based on patterns of 169 regions of brain volume, in SHIP (N=690; mean age, 53 years; 49% females).<sup>79</sup>

**Smoking**

- Smoking is a risk factor for dementia and poor cognitive outcomes, and studies suggest that quitting smoking is beneficial for brain health.<sup>80–82</sup>
- Current smoking was associated with increased risk of dementia, AD, and vascular dementia (RR, 1.30 [95% CI, 1.18–1.45], 1.40 [95% CI, 1.13–1.73], and 1.38 [95% CI, 1.15–1.66], respectively) in a meta-analysis of 37 prospective studies.<sup>83</sup> Former smoking was not associated with dementia or either subtype. In a stratified analysis by *APOE* status, the association between current smoking and increased risk of AD was observed only among those without an  $\epsilon 4$  allele.

- In an analysis from the National Alzheimer's Coordinating Center's Uniform Data Set, current smoking was associated with incident dementia (HR, 1.88 [95% CI, 1.08–3.27]) compared with nonsmoking. Participants who quit within the past 10 years compared with nonsmokers were not more likely to develop dementia.<sup>81</sup>
- Early adult trajectories of smoking are also associated with worse cognitive outcomes. In CARDIA (N=3364; mean age at cognitive assessment, 50 years; 46% Black participants; 56% female), investigators identified 5 smoking trajectories over 25 years from early adulthood to midlife: 19% quitters, 40% minimal stable, 20% moderate stable, 15% heavy stable, and 5% heavy declining smokers. Compared with nonsmokers, heavy stable smokers had worse performance on processing speed, executive function, and memory at midlife (OR, 2.22 [95% CI, 1.53–3.22], 1.58 [95% CI, 1.05–2.36], and 1.48 [95% CI, 1.05–2.10], respectively). Heavy declining and moderate stable smokers also had worse processing speed (OR, 1.95 [95% CI, 1.06–3.68] and 1.56 [95% CI, 1.11–2.19]). Minimal stable smokers and quitters were not more likely than nonsmokers to have worse cognitive performance at midlife.<sup>80</sup>

**Cardiovascular Risk Factor Burden**

- The AHA's ideal CVH metrics are associated with reduced cognitive decline. Among 1033 participants in NOMAS (mean age at initial cognitive assessment, 72 $\pm$ 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.<sup>84</sup> 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 also was associated with less decline in executive function and episodic memory testing. These results are consistent with findings in ARIC showing that ideal midlife vascular risk factors were associated with less cognitive decline over 20 years.<sup>85</sup>
- Ideal CVH metrics at 50 years of age were similarly associated with lower incidence of dementia over 25 years of follow-up in the Whitehall II Study.<sup>86</sup>
- In the 3C Study of 6626 older adults (mean age, 74 years; 63% female), 37% had 0 to 2 ideal CVH factors, 57% had 3 to 4 ideal factors, and 7% had 5 to 7 ideal factors. Ideal CVH was associated with lower risk of developing dementia (HR, 0.90 [95% CI, 0.84–0.97] per each additional ideal CVH metric)



and with better global cognition after 8.5 years of follow-up.<sup>87</sup>

- Conversely, greater cardiovascular risk factor burden is associated with increased risk of cognitive decline and dementia.<sup>88,89</sup>
- In CARDIA,<sup>88</sup> Framingham 10-Year CHD Risk Score  $\geq 10$  was associated with accelerated cognitive decline 5 years later in midlife (OR, 2.29 [95% CI, 1.21–4.34]).
- In the Harvard Aging Brain Study,<sup>90</sup> greater Framingham 10-Year Cardiovascular Disease Risk Score was associated with greater late-life cognitive decline ( $\beta$ ,  $-0.064$  [95% CI,  $-0.094$  to  $-0.033$ ]) over almost 4 years. There was also a significant interactive effect between cardiovascular risk and amyloid burden ( $\beta$ ,  $-0.040$  [95% CI,  $-0.062$  to  $-0.018$ ]).
- Midlife vascular risk factors are associated with amyloid deposition in the brain,<sup>91</sup> indicating AD pathology, as well as undifferentiated dementia 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 individuals 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.
- Higher Framingham 10-Year Cardiovascular Disease Risk Score in early adulthood also was associated with lower late-life total brain volume and higher WMH volume in the Insight 46 cohort.<sup>92</sup> The association of vascular risk score and markers of brain health was strongest in early adulthood compared with midlife and late life.

## Social Determinants of Health

### Race and Ethnicity

- A retrospective analysis of the 2016 BRFSS data found significant differences in subjective cognitive decline across all racial and ethnic groups compared with White adults in the 20843 respondents who had reported being diagnosed with stroke.<sup>93</sup> Compared with White adults, racial and ethnic minorities were more likely to report worsening confusion or memory loss that contributed to not participating in everyday activities or difficulty with work, volunteer, and social activities outside of the home at least some of the time. Binary logistic regression adjusted for sex, age, education, income,

and comorbidities found that Black adults (OR, 1.59 [95% CI, 1.54–1.63]) and Hispanic adults (OR, 2.30 [95% CI, 2.19–2.42]) had significantly higher odds compared with White adults to give up day-to-day household activities or chores as a result of confusion or memory loss. Black adults (OR, 2.94 [95% CI, 2.85–3.03]) and Hispanic adults (OR, 4.03 [95% CI, 3.83–4.24]) also reported higher odds of needing assistance with everyday activities compared with White adults.

- An analysis of baseline data (2008–2011) from 9019 individuals 45 to 74 years of age from HCHS/SOL examined the association between cognition and BP measures.<sup>94</sup> In age-, sex-, and education-adjusted models, they found consistent negative associations between indicators of arterial stiffness and cognitive function.
- An analysis of statewide encounter-level data for all hospital discharges in South Carolina between 2000 and 2012 included 68 758 individuals with a diagnosis of stroke before 2010.<sup>95</sup> The analysis identified individuals subsequently diagnosed with any of 5 categories of dementia. Adjusted Cox proportional hazards models showed that Black race was associated with increased risk for all-cause dementia after incident stroke (HR, 1.55 [95% CI, 1.48–1.63]) and ranged from an HR of 1.37 (95% CI, 1.28–1.47) for AD to an HR of 1.95 (95% CI, 1.80–2.11) for vascular dementia.

### Education

- A meta-analysis looked at factors predicting reversion from MCI to normal cognition.<sup>96</sup> The analysis included 17 studies with 6829 participants. An overall reversion rate from MCI to normal cognition of 27.6% was found, and several of the factors positively predicting reversion included higher education (standardized mean difference, 0.34 [95% CI, 0.12–0.56]).
- In the Uppsala Birth Cohort Multigenerational Study, better grades in elementary school were associated with lower dementia risk (HR, 0.79 [95% CI, 0.68–0.93]).<sup>97</sup> Professional/university education was also associated with lower dementia risk (HR, 0.74 [95% CI, 0.60–0.91]).

### Occupation

- An observational study collected occupational information on 2121 patients with dementia (57% male) from the Amsterdam Dementia Cohort with a mean  $67 \pm 8$  years of age.<sup>98</sup> The sample included patients with AD ( $n=1467$ ), frontotemporal dementia ( $n=281$ ), vascular dementia ( $n=98$ ), Lewy body disease ( $n=174$ ), and progressive supranuclear palsy/corticobasal degeneration ( $n=101$ ). Patients were categorized into 11 occupational classes. Significant differences in distribution of dementia types

were seen across occupation groups ( $P<0.001$ ). Unadjusted logistic regression showed that transportation/logistics occupations were significantly related to vascular dementia (OR, 3.41;  $P<0.01$ ) and AD (OR, 0.43;  $P<0.001$ ), whereas health care/welfare occupations were significantly associated with AD (OR, 1.74;  $P<0.01$ ).

- In the Uppsala Birth Cohort Multigenerational Study, data-complex occupations were associated with lower dementia risk (HR, 0.77 [95% CI, 0.64–0.92]).<sup>97</sup> The combination of better grades in elementary school and data-complex occupation was more strongly associated with lower dementia risk (HR, 0.61 [95% CI, 0.50–0.75]).

### Geography/Dementia Belt

- 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]).<sup>99</sup> These results suggest that early-life behavioral and other patterning may influence late-life development of dementia.

## Risk Prediction

### Polygenic Risk Scores

- Among 6815 stroke-free people in the Generation Scotland: Scottish Family Health Study, a polygenic risk score for ischemic stroke was inversely correlated with several cognitive measures: logical memory (correlation coefficient  $r=-0.04$ ;  $P=4.8\times 10^{-4}$ ); digit symbol substitution ( $r=-0.05$ ;  $P=2.1\times 10^{-5}$ ); verbal fluency ( $r=-0.03$ ;  $P=0.023$ ); general fluid cognitive ability ( $r=-0.06$ ;  $P=1.3\times 10^{-6}$ ); Mill Hill vocabulary ( $r=-0.07$ ;  $P=4.3\times 10^{-8}$ ); and general cognitive ability ( $r=-0.07$ ;  $P=2.0\times 10^{-8}$ ).<sup>100</sup>
- According to genetic data from 60801 cases of CAD and 17008 cases of LOAD, each increment in polygenic risk score for CAD was associated with 7% higher odds of LOAD (95% CI, 1%–15%).<sup>101</sup> This association was no longer present after removal of the *APOE* locus from the polygenic risk score.

### Risk Scores That Emphasize Vascular Risk Factors

- Among 60 patients with vascular dementia and 70 control subjects at a single center in China, the Framingham 10-Year CHD Risk Score was more strongly predictive of vascular dementia (AUC, 0.83 [95% CI, 0.73–0.93]) than were white matter lesions (AUC, 0.79 [95% CI, 0.67–0.88]).<sup>102</sup>

The combination of white matter lesions with Framingham 10-Year CHD Risk Score had an AUC of 0.86 (95% CI, 0.75–0.94) for predicting vascular dementia.

- The LIBRA index for predicting dementia includes depression, diabetes, PA, hypertension, obesity, smoking, hypercholesterolemia, CHD, and mild/moderate alcohol use. Among 9387 European adults without dementia, LIBRA index assessed in midlife (55–69 years of age) and late life (70–79 years of age) was associated with dementia risk over a 7-year follow-up (HR for high LIBRA versus low in midlife, 2.36 [95% CI, 1.53–3.64]; HR for high LIBRA versus low in late life, 2.12 [95% CI, 1.73–2.61]). LIBRA index measured in the oldest old (80–97 years of age) was not associated with dementia risk.<sup>103</sup> Among 1024 adults in the Finnish CAIDE study, higher LIBRA score in midlife was associated with a 27% higher incidence of dementia (95% CI, 13%–43%), but a higher LIBRA score in late life was not associated with dementia risk (HR, 1.02 [95% CI, 0.84–1.24]).<sup>104</sup>
- Among 34083 female and 39998 male patients with AF with no history of dementia, CHA<sub>2</sub>DS<sub>2</sub>-VASc scores  $\geq 3$  (versus  $\leq 1$ ) were associated with 7.8 times the risk of dementia in females (95% CI, 5.9–10.2) and 4.8 times the risk of dementia in males (95% CI, 4.2–5.4). Similarly, the blood biomarker-based Intermountain Mortality Risk Score (high versus low) was associated with 3.1 times the risk of dementia in females (95% CI, 2.7–3.5) and 2.7 times the risk of dementia in males (95% CI, 2.4–3.1).<sup>105</sup>

## Subclinical/Unrecognized Disease

- Among 896 people in Washington Heights-Inwood Columbia Aging Project (WHICAP) without MCI or dementia, an MRI index of cerebrovascular and neurodegenerative pathology, including WMHs, infarcts, hippocampal volumes, and cortical thicknesses, was associated with a higher incidence of MCI or LOAD (HR per SD of MRI score, 1.68 [95% CI, 1.44–1.96]).<sup>106</sup>
- In a meta-analysis of 3 population-based cohort studies (Rotterdam Study, FHS, and AGES Reykjavik Study), presence of cortical microbleeds on MRI was associated with a higher risk for incident all-cause dementia (unadjusted OR, 2.01 [95% CI, 0.92–4.36]; adjusted HR, 1.35 [95% CI, 1.00–1.82]).<sup>107</sup>
- Among 152 patients diagnosed with MCI and cerebral small vessel disease, 41 (27%) had  $\geq 1$  cerebral microbleeds.<sup>108</sup> Total number of cerebral microbleeds was correlated with lower scores on measures of attention/executive function (Spearman  $\rho=-0.282$ ;  $P=0.003$ ) and fluency (Spearman

$\rho=-0.166$ ;  $P=0.041$ ) but not with memory (Spearman  $\rho=-0.055$ ;  $P=0.505$ ) or with global cognitive ability (Spearman  $\rho=-0.57$ ;  $P=0.487$ ).

- In a meta-analysis of 9 studies, covert vascular brain injury was associated with decline in cognitive dysfunction on the Mini-Mental State Examination score (standardized mean difference,  $-0.47$  [95% CI,  $-0.72$  to  $-0.22$ ]).<sup>109</sup> In the same meta-analysis, among 4 studies, covert vascular brain injury was associated with cognitive dysfunction on the Montreal Cognitive Assessment Scale (standardized mean difference,  $-3.36$  [95% CI,  $-5.90$  to  $-0.82$ ]).
- Among 282 patients with AD (mean age, 73 years; 54% female), annual change in Clinical Dementia Rating Sum of Boxes scores was not significantly associated with any MRI findings, adjusted for age and sex, including presence of cortical infarcts (annual change, 0.7 points [95% CI,  $-0.5$  to  $1.9$ ]), lacunes ( $-0.2$  [95% CI,  $-0.9$  to  $0.5$ ]), any infarcts ( $0.0$  [95% CI,  $-0.6$  to  $0.7$ ]), WMH Fazekas 3 ( $-0.3$  [95% CI,  $-0.9$  to  $0.3$ ]), and WMH Fazekas 2 or 3 ( $-0.2$  [95% CI,  $-0.8$  to  $0.4$ ]).<sup>110</sup>

## Genetics and Family History

### APOE

- Among 8263 Latino people in the United States, prevalence of  $\geq 1$  *APOE*  $\epsilon 4$  alleles (associated with higher risk for LOAD) varied by genetically determined ancestry group: 11.0% (95% CI, 9.6%–12.5%) in Central American individuals; 12.6% (95% CI, 11.5%–13.7%) in Cuban individuals; 17.5% (95% CI, 15.5%–19.4%) in Dominican individuals; 11.0% (95% CI, 10.2%–11.8%) in Mexican individuals; 13.3% (95% CI, 12.1%–14.6%) in Puerto Rican individuals; and 11.2% (95% CI, 9.4%–13.0%) in South American individuals.<sup>111</sup> Prevalence of  $\geq 1$  *APOE*  $\epsilon 2$  allele (associated with lower risk for LOAD) was highest in Dominican individuals (8.6% [95% CI, 7.2%–10.1%]) and lowest in Mexican individuals (2.9% [95% CI, 2.4%–3.3%]).
- *APOE* genotype is associated not only with risk for AD but also with risk for vascular dementia.<sup>112</sup> Among 549 cases of vascular dementia and 552 controls without dementia in Europe, having  $\geq 1$  *APOE*  $\epsilon 4$  alleles was associated with 1.85 times the odds of vascular dementia (95% CI, 1.35–2.52), and having  $\geq 1$  *APOE*  $\epsilon 2$  alleles was associated with 0.67 times the odds of vascular dementia (95% CI, 0.46–0.98).

### Other LOAD Genes

- A GWAS conducted in 2058 cases of AD and 13618 controls from 4 US cohort studies identified 15 novel polymorphisms associated with AD

( $P < 5 \times 10^{-6}$ ) in proximity to genes that were not in the chromosomal region of *APOE* (19q13) and had not been associated with AD at that level of statistical significance in previous GWASs.<sup>113</sup> Four of the novel polymorphisms were located in chromosomal regions 3q13.11 and 17q21.2, which had not been associated with AD in prior studies.

- A GWAS in 116 196 people in the UK Biobank, comparing those who reported having a parent with AD (proxy cases) with control subjects who reported having no parent with AD and then meta-analyzing the UK Biobank findings with published GWASs, identified 4 novel polymorphisms ( $P < 5 \times 10^{-8}$ ) that had not been associated with AD at that level of statistical significance in previous GWASs.<sup>114</sup> These novel polymorphisms were on chromosomes 5 (near *HBEFGF*), 10 (near *ECHDC3*), 15 (near *SPPL2A*), and 17 (near *SCIMP*).

## Prevention

### Exercise

- A 2015 Cochrane review of 12 clinical trials including  $\geq 750$  participants found no evidence that aerobic exercise has any cognitive benefit in cognitively healthy older adults.<sup>115</sup>
- A 2019 randomized, parallel-group, community-based clinical trial of 132 multiracial, multiethnic cognitively normal individuals (mean age, 40 years) with below-median aerobic capacity in New York found that aerobic exercise, compared with stretching/toning, for 6 months improved executive function with greater improvement as age increased (increase at 40 years of age, 0.228 SD [95% CI, 0.007–0.448]; increase at 60 years of age, 0.596 SD [95% CI, 0.219–0.973]) and less improvement in the presence of  $\geq 1$  *APOE*  $\epsilon 4$  alleles.<sup>116</sup>

### BP Control

- Among 9361 participants with hypertension and high cardiovascular risk in the United States and Puerto Rico (mean age, 67.9 years; 35% females; 58% White, 30% Black, 10% Hispanic), targeting an SBP  $< 120$  mmHg, compared with targeting a systolic BP  $< 140$  mmHg, for a median of 3.34 years reduced the risk of MCI (14.6 versus 18.3 cases per 1000 person-years; HR, 0.81 [95% CI, 0.69–0.95]) and the combined rate of MCI or probable dementia (20.2 versus 24.1 cases per 1000 person-years; HR, 0.85 [95% CI, 0.74–0.97]) but not the risk of adjudicated probable dementia (7.2 versus 8.6 cases per 1000 person-years; HR, 0.83 [95% CI, 0.67–1.04]) over a total median follow-up of 5.11 years.<sup>117</sup>
- In a meta-analysis of 12 RCTs ( $> 92$  000 participants; mean age, 69 years; 42% females), BP lowering with

antihypertensive agents compared with control was associated with a lower risk of incident dementia or cognitive impairment (7.0% versus 7.5% of patients over a mean trial follow-up of 4.1 years; OR, 0.93 [95% CI, 0.88–0.98]; absolute risk reduction, 0.39% [95% CI, 0.09%–0.68%];  $P=0.0\%$ ).<sup>118</sup>

- An individual patient meta-analysis of 19 378 participants from 5 cohort studies found that differences between Black and White individuals in global cognition decline were no longer statistically significant after adjustment for cumulative mean systolic BP, suggesting that Black individuals' higher cumulative BP levels might contribute to racial disparities in cognitive decline.<sup>119</sup>

### Glycemic Control

- Evidence for dementia prevention strategies in patients with diabetes is lacking.
- Among 2977 patients (mean age, 62.5 years; 48% females) with type 2 diabetes, high HbA1c (>7.5%), and high cardiovascular risk who had been randomly assigned to treatment groups in ACCORD, there was no evidence of a significant difference in mean 40-month cognitive test scores between the intensive glycemic control group targeting an HbA1c <6% compared with a standard treatment group targeting a HbA1c of 7.0 to 7.9%.<sup>120</sup> Similarly, at 40 months, no differences in cognitive function were found between the intensive BP-lowering group (targeting systolic BP <120 mm Hg) and the standard treatment group (targeting systolic BP <140 mm Hg) or between the fibrate group and the placebo group.<sup>121</sup>
- In a secondary analysis of 2880 participants (mean age, 63.1 years; 67% females) of the DPP, neither exposure to intensive lifestyle intervention nor metformin was associated with cognition at 8 years.<sup>122</sup>
- In adults ≥60 years of age with type 1 diabetes, continuous glucose monitoring compared with standard blood glucose monitoring resulted in a small but statistically significant reduction in hypoglycemia but no differences in cognitive outcomes over 6 months.<sup>123</sup>

### Other Preventive Strategies

- Among 1260 participants with elevated cardiovascular risk in Finland (mean age, 69 years; 45% females; all White), those randomized to a 2-year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring had a larger increase in global cognition (0.20-point increase in neuropsychological test battery total z score [SE, 0.02]) compared with those randomized to a control condition of general health advice (0.16-point increase [SE, 0.01]). The intervention group also had larger increases in executive function and processing speed but not memory.<sup>124</sup>

- Evidence from a secondary analysis of the HPS suggests that statin therapy for 5 years in adults with vascular disease or diabetes (mean age, 63 years; 25% females) resulted in 2.0% of participants avoiding a nonfatal stroke or TIA and 2.4% avoiding a nonfatal cardiac event, which yielded an expected reduction in cognitive aging of 0.15 years (95% CI, 0.11–0.19).<sup>125</sup>
- Among 221 Black participants with MCI (mean age, 75.8 years; 79% females), behavioral activation, which aimed to increase cognitive, physical, and social activity, compared with supportive therapy, an attention control treatment, reduced the 2-year incidence of memory decline (absolute difference, 7.1%; RR, 0.12 [95% CI, 0.02–0.74];  $P=0.02$ ).<sup>126</sup> Compared with supportive therapy, behavioral activation also was associated with improvement in executive function and preservation of everyday function.
- Observational studies suggest that preventing stroke is one of the most effective strategies for preventing dementia,<sup>127</sup> including LOAD,<sup>128</sup> and cognitive decline.<sup>129</sup>

## Mortality

### In Hospitalized Patients

- In a 5-year retrospective review of 9519 adult patients with trauma, 195 (2.0%) who had a diagnosis of dementia at an American College of Surgeons–verified level I trauma center,<sup>130</sup> patients with dementia ( $n=195$ ) were matched with dementia-free patients ( $n=195$ ) and compared on mortality, ICU length of stay, and hospital length of stay. The comorbidities and complications were similar between the groups (11.8% versus 12.4%). Mortality was 5.1% in both the dementia and control groups. The study found that dementia did not increase the risk of mortality in patients with trauma.

### In Patients With COVID-19

- A systematic review and meta-analysis on the impact of dementia on the clinical outcomes of COVID-19 used 10 studies including 119 218 individuals.<sup>131</sup> The review found that overall the incidence of dementia in patients with COVID-19 was 9% (95% CI, 6%–13%). In the meta-analysis of 9 studies, the mortality rate of individuals with dementia after being infected with COVID-19 was significantly higher than in those without dementia (OR, 5.17 [95% CI, 2.31–11.59]).
- An observational case series looked at the frequency and mortality of COVID-19 in patients with a prior diagnosis of AD and frontotemporal dementia in a tertiary hospital in Madrid, Spain.<sup>132</sup> A total of 204 patients (72.1% with AD and 27.9% with frontotemporal dementia) were included (mean age, 78 years;



58.3% female). Of those patients, 31 (15.2%) were diagnosed with COVID-19. In the patients included in the study, death was associated with older age ( $83.92 \pm 6.76$  years versus  $77.59 \pm 9.48$  years [ $t, 2.77$ ];  $P=0.015$ ) and with an advanced clinical dementia stage ( $\chi^2=8.58$ ;  $P=0.035$ ). Living in a care home and diagnosis of AD were independently associated with a higher probability of death ( $R^2=0.445$ ; correct classification rate, 94.6%;  $P<0.001$ ).

## Complications

- In a study from the NCDR Chest Pain-MI Registry of 43812 participants >65 years of age with MI, MCI was found in 3.9% of those presenting with a STEMI and in 5.7% of those presenting with an NSTEMI.<sup>133</sup> After adjustment for potential confounders, MCI was associated with a higher risk of all-cause in-hospital mortality (STEMI cohort: OR, 1.3 [95% CI, 1.1–1.5]; NSTEMI cohort: OR, 1.3 [95% CI, 1.2–1.5]). In addition, among those presenting with STEMI, PCI use was relatively similar in those with MCI (92.8%) and those without cognitive impairment (92.1%), but fibrinolytic use was lower in those with MCI (27.4%) than in those without cognitive impairment (40.9%). Finally, among patients with an NSTEMI, rates of angiography, PCI, and CABG were 50.3%, 27.3%, and 3.3% in those with MCI compared with 84.7%, 49.4%, and 10.9% in those without cognitive impairment.
- In a study from the French Dijon Stroke Registry of 1048 patients with ischemic stroke, prestroke MCI or dementia was associated with more severe stroke using the NIHSS score compared with those without cognitive impairment (adjusted OR for MCI, 1.52 [95% CI, 1.02–2.28]; adjusted OR for dementia, 2.16 [95% CI, 1.45–3.22]).<sup>134</sup>
- In a study from the CROMIS-2 cohort of 1102 patients with AF-associated TIA or stroke, preexisting cognitive impairment was associated with worse functional outcome at 24 months of follow-up (adjusted OR for modified Rankin Scale score >2, 2.43 [95% CI, 1.42–4.2]).<sup>135</sup>

## Health Care Use

- In a retrospective analysis of 3019 dementia-free participants, 494 developed dementia. Among those with a dementia diagnosis, 86% were admitted at least once during the study period versus 59% of those who remained dementia-free.<sup>136</sup> The unadjusted all-cause admission rate in the dementia group was 419 per 1000 person-years versus 200 per 1000 person-years in the dementia-free group. After adjustment for age, sex, and other potential confounders, the ratio of admission rates for

all-cause admissions was 1.41 (95% CI, 1.23–1.61;  $P<0.001$ ).

- A structured dementia care program was examined with regard to health care use and cost outcomes.<sup>137</sup> The program included structured needs assessments of patients and caregivers, individualized care plans, coordination with primary care, referrals to community organizations for dementia-related services and support, and continuous access to clinicians for assistance and advice. Compared with community control subjects ( $n=2163$ ), those in the program ( $n=1083$ ) were less likely to be admitted to a long-term care facility (HR, 0.60 [95% CI, 0.59–0.61]). There were no differences between groups in terms of hospitalizations, ED visits, or 30-day readmissions. The total cost of care to Medicare, excluding program costs, was \$601 less per patient per quarter (95% CI, 5–1198). After accounting for the estimated program costs of \$317 per patient per quarter, the program was cost-neutral for Medicare, with an estimated net cost of  $-\$284$  (95% CI,  $-881$  to 312) per program participant per quarter.

## Cost

- 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.<sup>138</sup>
- In HRS, a retrospective cohort of Medicare fee-for-service beneficiaries  $\geq 70$  years of age who died between 2005 and 2010 ( $N=1702$ ) was stratified into 4 groups to examine social costs and financial risks faced by Medicare beneficiaries 5 years before death.<sup>139</sup> Average total cost per decedent with dementia (\$287 038) was significantly greater than that of those who died of HD (\$175 136), cancer (\$173 383), or other causes (\$197 286;  $P<0.001$ ). Although Medicare expenditures were similar across groups, average out-of-pocket spending for patients with dementia (\$61 522) was 81% higher than that for patients without dementia; a similar pattern held for informal care.
- In a subsample ( $n=856$ ) of individuals in HRS determined to have a high probability of dementia, the market costs associated with dementia care were determined on the basis of self-reported out-of-pocket spending, use of nursing home care, and Medicare claims data.<sup>140</sup> The yearly monetary cost per person in 2010 attributable to dementia was either \$56 290 (95% CI, 42 746–69 834) or \$41 689 (95% CI, 31 017–52 362), depending on the method used to value informal care. These

individual costs suggest that the total monetary cost of dementia in 2010 was between \$157 billion and \$215 billion (based on an estimated 14.7% prevalence of dementia among people >70 years of age in the United States in 2010).

- Among an estimated 690 000 people with dementia in England, 565 000 received unpaid care, received community care, or lived in a care home (assisted-living residence or nursing home).<sup>141</sup> Total annual cost of dementia care in England was estimated to be £24.2 billion in 2015, of which 42% (£10.1 billion) was attributable to unpaid care. Social care costs (£10.2 billion) were 3 times larger than health care costs (£3.8 billion), and £6.2 billion of the total social care costs was met by users themselves and their families, with £4.0 billion (39.4%) funded by government. The economic impact of dementia weighs more heavily on the social care than on the health care sector and on people with more severe dementia.

## Global Burden

All prevalence and mortality estimates cited here are from the GBD 2020 Study and pertain to all types of dementia combined (Data courtesy of the Global Burden of

Disease Study 2020.). The GBD 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020.

### Prevalence: GBD 2020 Study

(See Table 16-1 and Chart 16-1)

- There were 54.69 million (95% UI, 46.89–63.50 million) prevalent cases of AD and other dementias in 2020, with 19.99 million (95% UI, 17.00–23.32 million) among males and 34.71 million (95% UI, 29.82–40.29 million) among females (Table 16-1).
- In 2020, the highest age-standardized prevalence rates of AD and other dementias were found in East Asia and parts of high-income North America. (Chart 16-1)

### Mortality: GBD 2020 Study

(See Table 16-1 and Chart 16-2)

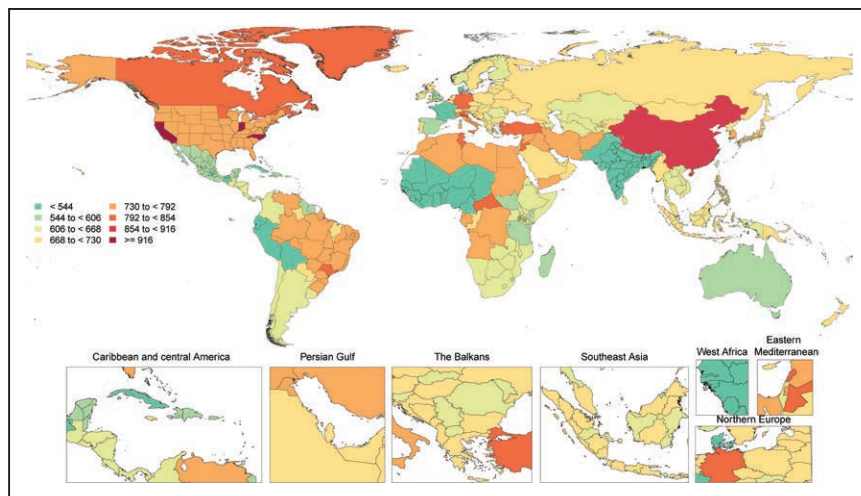
- There were 1.89 million (95% UI, 0.48–4.85 million) deaths attributable to AD and other dementias in 2020 (Table 16-1).
- In 2020, age-standardized mortality rates estimated for AD and other dementias were highest in parts of central sub-Saharan Africa, East Asia, and tropical Latin America (Chart 16-2).

**Table 16-1. Global Mortality and Prevalence of AD and Other Dementias, by Sex, 2020**

	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), 2020	1.89 (0.48 to 4.85)	54.69 (46.89 to 63.50)	0.61 (0.15 to 1.66)	19.99 (17.00 to 23.32)	1.28 (0.32 to 3.27)	34.71 (29.82 to 40.29)
Percent change in total number, 1990–2020	184.56 (168.61 to 206.99)	144.28 (139.51 to 148.97)	207.23 (187.10 to 231.05)	155.86 (149.55 to 161.51)	174.92 (157.47 to 201.04)	138.08 (133.71 to 142.98)
Percent change in total number, 2010–2020	44.45 (39.49 to 50.56)	37.67 (36.37 to 39.14)	49.51 (42.06 to 57.27)	39.58 (38.08 to 41.21)	42.16 (36.32 to 49.71)	36.60 (35.21 to 38.08)
Rate per 100 000, age standardized, 2020	25.78 (6.46 to 66.27)	697.99 (598.01 to 814.17)	21.46 (5.21 to 57.21)	595.61 (504.29 to 696.25)	28.38 (7.15 to 72.30)	771.39 (662.14 to 895.52)
Percent change in rate, age standardized, 1990–2020	−0.40 (−4.28 to 5.20)	−1.02 (−2.33 to −0.08)	2.15 (−2.02 to 7.43)	−0.91 (−2.54 to 0.24)	−0.12 (−5.08 to 7.37)	0.11 (−0.98 to 1.13)
Percent change in rate, age standardized, 2010–2020	−0.97 (−4.17 to 2.68)	−0.38 (−1.20 to 0.44)	0.18 (−3.44 to 4.27)	−0.34 (−1.06 to 0.49)	−0.91 (−5.10 to 3.97)	0.05 (−0.87 to 0.91)

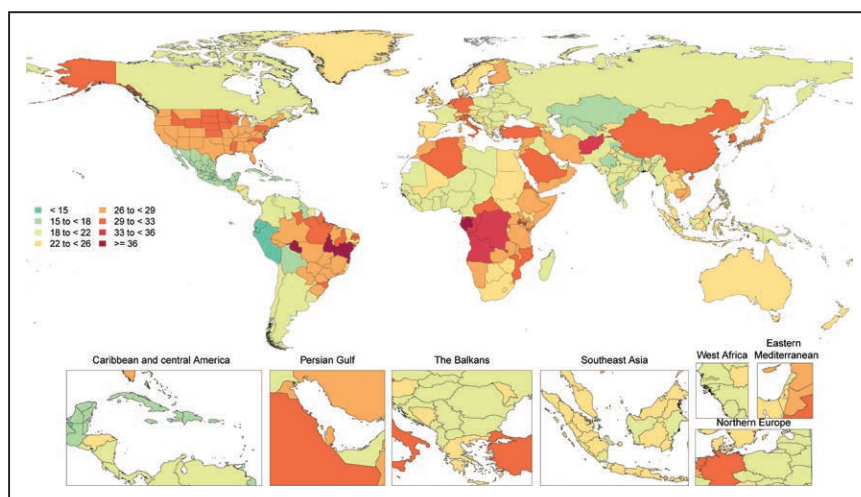
AD indicates Alzheimer Disease; and UI, uncertainty interval.

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington.



**Chart 16-1. Age-standardized global prevalence rates of AD and other dementias per 100,000, both sexes, 2020.**

AD indicates Alzheimer disease. Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the GBD website.<sup>143</sup>



**Chart 16-2. Age-standardized global mortality rates of AD and other dementias per 100,000, both sexes, 2020.**

AD indicates Alzheimer disease. Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the GBD website.<sup>143</sup>

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## 17. CONGENITAL CARDIOVASCULAR DEFECTS AND KAWASAKI DISEASE

See Tables 17-1 and 17-2 and Charts 17-1 through 17-7

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### Congenital Cardiovascular Defects

#### ICD-9 745 to 747; ICD-10 Q20 to Q28.

CCDs, which arise from abnormal or incomplete formation of the heart, valves, and blood vessels, are the most common birth defect worldwide. CCDs range in severity from minor abnormalities that spontaneously resolve or are hemodynamically insignificant to complex malformations, including absent, hypoplastic, or atretic portions of the heart. There is significant variability in the presentation of CCDs, resulting in heterogeneous morbidity, mortality, and health care costs across the life span. Some types of CCDs are associated with diminished quality of life,<sup>1</sup> on par with what is seen in other chronic pediatric health conditions,<sup>2</sup> as well as deficits in cognitive functioning<sup>3</sup> and neurodevelopmental outcomes.<sup>4</sup> However, health outcomes generally continue to improve for CCDs, including survival.

#### Overall Life Span Prevalence

It is estimated that 13.3 million (95% CI, 11.5–15.4 million) people globally were living with CCDs in 2019.<sup>5</sup> CCD prevalence increased by 28% between 1990 and 2019, driven largely by increases in the number of adolescents and younger adults (15–49 years of age increased by 42%) and middle-aged adults (50–69 years of age increased by 117%) living with CCDs.<sup>5</sup> The change was greatest in low- and middle-income countries, attributed to both increasing population growth and improving survival.<sup>5</sup>

The 2017, the all-age prevalence of CCDs in the United States was estimated at 466 566 (95% CI, 429 140–505 806) individuals, with 279 320 (95% CI, 266 461–331 437; 60%) of these <20 years of age.<sup>6</sup> This figure represents a fairly drastic downshift from the 32nd Bethesda Conference estimate (2000; estimate, 800 000)<sup>7</sup> and estimates provided by the CDC (2010;

1.4 million adults and 1 million children),<sup>8</sup> reflecting a change in GBD modeling strategy. In prior estimates, every person born with CCDs, regardless of type or severity, was assumed to have a CCD across their life span. In 2017, the GBD took a more nuanced approach that allowed for “cure” of simple lesions such as atrial septal defects that undergo spontaneous closure for which there was no known associated morbidity or mortality, thus lowering the overall population considered to be living with a CCD.<sup>6</sup> With the same modeling strategy, 2017 estimates place the global prevalence of CCDs at 157 per 100 000 (95% CI, 143–172), with the highest prevalence estimates in countries with a low sustainable development index (238 per 100 000 [95% CI, 216–261]) and the lowest in those with a high-middle or high sustainable development index (112 per 100 000 [95% CI, 102–114] and 135 per 100 000 [95% CI, 125–145], respectively).<sup>6</sup>

#### Birth Prevalence

(See Table 17-1)

- In high-income North America, including the United States, the birth prevalence of CCDs is estimated to be 12.3 per 1000 (95% CI, 10.9–13.8).<sup>6</sup>
- An estimated 1% or a minimum of 40 000 infants are expected to be affected by CCDs each year in the United States.<sup>9</sup> Of these, ≈25%, or 2.4 per 1000 live births, require invasive treatment in the first year of life (Table 17-1).

#### 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).<sup>10</sup>
- 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).<sup>11</sup>
- 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.<sup>9</sup>

#### Risk Factors

- Numerous nongenetic risk factors are thought to contribute to CCDs.<sup>12,13</sup>
  - CCDs appear to be more common among infants born to mothers with low SES. In Ontario,

The 2022 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 2022. 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.



mothers who lived in the lowest -income neighborhoods had a higher risk of having an infant with a CCD compared with mothers living in the highest-income neighborhoods (OR, 1.29 [95% CI, 1.20–1.38]). Furthermore, this discrepancy between low and high was also found across measures of neighborhood education (OR, 1.34 [95% CI, 1.24–1.44]) and employment rate (OR, 1.18 [95% CI, 1.10–1.26]).<sup>14</sup>

- Known risks generally focus on maternal exposures, but a study of paternal occupational exposure documented an overall higher incidence of CCDs,<sup>15</sup> with additional studies showing paternal exposure to phthalates<sup>16</sup> and attributable fractions of TOF to paternal anesthesia (3.6%), coarctation of the aorta to parental sympathomimetic medication exposure (5.8%), VSDs to paternal pesticide exposure (5.5%), and HLHS to paternal solvent exposure (4.6%).<sup>17</sup>
- Known maternal lifestyle risks include smoking<sup>18–20</sup> during the first trimester of pregnancy, which has also been associated with a  $\geq 30\%$  increased risk of the following lesions in the fetus: ASD, pulmonary valvar stenosis, truncus arteriosus, TGA,<sup>21</sup> and septal defects (particularly for heavy smokers [ $\geq 25$  cigarettes daily]).<sup>22</sup>
- Exposure to secondhand smoke also has been implicated as a risk factor.<sup>20</sup>
- Maternal alcohol intake of  $>1$  drink per week has been correlated with CCDs.<sup>20</sup> Maternal binge drinking 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 may be at increased risk of giving birth to a child with a CCD compared with mothers who report only any binge drinking (aOR, 12.65 [95% CI, 3.5–45.2] versus 9.45 [95% CI, 2.5–35.3]).<sup>23</sup>
- Air pollutants may also increase the risk of CCDs. A systematic review and meta-analysis including 26 studies showed that risk of TOF (OR, 1.21 [95% CI, 1.04–1.41]) was associated with high versus low carbon monoxide exposure, increasing risk of ASD was proportionally associated with increasing exposure to particular matter ( $\leq 10 \mu\text{m}$ ) and ozone (OR, 1.04 per  $10 \mu\text{g}/\text{m}^3$  [95% CI, 1.00–1.09] and 1.09 [95% CI, 1.02–1.17], respectively), and increased risk of aortic coarctation was associated with high versus low nitrogen dioxide exposure (OR, 1.14 [95% CI, 1.02–1.26]).<sup>24</sup>
- Maternal obesity is consistently 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.<sup>25–28</sup> 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.<sup>26</sup>

- Maternal diabetes, including gestational diabetes, is associated with CCDs, both isolated (CCD[s] as the only major congenital anomaly) and multiple (CCD[s] plus  $\geq 1$  noncardiac major congenital anomalies).<sup>29,30</sup> Pregestational diabetes has been associated with CCDs, specifically TOF.<sup>31</sup>
- Folate deficiency is a well-documented risk for congenital malformations, including CCDs, and folic acid supplementation is routinely recommended during pregnancy.<sup>12</sup> 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]).<sup>32</sup> 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).<sup>33</sup>
- 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.<sup>34</sup>
- Maternal infections, including rubella and chlamydia, have been associated with congenital heart defects.<sup>35,36</sup>
  - Exposure to other teratogens also may be associated with CCDs at birth. In an Iranian cohort, exposure to teratogens in the first trimester of pregnancy (hair color, canned foods, detergents) increased the odds of CCDs (OR, 2.32 [95% CI, 1.68–3.20]).<sup>28</sup>
  - There are inconclusive data showing an increased risk of serious adverse events from COVID-19 infection in children and adults with CCDs.<sup>37</sup>

### 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.<sup>38,39</sup> At present, all 50 states and the District of Columbia have laws or regulations mandating newborn screening for identification of previously unidentified CCDs,<sup>40</sup> and several studies have demonstrated the benefit of such screening.<sup>41–43</sup>

- 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).<sup>44</sup>

- A meta-analysis of 19 studies that included 436 758 newborns found that pulse oximetry had a sensitivity of 76.3% (95% CI, 69.5%–82.0%) and a specificity of 99.9% (95% CI, 99.7%–99.9%) for detection of critical CCDs with a false-positive rate of 0.14% (95% CI, 0.07%–0.22%).<sup>45</sup> On the basis of these data, among healthy-appearing late-preterm or full-term infants, pulse oximetry screening will detect 5 of 6 per 10 000 with critical CCDs and falsely identify an additional 14 per 10 000 screened.
- 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.<sup>46</sup>
- Reports outside of the United States and other high-income settings have shown similar performance of pulse oximetry screening in identifying critical CCDs,<sup>47</sup> 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 incidence and outcomes based on factors such as ethnicity, race, and socioeconomics.<sup>48–52</sup>

- 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]).<sup>48</sup>
- A subanalysis of 525 patients from the Pediatric Heart Network Single Ventricle Reconstruction trial found that patients in the lowest SES tercile had more complications and fewer cardiac catheterizations and were older at the stage 2 and Fontan procedure compared with those in the highest SES tercile. Children in the lowest SES also were more likely to be from an underrepresented racial group and had significantly higher unadjusted mortality, attenuated somewhat by birth and stage 1 confounders. Developmental and functional outcomes also were worse in the lowest SES tercile, even after adjustment for confounders.<sup>53</sup>
- 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 whose fathers were younger (59.7% [95% CI,

54.6%–65.2%]). Factors associated with survival in biventricular CCDs included maternal education, race or ethnicity, and marital status.<sup>49</sup>

- A single-center cross-sectional study in China reviewed 2037 survivors of critical CCDs 2 to 12 years of age between 2012 and 2015. Mean health-related quality of life scores were significantly lower in the low socioeconomic group than in the medium and high socioeconomic groups.<sup>54</sup>
  - In Colorado, adolescents and adults with CCDs living in areas with the most deprived quintile (as defined by census tract area deprivation index) had 51% higher odds of inpatient admission, 74% higher odds of ED visit, and 45% higher odds of major cardiac events compared with those in the least deprived quintile.<sup>55</sup>
  - A systematic review of the impacts of social determinants of health found those with negative social determinants had (1) lower rates of fetal diagnosis, (2) higher CCD incidence and prevalence, (3) higher adverse surgical outcomes, (4) greater likelihood of impaired neurodevelopmental outcomes, (5) lower quality of life, and (6) greater likelihood of adverse adult congenital heart disease outcomes.<sup>56</sup>
- 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.<sup>57</sup>

### Genetics and Family History

- CCDs can have a heritable component, and parental consanguinity is a known risk factor.<sup>28</sup> There is a greater concordance of CCDs in monozygotic than dizygotic twins.<sup>58</sup> A report from Kaiser Permanente data showed that monozygotic twins were at particularly increased risk for CCDs (RR, 11.6 [95% CI, 9.2–14.5]).<sup>59</sup>
- Among parents with ASD or VSD, 2.6% and 3.7%, respectively, have children who are similarly affected, 21 times the estimated population frequency.<sup>60</sup> 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.<sup>61</sup>
- Large chromosomal abnormalities are found in 8% to 10% of individuals with CCDs.<sup>61</sup> For example, aneuploidies such as trisomy 13, 18, and 21 account for 9% to 18% of CCDs.<sup>62</sup> 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.<sup>63</sup>

- 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.<sup>64</sup> The most common copy number variant is del22q11, which encompasses the T-box transcription factor (*TBX1*) gene and presents as DiGeorge syndrome and velocardiofacial syndrome. Others include del17q11, which causes William syndrome.<sup>65</sup>
- Point variants in single genes are found in 3% to 5% of CCDs<sup>61</sup> and include variants in a core group of cardiac transcription factors (*NKX2.5*, *TBX1*, *TBX2*, *TBX3*, *TBX5*, *GATA4*, and *MEF2*),<sup>65–67</sup> *ZIC3*, and the *NOTCH1* gene (dominantly inherited and found in ≈5% of cases of bicuspid aortic valve) and related NOTCH signaling genes.<sup>68</sup>
  - Consortia studies have allowed analysis of specific subtypes of CCDs 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 previously been associated with heart development.<sup>69</sup> Another study of nonsyndromic TOF in 829 patients with TOF found rare variants in *NOTCH1* and *FLT4* in almost 7% of patients with TOF.<sup>70</sup> A GWAS in 5 cohorts inclusive of 1025 conotruncal case-parent trios, 509 left ventricular obstructive tract defect case-parent trios, 406 conotruncal defect cases, and 2976 controls found intronic variants in the *MGAT4C* gene associated with conotruncal defects, and in meta-analyses, 1 genome-wide significant association was found in an intragenetic SNP associated with left ventricular outflow tract defect.<sup>71</sup> Whole-genome sequencing has identified additional genetic loci for CCDs. In a study of whole-genome sequencing in 749 CCD case-parent trios with 1611 unaffected trios, a burden of de novo noncoding variants was identified in cases compared with controls, including in established CCD genes (*PTPN11*, *NOTCH1*, *FBN1*, *FLT4*, *NR2F2*, *GATA4*), with higher representation of variants in RNA-binding-protein regulatory sites.<sup>72</sup> These results suggest that noncoding de novo variants play a significant role in CCDs in addition to coding de novo variants.
- Rare monogenic CCDs also exist, including monogenic forms of ASD, heterotaxy, severe mitral valve prolapse, and bicuspid aortic valve.<sup>65</sup>
- 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.<sup>73</sup>

- There is no exact consensus currently on the role, type, and utility of clinical genetic testing in people with CCDs,<sup>65</sup> 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.<sup>7</sup>
- The diagnostic yield for CCD genetic panels in familial, nonsyndromic cases is 31% to 46% and is even lower in nonfamilial disease.<sup>74,75</sup> Use of whole-exome genetic testing has been shown to improve rates of detection.<sup>76</sup>
- A Pediatric Cardiac Genomics Consortium has been developed to provide and better understand phenotype and genotype data from large cohorts of patients with CCDs.<sup>77</sup>

### Mortality

(See Table 17-2 and Charts 17-1 through 17-5)

- In 2017, CCDs were among the top 8 causes of infant mortality in all global regions.<sup>6</sup>
- In 2019, mortality related to CCDs was 2890 deaths (Table 17-2) in the United States, a 9.4% decrease from the number of deaths in 2009 (unpublished NHLBI tabulation using NVSS<sup>78</sup>).
- CCDs (*ICD-10* Q20–Q28) were the most common cause of infant deaths resulting from birth defects (*ICD-10* Q00–Q99) in 2019; 21.6% of infants who died of a birth defect had a heart defect (*ICD-10* Q20–Q24; unpublished NHLBI tabulation using NVSS<sup>78</sup>).
- In 2019, the age-adjusted death rate (deaths per 100 000 people) attributable to CCDs was 0.9, a 18.2% decrease from 2009 (unpublished NHLBI tabulation using CDC WONDER<sup>79</sup>).
- Death rates attributed to CCDs decrease as gestational age advances to 40 weeks.<sup>80</sup> 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.<sup>81,82</sup>
- Analysis of the STS Congenital Heart Surgery Database, a voluntary registry with self-reported data from 116 centers performing CCD surgery (112 based in 40 US states, 3 in Canada, and 1 in Turkey),<sup>83</sup> showed that of 31 102 analyzable CCD surgeries in 2018, there were 662 mortalities among the 25 608 patients included (2.5% [95% CI, 2.3%–2.7%]). For this same time period (2018), the mortality rate was 6.9% (95% CI, 6.2%–7.8%) for neonates, 2.4% (95% CI, 2.1%–2.8%) for infants, 1.1% (95% CI, 0.9%–1.3%) for children (1–18

- years of age), and 1.2% (95% CI, 0.8%–1.7%) for adults (>18 years of age).<sup>84</sup>
- Another analysis of mortality after CCD surgery, culled from the US-based multicenter data registry of the Pediatric Cardiac Care Consortium, 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%).<sup>85</sup>
  - In Mexico, 70 741 deaths were attributed to CCD during the years 2000 to 2015, with the standardized mortality rates increasing from 3.3 to 4 per 100 000 individuals and mortality rates increasing in the group <1 year of age from 114.4 to 146.4 per 100 000 live births.<sup>86</sup>
  - Trends in overall age-adjusted death rates attributable to CCDs showed a decline from 1999 to 2019 (Chart 17-1); this varied by race, ethnicity, and sex (Charts 17-2 and 17-3). 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 17-2), although death rates increased between 2017 and 2018 for NH White and NH Black people and between 2018 and 2019 in Hispanic people. From 1999 to 2019, death rates declined in both males and females (Chart 17-3) and in the groups 1 to 4, 5 to 14, 15 to 24, and ≥25 years of age (Chart 17-4) 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 2019 (Chart 17-4).
  - The US 2019 age-adjusted death rate (deaths per 100 000 people) attributable to CCDs was 1.01 for NH White males, 1.35 for NH Black males, 0.83 for Hispanic males, 0.82 for NH White females, 1.09 for NH Black females, and 0.71 for Hispanic females (Chart 17-5). Infant (<1 year of age) mortality rates were 27.2 for NH White infants, 37.0 for NH Black infants, and 28.5 for Hispanic infants (unpublished NHLBI tabulation using CDC WONDER<sup>79</sup>).
  - Mortality after congenital heart surgery also differs between races and ethnicities, even after adjustment for access to care. One study found that a higher risk of in-hospital mortality was associated with underrepresented race (OR, 1.36 [95% CI, 1.19–1.54]) and Medicaid insurance (OR, 1.26 [95% CI, 1.09–1.46]).<sup>87</sup> Experience at 1 center suggested that race was independently associated with neonatal surgical outcomes only in patients with less complex CCDs.<sup>88</sup> Another center found that a home monitoring program can reduce mortality even in this vulnerable population.<sup>89</sup>

- Analysis of the National Inpatient Sample Database of 20 649 neonates with HLHS showed a 20% decrease in mortality for neonates with HLHS between the time periods of 1998 to 2005 and 2006 to 2014 (95% CI, 25.3%–20.6%;  $P=0.001$ ), despite the later cohort having more comorbidities, including prematurity and chromosomal abnormalities, among others.<sup>90</sup>
  - A meta-analysis of outcomes for 848 patients with heterotaxy who underwent a Fontan procedure showed survival at 1, 5, and 10 years to be 86% (95% CI, 79%–91%), 80% (95% CI, 71%–87%), and 74% (95% CI, 59%–85%), respectively.<sup>91</sup>
- 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  $152\,277 \pm 7875$  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%;  $P<0.0001$ ).<sup>92</sup> For adults with CCDs, specialist care is a key determinant of mortality and morbidity. In a single-center report of 4461 adult patients with CCDs with 48 828 patient-years of follow-up, missed appointments and delay in care were predictors of mortality.<sup>93</sup>

### Complications

- Long-term effects of CCDs include arrhythmias, IE, and HF.<sup>94–96</sup>
- 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, the 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.<sup>97</sup> By 42 years of age, ≈8% of patients with congenital HD had been diagnosed with AF.
  - Children with CCDs may be at risk for adverse neurodevelopmental outcomes, including mild motor impairments,<sup>98</sup> increased attention-deficit/hyperactivity disorder–related behaviors, and difficulties in social interaction,<sup>99</sup> and depression and anxiety.<sup>100,101</sup>
  - Adults also may carry a higher burden of neurocognitive dysfunction and mental health complications. In the United Kingdom, adults with mild to moderate CCDs showed significantly lower performance on neurocognitive testing compared



with individuals without CCDs, even when those with prior stroke or CAD were excluded.<sup>102</sup> Of 121 patients with adult congenital heart disease in Australia with moderate or complex CCD, just more than 60% of those with TOF or CoA remained employed, and approximately half had been diagnosed with anxiety or depression.<sup>103</sup>

- In patients with HLHS, an older age at Fontan procedure and a history of sepsis were independent predictors of poor neurocognitive outcomes.<sup>104</sup>

### Health Care Use: Hospitalizations

#### (See Table 17-2)

- In 2018, the total number of first-listed hospital discharges for CCDs for all ages was 43 000 (Table 17-2).
- Hospitalization of infants with CCDs is common; one-third of patients with congenital heart defects require hospitalization during infancy,<sup>105,106</sup> often in an ICU.
- Adults with CCD and HF-related admissions increased according to data from the Pediatric Health Information Systems database from 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.<sup>107</sup> Compared with adults with non-CCD HF-related admissions, adults with CCD and HF-related admissions also demonstrated increased length of stay  $\geq 7$  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]).<sup>108</sup>
  - Among adults with commercially purchased insurance, those with CCDs had more health care visits and higher expenditures than those without CCD, even when controlling for baseline characteristics and comorbidities.<sup>109</sup>

### 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.<sup>110</sup>
- Among pediatric hospitalizations (0–20 years of age) in the HCUP 2012 Kids' Inpatient Database<sup>111</sup>:
  - 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 hospital cost was \$51 302 (IQR, \$32 088–\$100 058) in children who underwent cardiac surgery, \$21 920 (IQR, \$13 068–\$51 609) in

children who underwent cardiac catheterization, \$4134 (IQR, \$1771–\$10 253) in children who underwent noncardiac surgery, and \$23 062 (IQR, \$5529–\$71) in children admitted for medical treatments.

- The mean cost of CCDs was higher in infancy (\$36 601) than in older ages and in those with critical congenital heart defects (\$52 899).
- 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.<sup>112</sup>
- A US study evaluating cost and length of stay in neonates with HLHS revealed significant regional differences in cost, length of stay, and mortality.<sup>113</sup>
  - A 2021 study in Queensland, Australia, of 2519 patients found that catheter-based and surgical interventions accounted for 90% of the total costs of caring for patients with CCDs.<sup>114</sup>
  - In New York State, between 2009 and 2013, total costs of inpatient admission for individuals 11 to 30 years of age with CCDs rose from \$27.2 million in 2009 to \$52.2 million in 2013, increasing faster for those with nonsevere versus severe CCD.<sup>115</sup>
  - A Pediatric Heart Network study found an overall cost reduction for TOF repair of 27% after a clinical practice guideline including early extubation was introduced. Similar cost reduction was not found for patients with aortic coarctation repair.<sup>116</sup>
  - A cross-sectional survey from the NHIS of US households (2011–2017) found that nearly half (48.9%) of families of children with CCD had some financial hardship attributable to medical bills. Among 17% of families who reported that they could not pay their medical bills (most severe hardship category), there were significantly higher rates of food insecurity and delays in care because of cost.<sup>117</sup>

### Global Burden of CCDs

#### (See Charts 17-6 and 17-7)

- A total of 3.12 million (95% UI, 2.40–4.11 million) babies were born with congenital heart anomalies in 2019, representing 2305.2 per 100 000 live births (95% UI, 1772.9–3039.2).<sup>5</sup>
- As with all-age prevalence, there is global variability in birth prevalence by sustainable development index. In 2017, prevalence was estimated to be 25.0 per 1000 in countries with low sustainable development index and 11.8 to 12.6 per 1000 in countries with high-middle or high sustainable development index.<sup>6</sup>
- A 2019 systematic review including 103 632 049 live births globally showed the following per 1000

births in order of prevalence: VSD, 3.071; ASD, 1.441; patent ductus arteriosus, 1.004; pulmonary stenosis, 0.546; TOF, 0.356; TGA, 0.295; atrioventricular septal defects, 0.290; aortic coarctation, 0.287; HLHS, 0.178; double-outlet right ventricle, 0.106; and truncus arteriosus, 0.078 (among others reviewed).<sup>118</sup>

- CCDs were responsible for 261 247 deaths globally in 2017 (95% CI, 216 567–308 159), which is a 30% decline from 1990.<sup>6</sup> The majority of these deaths (69%) were in infants <1 year of age (180 624 [95% CI, 146 825–214 178]). In large part, CCD mortality tracks socioeconomic development index, with the highest mortality in low and low-middle socioeconomic development index quintiles.<sup>6</sup>
- The GBD 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020. (Data courtesy of the Global Burden of Disease Study 2020.) In 2020:
  - The prevalence of congenital heart anomalies was 14.78 million (95% UI, 13.35–16.47 million) cases.
  - There were 0.21 million (95% UI, 0.18–0.25 million) deaths estimated for congenital heart anomalies worldwide.
  - Age-standardized mortality rates of congenital heart anomalies were highest in Oceania, North Africa and the Middle East, and the Caribbean. They were lowest in high-income Asia Pacific, Western Europe, and Australasia (Chart 17-6).
  - The age-standardized prevalence of congenital heart anomalies was highest in high-income Asia Pacific, Central Asia, and Western Europe (Chart 17-7).
- In a 2019 systematic review including 103 632 049 live births globally, the mean prevalence of CCDs globally was 8.224 per 1000. Prevalence of CCDs in Africa was estimated at ≈25% of that in other regions, likely attributable to sparse population-level data and low diagnostic access.<sup>118</sup>
- According to a systematic review and meta-analysis of CCD data from China, birth prevalence of CCD has increased from 0.2 per 1000 live births (1980–1984) to 4.9 per 1000 live births (2015–2019), with higher rates among males (4.2 per 1000 versus 3.5 per 1000), individuals living in urban compared with rural areas (2.5 per 1000 versus 4.3 per 1000), and those in higher income brackets (no data from lower-income regions but 4.0 per 1000 in high-income areas versus 1.5 per 1000 in upper-middle income areas),<sup>120</sup> possibly reflecting differences in diagnostic access.
- Birth incidence is increasing in the Kingdom of Bahrain, with 9.45 per 1000 live births in 2016

compared with 6.45 per 1000 live births affected in 2000.<sup>121</sup>

- According to a population-based study from Malaysia, CCDs occurred in 1.26 of every 1000 births (2006–2015) with no significant change in incidence over time.<sup>122</sup>

## 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.<sup>123</sup> The cause of KD is unknown but may be an immune response to an acute infectious illness based in part on genetic susceptibilities.<sup>124,125</sup>

### Prevalence

- KD is the most common cause of acquired HD in children in the United States and other high-income countries.<sup>126</sup>

### 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.<sup>127</sup>
- The incidence was estimated 20.8 per 100 000 US children <5 years of age in 2006.<sup>128</sup> 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.<sup>128</sup>
- Although KD can occur into adolescence (and rarely adulthood), 76.8% of US children with KD are <5 years of age.<sup>128</sup>
- 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).<sup>128</sup>
- 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.<sup>129</sup> 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.<sup>129</sup>

- 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.<sup>128,129</sup>
- KD rarely recurs. Recurrences constitute 2% to 4% of total KD cases in both the United States and Japan,<sup>130</sup> 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).<sup>131,132</sup>

### 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.<sup>128</sup>

### Genetics/Family History

- Approximately 1% of patients with KD 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%.<sup>126</sup>
- 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).<sup>124,133</sup>

### 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).<sup>126</sup> 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.<sup>134</sup>
- 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.<sup>126</sup>

- 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).<sup>135,136</sup>

### 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 patients with KD and is associated with higher risk of coronary arterial dilation, resistance to IVIG treatment, and, rarely, long-term myocardial dysfunction or death.<sup>126,137</sup>
- 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).<sup>126</sup> 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 patients with KD up to 12 weeks from fever onset, including medium (z score ≥5–<10) and giant aneurysms in ≈6% and ≈3% of patients with KD, respectively.<sup>138</sup> Risk factors for coronary artery abnormalities include younger age, male sex, late treatment, and failure to respond to initial IVIG with defervescence.<sup>138–141</sup>
  - In Latin America, children <6 months of age were more likely to have delayed diagnoses and less obvious clinical features and were at greater risk of developing coronary artery aneurysm, even after controlling for day of treatment initiation.<sup>142</sup>
- 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.<sup>143–145</sup> Mortality is related to thrombosis or rupture of rapidly expanding aneurysms or, less commonly, shock or macrophage activation syndrome with multiorgan failure.<sup>126,145,146</sup>
- 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 patients with 1073 KD from 1980 to 2012, coronary artery aneurysms were present in 18.3% beyond 1 month, including 11.6% small, 4.1% medium, and 2.5% 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 of 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.<sup>147</sup> 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.<sup>135,148</sup>

- 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).<sup>149</sup> Significant risk factors included giant 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.<sup>150</sup>
- In 2019, US mortality attributable to KD was 4 patients for underlying mortality and 8 patients for all-cause mortality (unpublished NHLBI tabulation using CDC WONDER<sup>79</sup>).

### Health Care Use

- In 2018, there were 6000 all-listed diagnoses hospital discharges for KD (HCUP;<sup>151</sup> 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 of 2000 to 2014.<sup>145,152,153</sup>
- 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.<sup>154</sup> With the use of 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.<sup>153</sup>

- The incidence of KD is lower in Canada, at 19.6 per 100 000 children <5 years of age for the period of 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.<sup>132,155–159</sup>
- However, the incidence of KD is rising worldwide, with potential contributions from improved recognition, diagnosis of incomplete KD more often, and true increasing incidence.<sup>145,153,156,159</sup>

## Multisystem Inflammatory Syndrome in Children

MIS-C is an emergency clinical syndrome characterized by fever, inflammation, and multiorgan dysfunction that most commonly manifests late in the course of severe acute respiratory syndrome coronavirus 2 infection. We are just beginning to understand MIS-C, which has overlapping signs and symptoms of KD and toxic shock syndrome. The first case reports of MIS-C (which has gone by many names) came from the United States and Europe in April 2020,<sup>160</sup> with dozens of case series now reported from around the world.

- Since May 2020, the CDC has been tracking reports of MIS-C. As of June 28, 2021, 4196 cases and 37 attributable deaths (0.89%) have been reported. Median age of cases was 9 years; 62% of cases have occurred in children who are Hispanic or Latino (1246 cases) or Black (1175 cases); 99% tested positive for severe acute respiratory syndrome coronavirus 2 (reverse transcriptase-polymerase chain reaction, serology, or antigen test); and 60% of reported patients were male.<sup>161</sup>
- A meta-analysis of patient characteristics in MIS-C shows that more males are affected (55.8% [95% CI, 50.3%–61.2%]), most patients (79.1% [95% CI, 70.8–85.5]) require intensive care admission, nearly one-third of patients require mechanical ventilation (29.2% [95% CI, 19.9%–40.5%]), and a small number require extracorporeal membrane oxygenation (7.6% [95% CI, 4.1%–13.8%]).<sup>162</sup>
- Risk of MIS-C may vary with ethnicity, with apparently higher risk among those of African descent.<sup>163,164</sup>
- MIS-C most commonly occurs 4 to 6 weeks after a population peak of severe acute respiratory syndrome coronavirus 2 infection.<sup>165</sup>
- Mortality from MIS-C is low in the largest pooled meta-analysis of cases to date, 11 of 625 cases (3.5%; 95% CI, 2.2%–5.5%).<sup>162</sup>



**Table 17-1. 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 the 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<sup>166</sup> and Parker et al.<sup>10</sup>

**Table 17-2. CCDs in the United States**

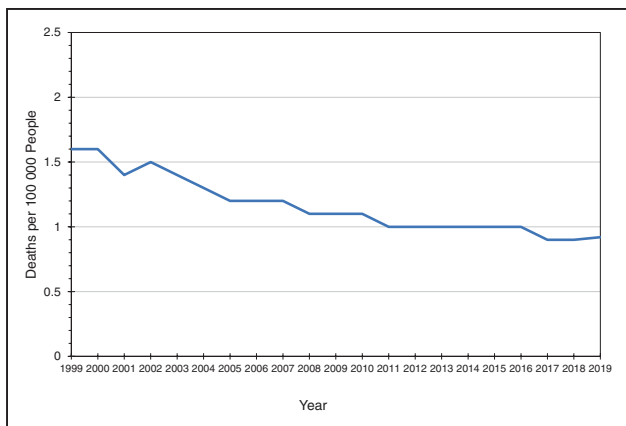
Population group	Estimated prevalence, 2010, all ages	Mortality, 2019, all ages*	Hospital discharges, 2018, all ages
Both sexes	2.4 million	2890	43 000
Males	...	1553 (53.7%)†	
Females	...	1337 (46.3%)†	
NH White males	...	941	...
NH White females	...	816	...
NH Black males	...	274	...
NH Black females	...	237	...
Hispanic males	...	266	...
Hispanic females	...	226	...
NH Asian or Pacific Islander males	...	50	...
NH Asian or Pacific Islander females	...	39	...
NH American Indian or Alaska Native	...	28	...

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.

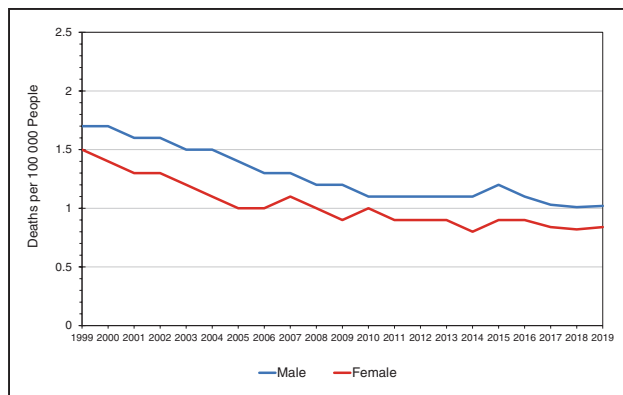
†These percentages represent the portion of total congenital cardiovascular mortality that is for males vs females.

Sources: Prevalence: Gilboa et al.<sup>8</sup> Mortality: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics System.<sup>78</sup> These data represent underlying cause of death only. Hospital discharges: unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2018.<sup>151</sup> Data include those inpatients discharged alive, dead, or status unknown.



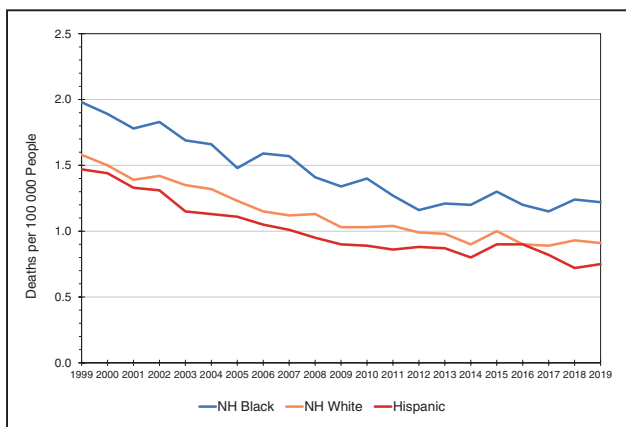
**Chart 17-1. Trends in age-adjusted death rates attributable to CCDs, United States, 1999 to 2019.**

CCD indicates congenital cardiovascular defect. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>79</sup>



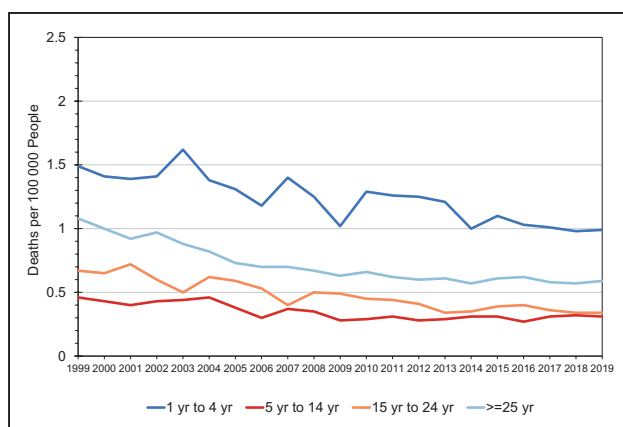
**Chart 17-3. Trends in age-adjusted death rates attributable to CCDs, by sex, United States, 1999 to 2019.**

CCD indicates congenital cardiovascular defect. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>79</sup>



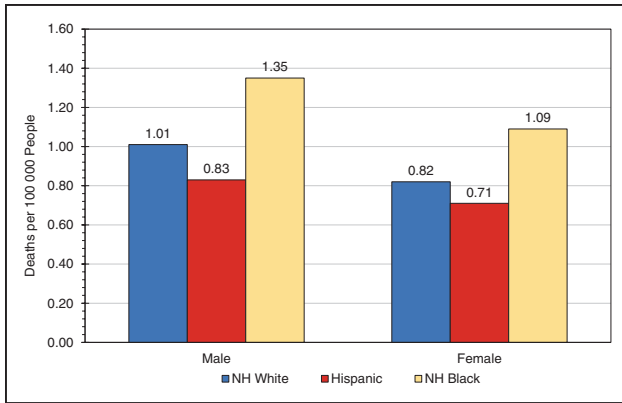
**Chart 17-2. Trends in age-adjusted death rates attributable to CCDs, by race and ethnicity, United States, 1999 to 2019.**

CCD indicates congenital cardiovascular defect; and NH, 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.<sup>79</sup>



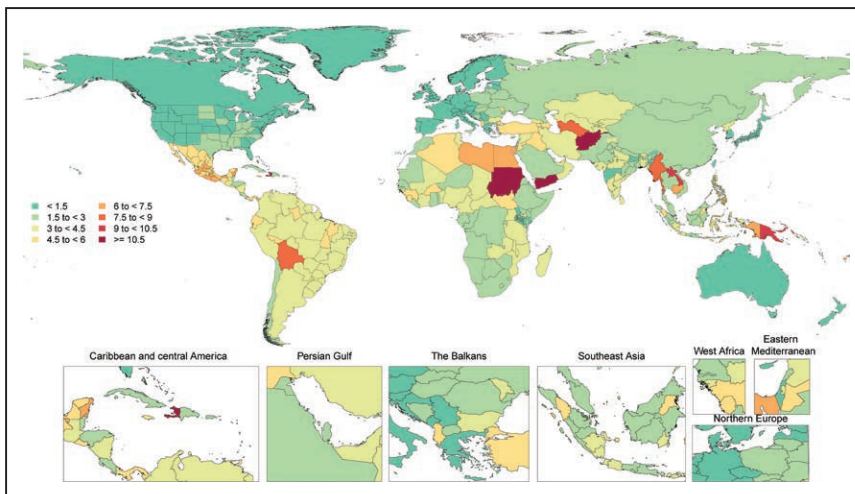
**Chart 17-4. Trends in age-specific death rates attributable to CCDs, by age at death, United States, 1999 to 2019.**

CCD indicates congenital cardiovascular defect. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>79</sup>



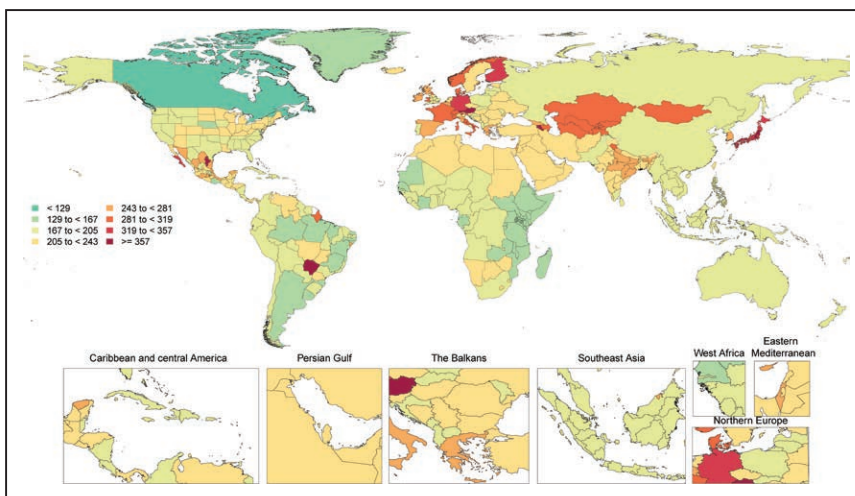
**Chart 17-5. Age-adjusted death rates attributable to CCDs, by sex, race, and ethnicity, United States, 2019.**

CCD indicates congenital cardiovascular defect; and NH, 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.<sup>79</sup>



**Chart 17-6. Age-standardized global mortality rates of congenital heart anomalies per 100 000, both sexes, 2020.**

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>167</sup>



**Chart 17-7. Age-standardized global prevalence rates of congenital heart anomalies per 100 000, both sexes, 2020.**

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021, University of Washington. More information is available on the Global Burden of Disease Study website.<sup>167</sup>

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## 18. DISORDERS OF HEART RHYTHM

See Table 18-1 and Charts 18-1 through 18-9

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### Arrhythmias (Disorders of Heart Rhythm)

2019: Mortality—54 104. Any-mention mortality—564 455.

#### Bradyarrhythmias

**ICD-9 426.0, 426.1, 427.81; ICD-10 I44.0 to I44.3, I49.5.**

2019: Mortality—1385. Any-mention mortality—7706.

2018: Hospital discharges—102 000.

2016: Mean hospital charges—\$74 846; in-hospital death rate—1.15%; mean length of stay—3.9 days.

### Disorders of Atrioventricular Conduction

#### Prevalence and Incidence

##### Prolonged PR Interval

- In a sample of healthy participants from the ARIC study (mean, 53 years of age), the prevalence of prolonged PR interval (first-degree atrioventricular block) was 7.8% in Black males, 3.0% in Black females, 2.1% in White males, and 1.3% in White females.<sup>1</sup> Lower prevalence estimates was 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.<sup>2</sup>
- 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.<sup>3–5</sup>

##### Second-Degree Atrioventricular Block

- 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 ( $\approx 0.003\%$ ), whereas Mobitz I (Wenckebach) is observed in 1% to 2% of healthy individuals <20 years of age, especially during sleep.<sup>6</sup>

##### Third-Degree or Complete Heart Block

- The prevalence of complete (third-degree) atrioventricular block in the general adult population is low. The prevalence was 0.04% in the Icelandic Reykjavik Study<sup>7</sup> and 0.6% in a large sample of people with hypertension and without diabetes enrolled with Veterans Health Administration hospitals.<sup>8</sup>
- 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  $\geq 80$  years of age.<sup>9</sup>
- 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 atrioventricular block) was 1.2% (1486 of all tracings).<sup>10</sup>
- An English registry study estimated the incidence of infant complete atrioventricular block as 2.1 per 100 000 live births.<sup>11</sup>

##### Risk Factors

- In healthy individuals from MESA without CVD or its risk factors, the PR interval was longer with advancing age, in males compared with females, and in Black compared with White individuals.<sup>12</sup>
- Although a prolonged PR interval and Mobitz type I second-degree atrioventricular block can occur in apparently healthy people, especially during sleep, presence of Mobitz II second- or third-degree atrioventricular block usually indicates underlying HD, including CHD, and HF.<sup>6</sup>
- 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.<sup>13</sup>
- Long sinus pauses and atrioventricular block can occur during sleep apnea. These abnormalities may be reversible with treatment of sleep apnea.<sup>13,14</sup>

##### 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.<sup>13</sup>

##### Complications

###### (See Chart 18-1)

- In the FHS, PR-interval prolongation ( $>200$  milliseconds) was associated with increased risk of AF (HR,

The 2022 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 2022. 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.

- 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]).<sup>15</sup> Compared with people with a PR interval  $\leq 200$  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 18-1).
- 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]).<sup>16</sup>

## Sinus Node Dysfunction

### Prevalence and Incidence

- There are no accurate estimates of the prevalence of SND in the general population.
- According to a survey of members of the North American Society of Pacing and Electrophysiology, SND accounted for 48% of implantations of first permanent pacemakers in the United States in 1997.<sup>17,18</sup>
- SND may coexist with other causes of bradyarrhythmias (carotid sinus hypersensitivity in 42% of patients and advanced atrioventricular conduction abnormalities in 17%).<sup>19,20</sup>
- The incidence rate of SND was 0.8 per 1000 person-years of follow-up in 2 US cohorts that included White and Black participants, ARIC and the CHS.<sup>21</sup> 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 SND per year would rise from 78 000 in 2012 to 172 000 in 2060.<sup>21</sup>

### Risk Factors

- The causes of SND 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).<sup>22</sup>
- Idiopathic degenerative disease is probably the most common cause of SND.<sup>23</sup>
- In 28 different studies on atrial pacing for SND, the median annual incidence of second- and third-degree atrioventricular block was 0.6% (range, 0%–4.5%) and the 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.<sup>24</sup>

- In the CHS and ARIC studies, factors associated with incident SND included White (versus Black<sup>24</sup>) 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, NT-proBNP, cystatin C, and history of a major cardiovascular event.<sup>21</sup>

### Family History and Genetics

- Bradycardia and atrioventricular block have a heritable component. Monogenic cardiomyopathies are associated with bradycardia. For example, *LMNA* cardiomyopathy is associated with atrioventricular block. Rare coding variants in genes affecting ion channels (eg, *HCN4*,<sup>25</sup> *SCN5A*,<sup>26</sup> *RYR2*,<sup>27</sup> *KCNJ3*,<sup>28</sup> and *KCNJ5*<sup>29</sup>) and variants in *ANKK2*<sup>30</sup> and *TRPM4*<sup>31</sup> have been associated with SND in families and sporadic cases with severe forms of disease. In a genome sequencing study of 792 Icelandic individuals with sick sinus syndrome, a missense variant in *MYH6* was found to be associated with SND (OR, 12.5 [95% CI, 8.1–19.4];  $P=1.5 \times 10^{-29}$ ).<sup>32</sup>

### Complications

#### (See Chart 18-2)

- The survival of patients with SND 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.<sup>33–35</sup>
- A randomized clinical trial of patients with SND requiring pacemakers demonstrated a significant reduction in the incidence of AF (HR, 0.79 [95% CI, 0.66–0.94]) and HF symptoms and improved quality of life with dual-chamber pacing compared with ventricular pacing ( $P<0.05$ ), although stroke-free survival was not affected (HR, 0.82 [95% CI, 0.54–1.25]).<sup>34</sup>
- In patients requiring pacemakers for either SND or atrioventricular conduction block, atrial or dual-chamber pacemakers are associated with significantly decreased development of chronic AF compared with ventricular demand pacemakers.<sup>36</sup> In this randomized trial, atrial or dual-chamber pacing reduced the development of AF from 3.84%/y with ventricular demand pacing to 2.8%/y ( $P=0.016$ ).
- In 19893 males and females  $> 45$  years of age from the ARIC and CHS cohorts, incident SND 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]).<sup>37</sup>

- A nationwide study in France demonstrated a higher incidence of stroke in patients with SND compared with a control population of patients with other cardiac conditions (HR, 1.27 [95% CI, 1.19–1.35]) but a lower incidence compared with patients with AF (HR, 0.77 [95% CI, 0.73–0.82]).<sup>38</sup>
- 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 survival rates similar to those of age- and sex-matched control subjects.<sup>39</sup>
- SVT, including AF, was prevalent in 53% of patients with SND.<sup>34</sup>
- 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).<sup>40</sup>
- On the basis of NHDS data, the escalating implantation rate was attributable to increasing implantation for isolated SND, which increased by 102%, whereas implantation for all other indications did not increase (Chart 18-2).<sup>41</sup>

## SVT (Excluding AF and Atrial Flutter)

### ICD-9 427.0; ICD-10 I47.1.

2019: Mortality—179. Any-mention mortality—1790.  
2018: Hospital discharges—41 000.

### Prevalence, Incidence, and Risk Factors

#### (See Chart 18-3)

- Data from the Marshfield Epidemiological 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  $\geq 65$  years (versus  $< 65$  years of age: RR, 5.3) were significant risk factors (Chart 18-3).<sup>42</sup>
- 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  $\approx 50$  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.<sup>43</sup> Rates were higher in individuals  $\geq 65$  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  $\geq 8$  beats) was 31%.<sup>44</sup>
- 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.<sup>45</sup>
- 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, 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.<sup>46</sup>

### Family History and Genetics

- Although general SVT does not appear to have a strong heritable component, atrioventricular nodal reentry tachycardia has shown familial clustering.<sup>47</sup> A study of candidate gene sequencing in 298 patients with atrioventricular nodal reentry tachycardia and 10 family members with atrioventricular nodal reentry tachycardia identified 229 coding variants, of which 65 were novel, with a large proportion of variants in the *HCN1* through *HCN4* genes.<sup>48</sup>

### Complications

- 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.<sup>49</sup>
- 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 (LBW, preterm labor, fetal stress, and obvious fetal abnormalities).<sup>50</sup>
- Rare cases of incessant SVT can lead to a tachycardia-induced cardiomyopathy,<sup>51</sup> and rare cases of sudden death attributed to SVT as a trigger have been described.<sup>52</sup>
  - In a Swedish study of 214 patients (51% females) with paroxysmal SVT undergoing ablation, females had a longer history of symptomatic arrhythmia ( $16.2 \pm 14.6$  years versus  $9.9 \pm 13.1$  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.<sup>53</sup>

### Types of SVT

- Among adults presenting for invasive electrophysiological study and ablation (a sample likely biased toward individuals with more frequent episodes and greater symptom severity), atrioventricular nodal reentrant tachycardia is the most common mechanism of SVT<sup>54,55</sup> and usually represents the majority of cases (56% in a series of 1754 cases).<sup>55</sup>
- The second most common type of SVT is atrioventricular reentrant tachycardia, a macroreentrant circuit that requires the presence of an extranodal connection or bypass tract between the atria and ventricles or specialized conduction tissue. In a series of 1754 patients with SVT undergoing catheter ablation,<sup>55</sup> atrioventricular reentrant tachycardia accounted for 27% of SVTs, and atrial tachycardia was the third most common (accounting for 17% of SVTs).
- In children, according to a US-based national pediatric electrophysiology registry study, atrioventricular reentrant tachycardia was the most common SVT mechanism (68%), and the remainder of the patients had atrioventricular nodal reentrant tachycardia (32%).<sup>56</sup>
- In 1754 patients undergoing catheter ablation of paroxysmal SVT, age was strongly associated with mechanism, with atrioventricular reentrant tachycardia accounting for more cases in younger ages (>60% of all cases in those 5–10 years of age to <10% in patients >80 years of age), and atrioventricular nodal reentrant tachycardia and atrial tachycardia prevalences being the predominant mechanism in older individuals (60% and 30%, respectively, among patients >80 years of age).<sup>55</sup>
- 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 a series of 1754 undergoing catheter ablation.<sup>55</sup>

- Multifocal atrial tachycardia is an arrhythmia that may be confused with AF and is characterized by  $\geq 3$  distinct P-wave morphologies, irregular R-R intervals, and a rate >100 bpm. It usually occurs as a complication of acute severe illness such as sepsis or acute pulmonary conditions. It is uncommon in both children<sup>57</sup> and adults,<sup>58</sup> with a prevalence in hospitalized adults estimated at 0.05% to 0.32%.<sup>58</sup> 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).<sup>58</sup> In a study of older ambulatory adults in Greece, the mortality in follow-up did not differ by the presence of multifocal atrial rhythms on baseline ECG.<sup>59</sup>

### WPW Syndrome

#### Prevalence

- WPW syndrome refers to the presence of ventricular preexcitation on the ECG combined with related arrhythmia (SVT). A WPW electrocardiographic pattern (ventricular preexcitation) 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.<sup>60</sup> In an electrocardiographic study of 32 837 Japanese students, ventricular preexcitation was reported in 0.07%, 0.07%, and 0.17% of elementary, junior high, and high school students, respectively.<sup>61</sup>

#### Complications

- WPW syndrome 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.<sup>62</sup>
- A cohort study from Intermountain Healthcare with  $\approx 8$  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.<sup>63</sup>
- Asymptomatic adults with ventricular preexcitation appear to be at no increased risk of sudden death compared with the general population.<sup>64,65</sup> Although there are rare exceptions, the majority of patients who experience cardiac arrest in association with WPW have had symptomatic SVT.
- 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.<sup>66</sup>

- In a meta-analysis of 20 studies involving 1869 asymptomatic patients with a WPW electrocardiographic pattern followed up for 11722 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. Risk factors for sudden death included male sex and age <18 years.<sup>67</sup>
- Several studies in asymptomatic children with ventricular preexcitation detected by screening suggest a benign prognosis.<sup>65,68</sup> 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.<sup>69</sup> 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.<sup>70</sup>
- A multicenter international survey of 1589 subjects  $\geq 21$  years of age (mean, 13 years of age) with preexcitation identified 15% with nonpersistent (intermittent) preexcitation.<sup>71</sup> Two percent of the study population experienced SCA. Patients with nonpersistent preexcitation were significantly less likely to exhibit high-risk conduction properties of the accessory pathway at electrophysiologic study. A total of 29 patients (2%) experienced SCA, and 3 of these individuals had nonpersistent preexcitation. Thus, 1.2% of 244 pediatric patients with nonpersistent preexcitation experienced SCA.

## AF and Atrial Flutter

### ICD-9 427.3; ICD-10 I48.

2019: Mortality—26535. Any-mention mortality—183321.  
2018: Hospital discharges—472000.

#### Prevalence

- The prevalence of AF in the United States is estimated to increase from  $\approx 5.2$  million in 2010 to 12.1 million in 2030.<sup>72</sup>
- 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 is projected to increase to 17.9 million (95% CI, 13.6–23.7 million) in 2060.<sup>73</sup>
- Among Medicare patients  $\geq 65$  years of age who were diagnosed from 1993 to 2007, the prevalence

of AF increased  $\approx 5\%/y$ , from 41.1 per 1000 beneficiaries to 85.5 per 1000 beneficiaries.<sup>74</sup>

- In 2007, in the 5% Medicare sample, there were 105701 older adults with AF: 93.8% were White, 3.7% were Black, and 2.6% were other/unknown race.<sup>74</sup>
- 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.<sup>74</sup>
- 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.<sup>75</sup>
- In an analysis involving the entire South Korean population, the prevalence of AF more than doubled from 0.73% in 2006 to 1.53% in 2015 and is estimated to reach 5.81% in 2060.<sup>76</sup>

#### Incidence

- 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 ( $P=0.02$ ).<sup>74</sup>
- 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.<sup>72</sup>
- 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.<sup>76</sup>

#### Racial Variation

##### (See Chart 18-4)

- 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.<sup>77</sup>
- 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 18-4).<sup>78</sup> 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.<sup>79</sup>

- Racial variation in AF incidence is also observed in other countries. For instance, in a study of the UK Clinical Practice Research Datalink cohort  $\geq 45$  years of age, 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.<sup>80</sup>

### Lifetime Risk and Cumulative Risk

#### (See Chart 18-5)

- 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%).<sup>81</sup>
- 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.<sup>82</sup> 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.<sup>83</sup>
- In studies from the FHS and the BiomarCaRE Consortium, the lifetime risk for AF in individuals of European ancestry was estimated to be  $\approx 1$  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.<sup>84</sup>
  - 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.<sup>85</sup> In a subsequent study from the FHS, the lifetime risk of AF varied by risk factor burden. In individuals with optimal cardiovascular 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%) in those with a borderline risk profile and 38.4% (95% CI, 35.5%–41.4%) in individuals with an elevated risk profile (Chart 18-5).<sup>86</sup>

### 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 (prevalence: from 2% to 10% in men, from 1% to 5% in women; incidence: from 4 to 13 per 1000 person-years in men, from 3 to 9 per 1000

person-years in women). However, when only AF that was ascertained on ECGs routinely collected in the FHS was considered, the prevalence (from 1.3% to 2.6% in males and from 0.8% to 1.2% in females), but not the incidence (remaining at  $\approx 2$  per 1000 person-years in males and females), 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.<sup>87</sup>

- Between 2000 and 2010 in Olmsted County, Minnesota, age- and sex-adjusted incidence rates and survival did not change over time.<sup>88</sup> However, over a similar time frame in the United Kingdom (2001–2013), the incidence of nonvalvular AF in people  $\geq 45$  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.<sup>80</sup>
- Between 1999 and 2013, among Medicare fee-for-service beneficiaries, rates of hospitalization for AF increased  $\approx 1\%/y$ . 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.
- 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.<sup>76</sup>
- COVID-19–related lockdowns have led to reductions of newly diagnosed AF. A nationwide study in Denmark reported a 47% reduction in the total number of AF diagnoses during the period of March 12 to April 1, 2020, compared with the same period in 2019 (562 versus 1053).<sup>89</sup>

### Risk Factors

#### (See Chart 18-6)

- The highest PAF for AF was for hypertension followed by BMI, smoking, cardiac disease, and diabetes in ARIC (Chart 18-6).

### BP and Hypertension

- Hypertension accounted for  $\approx 22\%$  of AF cases.<sup>90</sup>
- In MESA, the PAF of AF attributable to hypertension appeared to be higher in US Chinese (46.3%),

Hispanic (43.9%), and NH Black (33.1%) participants than in NH White participants (22.2%).<sup>77</sup>

- 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-mmHg increase in SBP and DBP was associated with a 4.3% and 4.6%, respectively, increased risk of incident AF.<sup>91</sup>

### 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.<sup>92</sup>
- Another meta-analysis of 29 studies examined various anthropometric components in relation to incident AF. A 5-kg/m<sup>2</sup> 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<sup>2</sup> was still associated with excess risk compared with a BMI of 20 kg/m<sup>2</sup>. WC, waist-hip ratio, fat mass, and weight gain also were associated with increased risk of AF.<sup>93</sup>
- 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]).<sup>94</sup>
- 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.<sup>95</sup>

### 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), of former smoking was 1.09 (95% CI, 1.00–1.18), and of 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).<sup>96</sup>

### Diabetes and HbA1c

- In a meta-analysis restricted to prospective studies, HbA1c 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]).<sup>97</sup>

- 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]).<sup>98</sup>
- 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]).<sup>99</sup>

### 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.<sup>100</sup> 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.<sup>101</sup>

### HD as a Risk Factor

- In the CHARGE-AF consortium, pooling data from the 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).<sup>102</sup>
- Among participants in the FHS, type of HF (HF<sub>r</sub>EF or HF<sub>p</sub>EF) 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 HF<sub>p</sub>EF (HR, 2.34 [95% CI, 1.48–3.70]) than with HF<sub>r</sub>EF (HR, 1.32 [95% CI, 0.83–2.10]).<sup>103</sup>
- 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.<sup>104</sup> 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,<sup>105</sup> CKD,<sup>106</sup> and moderate or heavy alcohol consumption.<sup>107</sup>
- Sleep disorders:
  - 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];  $P<0.001$ ).<sup>108</sup>
  - A systematic review reported an increased risk of AF with long sleep duration ( $\geq 8$  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]).<sup>109</sup>
  - 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]).<sup>110</sup>
- Air pollution:
  - A systematic review and meta-analysis of 18 published studies reported short-term and long-term associations of air pollution with AF.<sup>111</sup> For 10- $\mu\text{g}/\text{m}^3$  increases in PM<sub>2.5</sub> and PM<sub>10</sub> (particles with aerodynamic diameter  $< 10 \mu\text{m}$ ) concentrations, the OR of AF was 1.01 (95% CI, 1.00–1.02) and 1.03 (95% CI, 1.01–1.05), respectively. The corresponding ORs for long-term exposure were 1.07 (95% CI, 1.04–1.10) for PM<sub>2.5</sub> and 1.03 (95% CI, 1.03–1.04) for PM<sub>10</sub>. SO<sub>2</sub> and NO<sub>2</sub> also were associated with AF in the short term: ORs for 10-ppb increments were 1.05 (95% CI, 1.01–1.09) and 1.03 (95% CI, 1.01–1.04), respectively.
- Psychosocial factors:
  - Among close to 1 million individuals seeking care through the Veterans Health Administration between 2001 and 2014, a diagnosis of post-traumatic stress disorder was associated with a 13% increased risk of AF after adjustment for confounders (HR, 1.13 [95% CI, 1.02–1.24]).<sup>112</sup>
  - 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  $\geq 16$  in the Center for Epidemiological Studies Depression Scale were compared with those with a score  $< 2$ . Anger, anxiety, and chronic stress were not associated with AF risk.<sup>113</sup>
  - 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.<sup>114</sup>
  - 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) for those with job strain compared with those without job strain.<sup>115</sup>

- 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.<sup>116</sup>
  - Among 11 239 patients undergoing isolated CABG at 5 sites in the United States between 2002 and 2010, the risk-adjusted incidence of AF was 33.1%, which has not varied over time.<sup>117</sup>
  - A meta-analysis reported that new-onset AF has been observed in 10.9% of patients undergoing noncardiac general surgery.<sup>118</sup>
  - 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.<sup>119</sup> AF occurring in the context of sepsis is associated with an increased risk of stroke and death.<sup>120</sup>
  - AF is a common occurrence in hospitalized patients with COVID-19. A meta-analysis of 14 studies reported an incidence AF/atrial flutter/atrial tachycardia among these patients of 8.2% (95% CI, 5.5%–11.3%).<sup>121</sup>
- Reports suggest that cancer and cancer medications are associated with increased risk of AF (eg, ibrutinib; RR for AF, 4.69).<sup>122</sup> A meta-analysis of published studies evaluating the association between new-onset AF and risk of cancer reported a pooled RR of 1.24 (95% CI, 1.10–1.39).<sup>123</sup> The association was restricted to the first 90 days after AF diagnosis (RR, 3.44 [95% CI, 2.29–5.57]), with no association after that time.

### Social Determinants of AF

- 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.<sup>124</sup>

### 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]).<sup>125</sup>
  - 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]).<sup>126</sup>
- In 2363 participants of the ARIC study who underwent continuous electrocardiographic monitoring for 14 days, Life's Simple 7 score was associated with reduced risk of continuous AF (HR, 0.87 [95% CI, 0.79–0.95] per 1-point increase in Life's Simple 7 score) but not with risk of intermittent AF (HR, 0.92 [95% CI, 0.83–1.02]).<sup>127</sup>
  - 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 and ethnicity.<sup>128</sup>
  - ARIC,<sup>129</sup> the FHS,<sup>130</sup> and the WHS<sup>131</sup> have developed risk prediction models in individual cohorts 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 pooled individual-level data from these 3 cohorts as part of the CHARGE-AF consortium and developed and validated a risk prediction model for AF in White and Black participants, which was replicated in 2 European cohorts.<sup>102</sup> This CHARGE-AF model has been validated in a US multiethnic patient cohort,<sup>132</sup> in MESA,<sup>133</sup> in a UK cohort (EPIC Norfolk),<sup>134</sup> in a post-CABG cohort,<sup>135</sup> and in a large nationwide primary care database in the Netherlands.<sup>136</sup>
  - A study evaluating electronic health records from 2252219 individuals cared for in a hospital system in Colorado used machine-learning models to predict 6-month incident AF.<sup>137</sup> The resulting model had a similar C statistic (0.800) compared with a model using basic regression and established clinical risk factors for AF (C statistic, 0.794).

### 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.<sup>90</sup>

### 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 ( $\geq 5$  minutes: RR, 3.86;  $<1$  minute: RR, 1.77).<sup>138</sup>
- Another meta-analysis reported that high-atrial-rate episodes detected by cardiac implantable electronic devices were associated with a 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 17247 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.<sup>139</sup>
- 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.<sup>140</sup>

### Community Screening for Undiagnosed AF

- 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.<sup>141</sup> 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.<sup>141</sup>
- The prevalence of undiagnosed AF in the community is unknown. Using Medicare and commercial claims data, investigators have estimated that in 2009,  $\approx 0.7$  million (13.1%) of the  $\approx 5.3$  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) were in individuals  $\geq 65$  years of age and 163 500 (95% CI, 17 700–400 000) were in individuals 18 to 64 years of age.<sup>142</sup>
- A multicenter, open-label, randomized trial evaluated a 2-week continuous electrocardiographic patch and an automated home BP machine with

oscillometric AF screening capability for the detection of AF compared with usual care over a 6-month period in participants  $\geq 75$  years of age with hypertension.<sup>143</sup> AF detection was 5.3% in the screening group compared with 0.5% in the control group (risk difference, 4.8% [95% CI, 2.6%–7.0%]; number needed to screen, 21). By 6 months, anticoagulation was more frequently prescribed in the intervention group (4.1% versus 0.9%; risk difference, 3.2% [95% CI, 1.1%–5.3%]).

- Systematic reviews of screening:
  - 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 and usual care, and none examined health outcomes.<sup>144</sup>
  - 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  $\geq 65$  years of age and 0.41% in individuals  $< 65$  years of age. The study included low-income 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  $\geq 65$  years of age, 926 for 60 to 64 years of age, and 1089 for  $< 60$  years of age.<sup>145</sup>
  - 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.<sup>146</sup>
- Wearable, commercially available technology<sup>147</sup>:
  - 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%.<sup>148</sup>
  - 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.<sup>141</sup> To date, no studies have demonstrated that AF screening reduces mortality or incidence of thromboembolic complications. In addition, the minimum duration of AF episodes required to increase risk for stroke is unknown. However, longer episode duration is associated with increased thromboembolic risk; the threshold varies depending on the presence of other stroke risk factors.<sup>149</sup>

### Family History and Genetics

- AF is found to be a common presentation in certain monogenic genetic cardiomyopathies, for examples, in individuals with *PRKAG2*- or *TTN*-related cardiomyopathy.<sup>150,151</sup> 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 first-degree relative was  $\leq 65$  years of age at the onset (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]).<sup>152</sup>
- 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.<sup>153</sup>
- 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.<sup>154</sup>
- Racial variation in AF incidence is complex and not fully understood. One study of Black and White individuals from the CHS and ARIC suggested that genetic markers of European ancestry were associated with an increased risk of incident AF.<sup>155</sup>
- 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.<sup>156</sup> 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.<sup>157</sup>

- Whole-exome/genome sequencing studies have identified rare mutations in additional genes associated with AF, including *MYL4*,<sup>158</sup> and loss-of-function mutations in *SCN4B* and *KCNA5*, a conserved gene that encodes the voltage-gated Kv1.5 potassium channel.<sup>159,160</sup> Loss-of-function variants in the titin gene have been associated with early-onset AF.<sup>161,162</sup>
- 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 from thousands of variants associated with AF in the UK Biobank). 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%).<sup>85</sup>
- It is unclear whether genetic markers of AF could improve risk prediction for AF over models that include only clinical factors.<sup>131</sup> A study of 229 incident AF cases and >10 000 controls found that the net classification index for an AF GRS for incident AF was 10.0% (95% CI, 4.2%–15.7%), with slightly higher classification ability in early-onset AF cases (net reclassification index, 14.8% [95% CI, 3.8%–25.7%]).<sup>163</sup> In contrast, 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).<sup>164</sup>
- GRS also could identify patients at higher risk of cardioembolic stroke<sup>165</sup>; 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<sup>166</sup> and after CABG.<sup>167</sup>
- GWASs also have been conducted with variation in electrocardiographic traits used as a phenotype (ie, 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.<sup>168</sup> A GWAS meta-analysis of PR interval in 293 051 multiancestry individuals found 202 genomic loci associated with PR interval, with enrichment of cardiac muscle development/contractile and cytoskeletal genes.<sup>169</sup> A GRS of PR interval-associated

variants was found to be associated with higher risk of atrioventricular block (OR per SE of GRS, 1.11;  $P=7\times 10^{-8}$ ) and pacemaker implantation (OR, 1.06;  $P=1.5\times 10^{-4}$ ) and reduced risk of AF (OR, 0.95;  $P=4.3\times 10^{-8}$ ).

- In a study of 19 709 participants from ARIC, MESA, and the CHS, mitochondrial DNA copy number, a marker of mitochondrial dysfunction, was associated with incident AF, with participants with the lowest quintile of mitochondrial DNA copy number having an overall 13% increased risk (95% CI, 1%–27%) of AF compared with the those in the highest quintile in adjusted models.<sup>170</sup>

### 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.<sup>171</sup>

#### 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];  $P<0.001$ ).<sup>172</sup>
  - Overweight and obese individuals with symptomatic AF who opted to participate in weight loss and aggressive risk factor management interventions ( $n=208$ ; mean follow-up, 47 months) had fewer hospitalizations (0.7 versus 1.1), cardioversions (0.9 versus 1.5), and ablation procedures (0.6 versus 0.7) than their counterparts who declined enrollment ( $n=147$ ; mean follow-up, 49 months). The risk factor management group was associated with a predicted 10-year cost savings of \$12 094 per patient.<sup>173</sup>
  - 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 with at least a 10% weight loss reported fewer symptoms.<sup>174</sup>
  - 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 ( $\geq 2$  METs gained; 89% AF free).<sup>175</sup>
- Treatment of OSA has been noted to decrease risk of progression to permanent AF.<sup>176</sup> In a meta-analysis, CPAP was reported to be associated with a reduced risk of recurrent AF after ablation (pooled RR, 0.56 [95% CI, 0.47–0.68]).<sup>177</sup> 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.<sup>178</sup>
  - 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: 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.<sup>179</sup>

### Prevention: Randomized Data

#### Primary Prevention of AF: Randomized Data

- Intensive glycemic control was not found to prevent incident AF in the ACCORD study ( $P=0.52$ ).<sup>180</sup>
- 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.<sup>181</sup>
- 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.<sup>182</sup> However, the studies were primarily secondary or post hoc analyses, the intervention duration was modest, and the results were fairly heterogeneous.
- Among 8022 participants of SPRINT, intensive BP lowering (target SBP  $< 120$  mmHg) compared with standard BP lowering (target SBP  $< 140$  mmHg) was associated with a reduced incidence of AF (HR, 0.74 [95% CI, 0.56–0.98]).<sup>183</sup>
- 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 ( $n=65$ ).<sup>184</sup>

- 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]).<sup>185</sup>
- 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.<sup>186</sup>

#### 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.<sup>187</sup>
- An Australian multisite, open-label, controlled trial randomized 140 adults with a history of AF in sinus rhythm at baseline who consumed  $\geq 10$  drinks of alcohol per week either to abstain from alcohol or to continue their usual alcohol consumption.<sup>188</sup> 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% versus 1.2%;  $P=0.01$ ).

#### Awareness

- In REGARDS, a biracial US national 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.<sup>189</sup> 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.<sup>190</sup>
- 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 PR, 0.96 [95% CI, 0.94–0.98]).<sup>191</sup>

#### 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.<sup>192</sup>

- 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.<sup>193</sup>
- In the NCDR PINNACLE registry of outpatients with AF:
  - Fewer than half of high-risk patients, defined as those with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 4$ , received an oral anticoagulant prescription.<sup>194</sup>
  - Between 2008 and 2014, in individuals with a CHA<sub>2</sub>DS<sub>2</sub>-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.<sup>195</sup>
  - In the PINNACLE registry, females were significantly less likely to receive oral anticoagulant drugs at all levels of CHA<sub>2</sub>DS<sub>2</sub>-VASc scores (56.7% versus 61.3%;  $P < 0.001$ ).<sup>196</sup>
  - The PINNACLE registry investigators also reported that receipt of warfarin versus a direct oral anticoagulant varied significantly by type of insurance, with military-, private-, and Medicare-insured patients more likely to receive newer anticoagulants than individuals with Medicaid and other insurance.<sup>197</sup>
- 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).<sup>198</sup>

### 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 direct oral anticoagulants 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 direct oral anticoagulant use for AF between groups of White and Hispanic individuals. However, Black and Hispanic individuals were more likely than their White counterparts to receive inappropriate doses of direct oral anticoagulants.<sup>199</sup>

### Role of Coordinated Care

- A systematic review and meta-analysis identified 3 studies of coordinated systems of care that included 1383 patients.<sup>200</sup> 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 2019, AF was the underlying cause of death in 26 535 people and was listed on 183 321 US death certificates (any-mention mortality; unpublished NHLBI tabulation using NVSS<sup>201</sup> and CDC WONDER<sup>202</sup>).

- The age-adjusted mortality rate attributable to AF was 6.5 per 100 000 people in 2019 (unpublished NHLBI tabulation using CDC WONDER<sup>202</sup>).
- 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]).<sup>203</sup> 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]).<sup>204</sup>
- 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).<sup>88</sup>
- The association of AF with mortality has remained stable over time. In the FHS, the HR for the

association of AF with all-cause mortality was 1.9 (95% CI, 1.7–2.2) between 1972 and 1985, 1.4 (95% CI, 1.3–1.6) between 1986 and 2000, and 1.7 (95% CI, 1.5–2.0) between 2001 and 2015 ( $P$  for trend=0.70).<sup>205</sup>

- 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.<sup>206</sup>
- AF is also associated with increased mortality in subgroups of individuals, including the following:
  - Individuals with other cardiovascular conditions and procedures, including HCM,<sup>207</sup> MI,<sup>208</sup> pre-CABG,<sup>209</sup> post-CABG<sup>208,210,211</sup> (both short term<sup>210</sup> and long term<sup>210,211</sup>), post-transcatheter aortic valve implantation,<sup>212</sup> PAD,<sup>213</sup> and stroke.<sup>214</sup>
  - Individuals with AF have increased mortality with concomitant HF,<sup>215</sup> including HFpEF<sup>216</sup> and HFrEF.<sup>216</sup> 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 that with prevalent AF (RR, 1.19 [95% CI, 1.03–1.38];  $P$  for interaction<0.001).<sup>217</sup>
  - AF is also associated with an increased risk of death in individuals with other conditions, including patients with diabetes,<sup>180,218</sup> those with sepsis,<sup>120</sup> critically ill patients in the ICU,<sup>219</sup> patients after primary PCI,<sup>220</sup> and individuals ≥80 years of age with hypertension.<sup>221</sup>
- 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.<sup>222</sup> 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) in Black participants, which was higher than the 55.9 (95% CI, 48.1–63.7) rate difference in mortality observed for White participants.<sup>223</sup>
- In a US-based study, there was substantial variation in mortality with AF in US counties from 1980 to 2014.<sup>224</sup> 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.<sup>224</sup>

- In a study using the NIS for the period of 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.<sup>225</sup>
- 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]).<sup>226</sup>
- AF has been associated with increased mortality in patients with COVID-19. A meta-analysis of studies published in 2020 including 23 studies and 108 745 patients with COVID-19 showed that AF was associated with increased mortality (pooled effect size, 1.14 [95% CI, 1.03–1.26]).<sup>227</sup>
- 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]).<sup>228</sup> 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.<sup>229</sup>

### Complications

#### (See Table 18-1)

- 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 18-1).

### Extracranial Systemic Embolic Events

- Among 14 941 participants in the ARIC study, incident AF was associated with an increased risk of extracranial systemic embolic events (HR, 3.58 [95% CI, 2.57–5.00]) after adjustment for covariates.<sup>230</sup> This association was stronger in females (HR, 5.26 [95% CI, 3.28–8.44]) than in males (HR, 2.68 [95% CI, 1.66–4.32]).
- In pooled data from 4 large, contemporary, randomized anticoagulation trials with 221 systemic embolic events 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 a mean age and CHADS<sub>2</sub> score similar to those of individuals 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.<sup>231</sup>

### Stroke

- A systematic review of prospective studies found wide variability in stroke risk between studies and between patients with AF, ranging from 0.5%/y to 9.30%/y.<sup>232</sup>
- 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 ( $\approx$ 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  $\approx$ 1.5% of strokes in individuals 50 to 59 years of age and  $\approx$ 23.5% in those 80 to 89 years of age.<sup>233</sup>
- 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.<sup>222</sup> The increased risk persisted in analyses adjusted for anticoagulant therapy status.<sup>222</sup> Additional analyses from the Medicare registry demonstrated that the addition of Black race to the CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system significantly improved the prediction of stroke events among patients with newly diagnosed AF who were  $\geq$ 65 years of age.<sup>234</sup>
- 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.<sup>235</sup>
- In patients with COVID-19 in a global database, risk of ischemic stroke and other thromboembolic complications was higher in those with AF versus those without AF (9.9% versus 7.0%; RR, 1.41 [95% CI, 1.26–1.59]).<sup>236</sup>
- 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.<sup>204</sup>

### Cognition and Dementia

- A meta-analysis of 11 prospective studies including 112876 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.<sup>237</sup> 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];  $P<0.0001$ ).<sup>238</sup>
- 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.<sup>239</sup> Furthermore, in adjusted analyses of all the vascular brain features, large noncortical or cortical infarcts had the strongest association with reduced Montreal Cognitive Assessment score ( $\beta=-0.26$  [95% CI,  $-0.40$  to  $-0.13$ ];  $P<0.001$ ), even when restricted to individuals with clinically silent infarcts.

### Physical Disability and Subjective Health

- In systematic reviews of published studies (including prospective and cross-sectional studies), AF has been associated with physical disability, poor subjective health,<sup>240</sup> and diminished quality of life.<sup>241</sup>

### 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]).<sup>242</sup>

### Heart Failure

#### (See Chart 18-7)

- AF and HF share many antecedent risk factors, and  $\approx$ 40% of people with either AF or HF will develop the other condition.<sup>215</sup>
- In the community, estimates of the incidence of HF in individuals with AF ranged from 3.3<sup>215</sup> to 5.8<sup>243</sup> 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]).<sup>243</sup>

- Among older adults with AF in Medicare, the 5-year rates of CVD and death were high, with rates of death and HF exceeding those for stroke (Chart 18-7). Higher rates of death and CVD after new-onset AF were associated with older age and higher mean CHADS<sub>2</sub> score.<sup>244</sup>
- 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-aHR 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-aHR of AF of 4.80 (95% CI, 1.30–17.70).<sup>245</sup>
- 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]).<sup>246</sup>

### 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.<sup>246</sup>
- Both REGARDS<sup>247</sup> and the ARIC study<sup>248</sup> observed that the risk of MI after AF was higher in females than in males.
- For individuals with AF in both REGARDS<sup>247</sup> and the CHS,<sup>249</sup> 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* for interaction=0.03).<sup>249</sup>
- 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).<sup>248</sup>

### Chronic Kidney Disease

- 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).<sup>250</sup>

### SCD and VF

- 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.<sup>251</sup>

- 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).<sup>252</sup>

### 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).<sup>253</sup>
- 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.<sup>254</sup>

### 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]).<sup>255</sup>
- A national Taiwanese study compared the prognoses 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).<sup>256</sup>

### Hospitalizations and Ambulatory Care Visits

- According to HCUP data,<sup>257</sup> in 2018, there were 472 000 hospital discharges with AF and atrial flutter as the principal diagnosis (unpublished NHLBI tabulation).
- In 2018, there were 4 977 000 physician office visits (NAMCS, unpublished NHLBI tabulation)<sup>262</sup> and 701 000 ED visits for AF (HCUP,<sup>257</sup> unpublished NHLBI tabulation).
- Using cross-sectional data (2006–2014) from the HCUP's Nationwide Emergency Department Sample, 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.<sup>258</sup>

- 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).<sup>259</sup>

### 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.<sup>260</sup> 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%.
- Using cross-sectional data (2006–2014) from the HCUP's Nationwide Emergency Department Sample, 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.<sup>258</sup>
- 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.<sup>261</sup>

- During the period of 1999 to 2013, median Medicare inpatient costs per AF hospitalization increased substantially, from \$2932 (IQR, \$2232–\$3870) to \$4719 (IQR, \$3124–\$7209).<sup>262</sup>
- Costs of AF have been estimated for many other countries. Investigators estimated that the 3-year societal costs of AF were approximately €20 403 to €26 544 per person and €219 to €295 million for Denmark as a whole.<sup>263</sup>

### Global Burden of AF

#### (See Charts 18-8 and 18-9)

- The GBD 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020. (Data courtesy of the Global Burden of Disease Study 2020.)
  - The total number of global deaths estimated for AF/atrial flutter in 2020 was 0.33 million (95% UI, 0.28–0.36 million), with 0.13 million (95% UI, 0.11–0.14 million) among males and 0.20 (95% UI, 0.16–0.22 million) among females.
  - Globally, 50.00 million (95% UI, 40.31–62.09 million) individuals had prevalent AF/atrial flutter in 2020, with 26.66 million (95% UI, 21.33–33.04 million) among males and 23.35 million (95% UI, 18.76–29.26 million) among females.
  - Age-standardized mortality estimated for AF was highest in Western Europe and Australasia (Chart 18-8).
  - Age-standardized prevalence of AF was highest in high-income North America and Australasia in 2020 (Chart 18-9).
- 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%).<sup>265</sup>

**Table 18-1. Cumulative Incidence Rate Over 5 Years After AF Diagnosis, by Age,\* United States, Diagnosed 1999 to 2007**

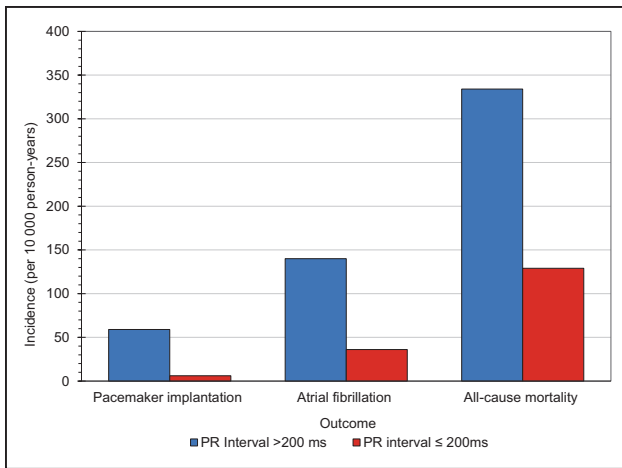
Age group, y	Mortality	HF	MI	Stroke	Gastrointestinal bleeding
67–69	28.8	11.0	3.3	5.0	4.4
70–74	32.3	12.1	3.6	5.7	4.9
75–79	40.1	13.3	3.9	6.9	5.9
80–84	52.1	15.1	4.3	8.1	6.4
85–89	67.0	15.8	4.4	8.9	6.6
≥90	84.3	13.7	3.6	6.9	5.4

All values are percentages.

AF indicates atrial fibrillation; HF, heart failure; and MI, myocardial infarction.

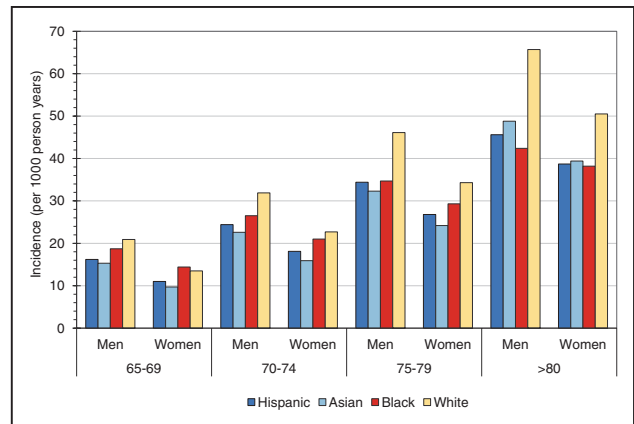
\*See Chart 18-7.

Source: Adapted from Piccini et al<sup>244</sup> with permission of the European Society of Cardiology. Copyright © 2013 The Authors.



**Chart 18-1. 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.<sup>15</sup>

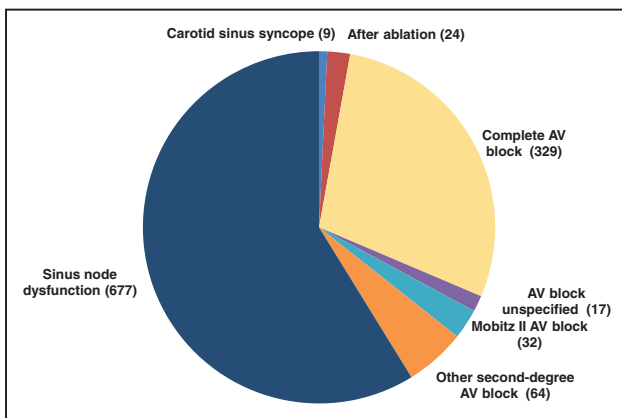


**Chart 18-4. AF incidence, by race, 2005 to 2009.**

Incidence increased with advancing age among different races and sexes in California.

AF indicates atrial fibrillation.

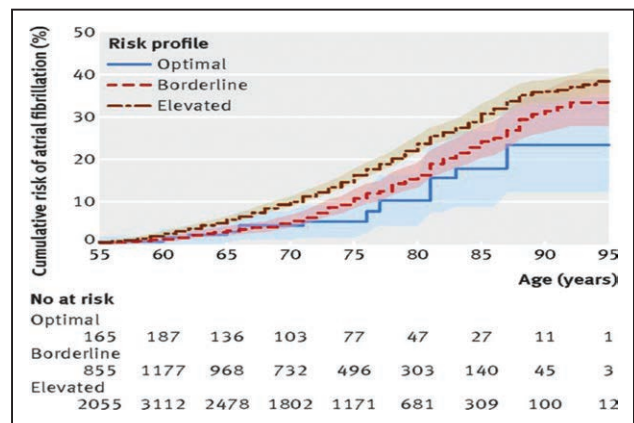
Source: Data derived from Dewland et al.<sup>78</sup>



**Chart 18-2. 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.<sup>41</sup>

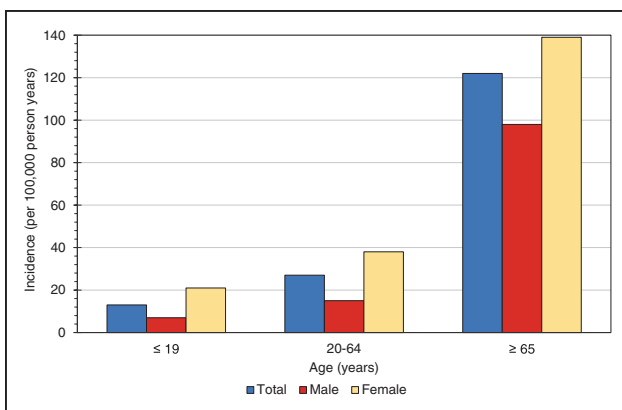


**Chart 18-5. Lifetime risk (cumulative incidence at 95 years of age) for AF at different ages (through 94 years of age), by sex in the FHS, 1968 to 2014.**

AF indicates atrial fibrillation; and FHS, Framingham Heart Study.

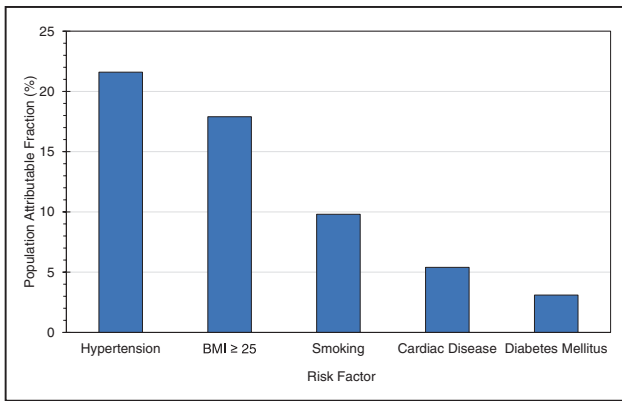
Source: Reprinted from Staerk et al.<sup>86</sup> Copyright © 2018, The Authors.

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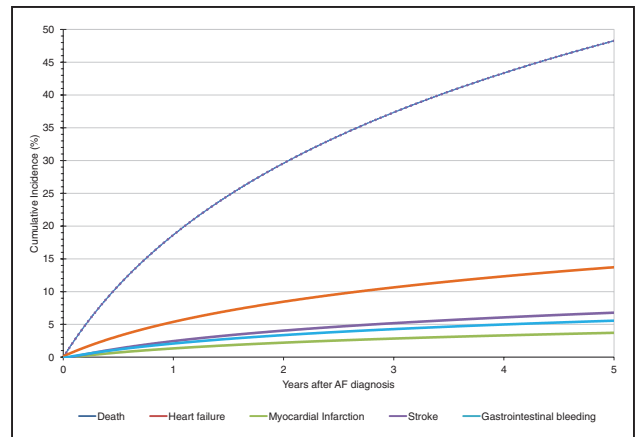
**Chart 18-3. Incidence rate of paroxysmal supraventricular tachycardia per 100,000 person-years, by age and sex, Marshfield area, Wisconsin, July 1, 1991, to June 30, 1993.**

Source: Data derived from Orejarena et al.<sup>42</sup>



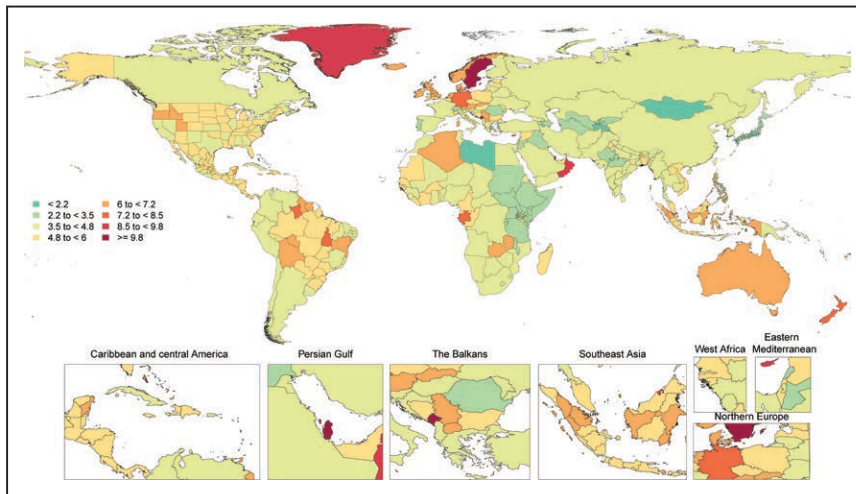
**Chart 18-6. PAF of major risk factors for AF in the ARIC study, 1987 to 2007.**

Cardiac disease includes a history of coronary artery disease or heart failure; smoking refers to current smoker. AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; and PAF, population attributable fraction  
Source: Data derived from Huxley et al.<sup>90</sup>



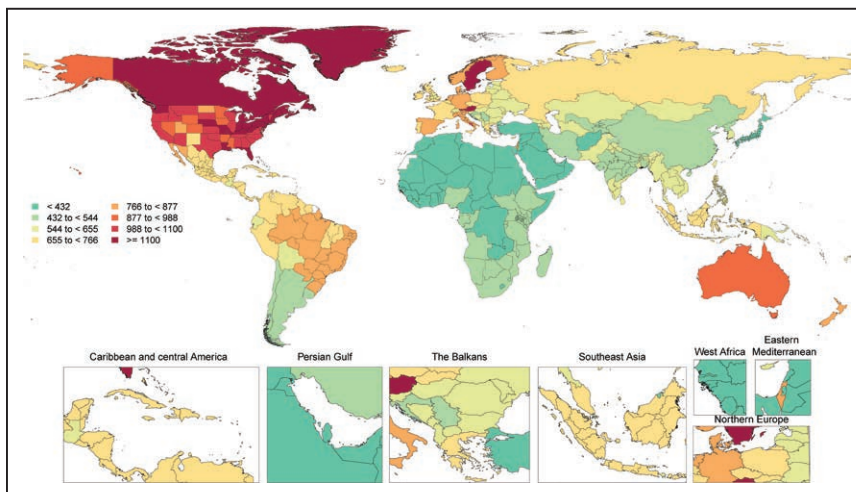
**Chart 18-7. Cumulative incidence of events in the 5 years after diagnosis of incident AF in Medicare patients in the United States, diagnosed 1999 to 2007.**

AF indicates atrial fibrillation.  
Source: Reprinted from Piccini et al<sup>244</sup> with permission of the European Society of Cardiology. Copyright © 2013 The Authors.



**Chart 18-8. Age-standardized global mortality rates of AF and atrial flutter per 100 000, both sexes, 2020.**

AF indicates atrial fibrillation.  
Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>266</sup>



**Chart 18-9. Age-standardized global prevalence rates of AF and atrial flutter per 100 000, both sexes, 2020.**

AF indicates atrial fibrillation.  
Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>266</sup>

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## 19. SUDDEN CARDIAC ARREST, VENTRICULAR ARRHYTHMIAS, AND INHERITED CHANNELOPATHIES

See Tables 19-1 through 19-7 and Charts 19-1 through 19-8

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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.**

2019: Mortality—18581. Any-mention mortality—370494.

### Tachycardia

**ICD-9 427.0, 427.1, 427.2; ICD-10 I47.1, I47.2, I47.9.**

2019: Mortality—1069. Any-mention mortality—8849.

Cardiac arrest is the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation.<sup>1</sup> 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.<sup>2</sup> Because of fundamental differences in the underlying pathogenesis and 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 70846 OHCA from 1992 to 2014, 92% of cases had medical causes. Among nonmedical cases, trauma was the most common cause.<sup>3</sup>

The 2022 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 2022. 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.

### Incidence

(See Tables 19-1 through 19-3)

- 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 19-1).
- The ongoing CARES registry<sup>4</sup> estimates the incidence of EMS-treated OHCA among individuals of any age in >2000 EMS agencies in the United States (Table 19-1). Differences in bystander intervention and survival by race, ethnicity, and sex are listed in Table 19-2.
- Incidence of EMS-treated OHCA in people of any age is 88.8 individuals per 100000 population based on the 2020 CARES registry, with great variation between states (range, 44.2–135.5; Table 19-3).
- Of the 3686296 hospital discharges from academic medical centers in 2012, 33700 (0.91%) included a cardiac arrest diagnosis.<sup>7</sup>
- The first 3 to 6 months after AMI is known to be a high-risk period for OHCA. However, the actual risk data have been based on older studies that antedated current standards of care for patients with AMI. A survey of >120000 AMI survivors from 2009 to 2017 in the Swedish Cardiopulmonary Resuscitation Registry followed up for up to 90 days after hospital discharge found the incidence of OHCA to be 0.29% (0.19% at 30 days).<sup>8</sup>
- Incidence of maternal cardiovascular collapse requiring CPR during childbirth was 10 in 250719 (4.0 per 100000 births) in a registry of births in New York.<sup>9</sup>
- Incidence of IHCA among 15953 rapid response team calls in Australia was 159 cases in 152 individuals or 0.62 IHCA per 1000 multiday admissions (IQR, 0.50–1.19).<sup>10</sup>
- In the NIS for 2016:
  - Cardiac arrest or VF/flutter was included in 273295 hospital discharges (rate of 84.6 per 100000 people). For 9.5% (26040), this was the principal diagnosis for hospital admission.
  - ICD-10 codes for CPR or defibrillation were included in 286945 hospital discharges (rate of 88.8 per 100000 people).<sup>11</sup>

### Incidence and Response: COVID Effects

(See Charts 19-1 through 19-3)

The COVID pandemic has had multiple effects on incidence of OHCA.

- In New York City, the incidence of OHCA attended by EMS (March 1–April 25, 2020) increased 3-fold over the same period 1 year earlier.<sup>12</sup> Compared



with the pre-COVID control period, subjects experiencing OHCA during COVID were older and more likely to be Asian, Black, Hispanic or of Mixed Race than White. There was a higher prevalence of asystole and pulseless electrical activity during the COVID period compared with the control period.

- In the Lombardy region of Italy, a 52% increase in the incidence of OHCA was observed in the first 2 months of the pandemic compared with the same period 1 year earlier. In addition, there was a 40% reduction in emergency calls that resulted in a diagnosis of STEMI.<sup>13</sup> Initiation of CPR by bystanders and EMS declined during the early stages of the pandemic in Lombardy, but the presence of suspected/confirmed COVID infection was not a predictor of attempts to resuscitate.<sup>14,15</sup> In Paris, France, the incidence of OHCA doubled during the pandemic, and survival to hospitalization decreased significantly. The proportion of OHCA occurring at home increased, and there was a lower rate of bystander CPR.<sup>16</sup>
- Hospitalizations for AMI in England during the first wave of COVID-19 were significantly reduced. Incidence of OHCA associated with AMI from February through May 2020 was 5.6% versus 3.6% for the same period in 2019, representing a 56% increase in the incidence of OHCA (IRR, 1.56 [95% CI, 1.39–1.74]).<sup>17</sup> Risk factors for OHCA included older age, female sex, and Asian ethnicity.
- A meta-analysis that included 10 studies from multiple countries found a 119% increase in OHCA during the pandemic compared with earlier control periods. For the patients with known outcomes (n=10992), mortality was 85% compared with 62% for the control periods.<sup>18</sup>
- It is likely that a significant contribution to the increase in OHCA was attributable to delay in seeking care for AMI, as documented in Switzerland.<sup>19</sup>
- A prospective nationwide Spanish registry examining OHCA from February 1 to April 30, 2020, compared with the same periods in 2017 and 2018 documented significantly increased delays from call for help to ambulance arrival. There were significantly fewer resuscitation attempts, lower rates of return of spontaneous circulation, and lower survival.<sup>15</sup>
- The French National OHCA registry reported significant declines in frequency of performance of basic life support and advanced life support during COVID.<sup>20</sup> Most characteristics of individuals with COVID-19 who experienced OHCA were similar to those of individuals without COVID-19, with several exceptions: Individuals with COVID-19 who experienced OHCA were more likely to be female and to have respiratory disease, longer no-flow duration, and longer time to return of spontaneous circulation.
- A multicenter prospective report from 68 US hospitals described outcomes of IHCA among 701 adults with COVID-19 in ICUs. Of these, 57% received CPR, and 12% survived to hospital discharge, and 58% of the 28 survivors had no significant neurological impairment.<sup>21</sup>
- Data from the CARES registry showed increased delays to initiation of CPR for OHCA (Chart 19-1) and reduced survival after OHCA coinciding with timing of the pandemic in the United States (Chart 19-2). Accompanying these effects were reductions in the frequency of shockable rhythms, OHCA in public locations, and bystander automated external defibrillator use, whereas field termination of resuscitation efforts increased (Chart 19-3). Despite this, there was no significant alteration in frequency of bystander CPR.

### OHCA: Adults (See Table 19-4)

- 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), on the basis of extrapolation from the ROC registry of OHCA to the total population of the United States (ROC Investigators, unpublished data, July 7, 2016).<sup>21a</sup>
- 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).<sup>22</sup>
- In Saskatoon, Saskatchewan, a retrospective survey of 372 adult OHCA from 2015 to 2017 found that First Nation people were significantly younger (mean, 46 years) than non-First Nation people (mean, 65 years). Survival and types of arrhythmias were similar.<sup>23</sup>
- In 2020, location of OHCA in adults was most often a home or residence (73.9%) followed by public settings (15.1%) and nursing homes (10.9%; Table 19-4). OHCA in adults was witnessed by a layperson in 37.1% of cases or by a 9-1-1 responder in 12.8% of cases. For 50.1% of cases, collapse was not witnessed.<sup>4</sup>

- Initial recorded cardiac rhythm was VF, VT, or shockable by an automated external defibrillator in 16.7% of EMS-treated adult OHCA in 2020 (Table 19-4).
- Of 4729 patients with STEMI in Los Angeles County, California, from 2011 to 2014, 422 (9%) had OHCA.<sup>24</sup>
- Of 851 line-of-duty firefighter fatalities with adjudicated cause of death, 319 (37%) were cardiac in origin.<sup>25</sup>
- 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.<sup>26</sup>

### IHCA: Adults

#### (See Table 19-4)

- Incidence of adult IHCA was a mean of 17.16 (SD, 83.29) per 1000 hospital admissions and 3.94 (SD, 26.98) per 1000 inpatient days in the 2020 GWTG data (GWTG–Resuscitation, unpublished data, 2020).
- Incidence of IHCA was 4.0 per 1000 hospitalizations (range, 1.4–11.8 per 1000 hospitalizations) on the basis of 2205123 hospitalizations at 101 Veterans Health Administration hospitals between 2008 and 2012.<sup>27</sup>
- Incidence of IHCA was 1.7 per 1000 hospital admissions on the basis of 18069 patients with IHCA in the Swedish Register of CPR.<sup>28</sup>
- IHCA within the first 24 hours after admission for STEMI occurred in 7.8% (136) of 1754 patients in the ARGENT-STEMI. Features associated with IHCA were older age and cardiogenic shock.<sup>29</sup>
- MI with OHCA or cardiac arrest in the ED occurred in 9682 (3.8%) of 252882 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).<sup>30</sup>
- IHCA incidence was 320 (1.50%) of 21337 patients with ACS admitted to 3 hospitals in China from 2012 to 2016.<sup>31</sup>
- According to 2020 GWTG data, location of adult IHCA was the ICU, operating room, or ED in 56.2% and noncritical care areas in 43.8% among 34200 events at 329 hospitals (Table 19-4).
- Initial recorded cardiac rhythm was VF or VT in 13.7% of adult IHCA in 2020 GWTG data (GWTG–Resuscitation, unpublished data, 2020; Table 19-4).
- Intraoperative cardiac arrest in adults occurred with an incidence of 5.7 per 10000 hospital admissions in which there was an operating room procedure

in a 2016 survey of the NIS.<sup>32</sup> In-hospital mortality was 36% in patients experiencing intraoperative cardiac arrest.

- Multiple studies have shown that risk for IHCA is predictable and that focused rapid response teams may reduce the risk of IHCA.<sup>33–36</sup>
- A New York academic medical center review of IHCA from 2012 to 2018 showed lower incidence in females but twice the in-hospital mortality compared with males.<sup>37</sup>

### Pathology of SCA/SCD

#### (See Chart 19-4)

- Two prospective autopsy studies of people with SCD have shed new evidence on underlying causes of sudden death. One study followed up patients with HF or reduced EF after a recent MI enrolled in a randomized trial of drug therapy.<sup>38</sup> The second study was a community-based survey of out-of-hospital SCD.<sup>39</sup> In each study, only one-half of the sudden deaths had no specific findings at autopsy. In these cases, the mechanism of death was classified as arrhythmic. However, approximately one-half of the sudden unexpected deaths in each study had specific findings at autopsy, supporting a nonarrhythmic mechanism for the sudden death, including AMI, cardiac rupture, acute HF, and acute pulmonary embolus (Chart 19-4). In addition, acute neurological events and occult drug overdoses were common in the San Francisco community study. EMS data were available for the San Francisco community study. When the initial rhythm recorded by EMS was VT or VF, the autopsy findings were likely to be consistent with sudden arrhythmic death, whereas when the initial finding was pulseless electrical activity, the autopsy was likely to result in a classification of non-sudden arrhythmic death.

### OHCA: Children

#### (See Table 19-4)

- Incidence of EMS-assessed OHCA in children in 2015 was 7037 (quasi-CI, 6214–7861) in the United States according to extrapolation from ROC for individuals <18 years of age (ROC Investigators, unpublished data, July 7, 2016).
- In 2020, location of EMS-treated OHCA was home for 87.5% of children in the CARES 2020 data. Location was a public place for 12.2% of children (Table 19-4).<sup>4</sup>
- Annual incidence of pediatric OHCA was 8.7 per 100000 population in Western Australia from 2011 to 2014.<sup>40</sup>

## 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).<sup>41</sup>
- Incidence of SCA or SCD was 1 per 44 832 athlete-years for males and 1 per 237 510 athlete-years for females according to a 2007 to 2013 registry of 104 cases of SCA and SCD in high school athletes.<sup>42</sup>
- 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.<sup>43</sup>
- Incidence of SCD, estimated from 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.<sup>44</sup>
- 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 with various methods used to ascertain events.<sup>45</sup> 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.<sup>46</sup>
- 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%).<sup>42</sup>
- 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%).<sup>47</sup>
- 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 age was 47 years (SD, 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.<sup>48</sup>

- Preparticipation screening of 51 69 middle and high school students (mean age, 13.06 years [SD, 1.78 years]) from 2010 to 2017 revealed high-risk cardiovascular conditions in 1.47%.<sup>49</sup> Anatomic findings included DCM (n=11), nonobstructive HCM (n=3), and anomalous coronary artery origins (n=23). Electrocardiographic findings included WPW syndrome (n=4), prolonged QT intervals (n=34), and Brugada pattern (n=1).

## IHCA: Children

### (See Table 19-4)

- Incidence of IHCA for children (30 days–18 years of age) was a mean of 9.03 (SD, 6.09) per 1000 admissions and 1.88 (SD, 2.13) per 1000 inpatient days for 746 events from 86 hospitals per 2020 GWTG data (GWTG–Resuscitation, unpublished data, 2020).
- Of 746 events of IHCA in children (30 days–18 years of age) at 86 hospitals, 86.6% occurred in the ICU, operating room, or ED and 13.4% in noncritical care areas per 2020 GWTG data (Table 19-4).
- 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.<sup>50</sup>
- 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).<sup>51</sup>
- Initial recorded cardiac arrest rhythm was VF or VT in 9.8% of 539 events at 80 hospitals in GWTG–Resuscitation in 2020 (Table 19-4).
- A retrospective analysis of 3 US pediatric ICUs from 2015 to 2017 found a 7% incidence of cardiac arrest in patients undergoing endotracheal intubation.<sup>52</sup>

## Lifetime Risk and Cumulative Incidence

### (See Table 19-5 and Chart 19-5)

- SCD appeared among the multiple causes of death on 13.0% of death certificates in 2019 (370 494 of 2 854 838; Table 19-5). Because some people survive SCA, the lifetime risk of cardiac arrest is even higher.

- In 2019, infants had a higher incidence of SCD (12.0 per 100 000) than older children (1.0–2.2 per 100 000). Among adults, risk of SCD increased exponentially with age, surpassing the risk for infants by 35 to 39 years of age (13.0 per 100 000; Chart 19-5).
- 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.<sup>53</sup>

## Secular Trends

### (See Table 19-1 and Charts 19-6 and 19-7)

- 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 19-1).
- The annual rate of SCD among patients with HFrEF has declined from 6.5% to 3.3% according to an analysis of 3583 cases of SCD among 40 195 patients enrolled in 12 clinical trials for which enrollment started between 1995 and 2010.<sup>54</sup> 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.<sup>40</sup>
- 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.<sup>55</sup> 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 (sub-HR, 0.46 [95% CI, 0.30–0.70]) decreased over time in outpatients with HFrEF (<40%) on the basis of 2 multicenter prospective registries (MUSIC [n=641; period, 2003–2004] and REDINSCOR I [n=1710; period, 2007–2011]).<sup>56</sup> This reduction in SCD was associated with more frequent use of  $\beta$ -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 91.2 per 100 000 person-years by 2019 (Chart 19-6).
- 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 19-1).
- 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.<sup>57</sup> Rates of return of spontaneous circulation also increased from 6.31 to 9.99 per 100 000.

- Survival to discharge after pulseless IHCA in children increased from 18.9% to 42.2% between 2000 and 2020 in GWTG data (Chart 19-7).
- A national database of 120 365 adult, medical OHCA 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%).<sup>58</sup> 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 19-8)

- 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 19-8).<sup>59</sup>
- 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.<sup>60</sup> Events were associated with larger left atrial end-systolic area and arrhythmogenic profile (history of syncope, nonsustained VT, at least 1000 premature ventricular contractions 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.<sup>61</sup> Noncardiac causes included 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.<sup>61</sup>

- Incidence of OHCA increased with daily atmospheric levels of particulate matter in 249372 OHCA cases in Japan from 2014 to 2015 (OR, 1.016 [95% CI, 1.009–1.023] per 10- $\mu\text{g}/\text{m}^3$  increase in PM<sub>2.5</sub>).<sup>62</sup>
- 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%).<sup>63</sup> Over time, the proportion of ischemic SCD declined from 78.8% (1998–2002) to 72.4% (2013–2017).
- An analysis of 8900 patients enrolled in 3 contemporary therapeutic trials of patients with HFpEF found that those with prior MI had  $\approx$ 50% increased risk of SCD compared with patients without prior MI.<sup>64</sup>

## Age

### (See Chart 19-5)

- In 2019, mortality rates for any mention of SCD decreased for those 0 to 9 years of age and increased for those  $\geq$ 10 years of age (Chart 19-5).

## 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.<sup>65</sup>
- In a registry that included 40159 OHCA cases 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%).<sup>66</sup> 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 OHCA cases from 2013 to 2015 that includes 90% of the population of New Zealand, OHCA was more common in males (69%) than females (31%).<sup>67</sup> 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 11237 (2.95%) White participants experienced SCD during 27.4 years of follow-up.<sup>68</sup> 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 people (42%) than White people (34%; aHR, 1.60 [95% CI, 1.18–2.17]).<sup>69</sup>

## 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.<sup>70</sup>
- 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]).<sup>71</sup>
- In a national database of 120365 adult, medical OHCA cases in the Republic of Korea from 2006 to 2015, there were differences from the lowest to highest socioeconomic quintiles for layperson CPR (5.5%–11.4%), survival to hospital discharge (3.8%–6.1%), and good functional recovery (1.9%–2.9%).<sup>58</sup>

## 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 3242 untreated hypertensive patients without evidence of coronary or cerebrovascular disease at entry who were followed up for an average of 10.3 years.<sup>72</sup> The prevalence of electrocardiographic LVH was 13.9%. For patients with electrocardiographic signs of LVH, the rate of SCD was 0.37 per 100 patient-years versus 0.05 per 100 patient-years for patients without electrocardiographic LVH (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]).<sup>53</sup>
- In a cohort of 233970 patients from the United Kingdom, resting heart rate  $>$ 90 bpm was associated with an increased hazard of SCD or cardiac

arrest as initial presentation of HD (aHR, 2.71 [95% CI, 1.90–3.83]).<sup>73</sup>

- 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.<sup>74</sup>
- 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.<sup>75</sup>
- 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).<sup>76</sup> 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]).<sup>77</sup>
- 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.<sup>78</sup>
- 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.<sup>79</sup>
- 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 the CHS).<sup>79</sup>
- 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]).<sup>80</sup>
- 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]).<sup>81</sup>
- In a cohort of 5211 Finnish people >30 years of age in 2000 to 2001 who were 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]).<sup>82</sup>

- In a meta-analysis that included 17 studies with 1 189 54 subjects, presence of depression or depressive symptoms was associated with increased risk of SCD (HR, 1.62 [95% CI, 1.37–1.92]), specifically for VT/VF (HR, 1.47 [95% CI, 1.23–1.76]).<sup>83</sup>
- The interaction among CHD, PA, and SCD is complex. Analysis from a Finnish registry of 1946 patients with angiographically documented CHD found that risk of SCD was increased in patients with more advanced angina (Canadian Cardiovascular Society angina grade  $\geq 2$ ) and both active (HR, 7.46 [95% CI, 2.32–23.9];  $P < 0.001$ ) and inactive (HR, 3.64 [95% CI, 1.16–11.5];  $P < 0.05$ ) lifestyles, whereas risk of SCD was decreased in active patients with lesser grades of angina (Canadian Cardiovascular Society angina grade 1 (HR,  $\approx 0.5$ )).<sup>84</sup>

## 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.<sup>85</sup>
- Early warning score systems using both clinical criteria and vital signs identified hospitalized patients with a higher risk of IHCA<sup>86</sup> (see also IHCA incidence above).
- 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.<sup>87</sup>
- 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.<sup>88</sup>

### 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  $\geq 40$  years of age, including Brugada syndrome in 0.13%, QTc  $< 340$  milliseconds in 0.18%, and QTc  $\geq 480$  milliseconds in 0.42%.<sup>89</sup>
- 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.<sup>90</sup>

- Among 20 177 subjects in the ARIC study followed up for 14 years (median), the incidence of SCD was 1.86 per 1000 person years. Five global markers of electrical heterogeneity measured on a standard 12-lead ECG at baseline and during follow-up demonstrated an independent predictor of risk for SCD.<sup>91</sup>
- 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.<sup>92</sup>

## 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.<sup>93,94</sup> Among children with exertion-related deaths, pathogenic variants 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.<sup>95</sup>
- Screening of 398 first-degree relatives of 186 probands with unexplained SCA and 212 probands with unexplained SCD revealed cardiac abnormalities in 30.2%: LQTS (13%), CPVT (4%), ARVC (4%), and Brugada syndrome (3%).<sup>96</sup>
- 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 in 11%, LQTS in 7.8%, DCM in 3.1%, and HCM in 3.1%.<sup>97</sup>
- Screening of 292 relatives of 56 probands with SCD revealed a diagnosis in 47 relatives (16.1%): LQTS in 12.7%, CPVT in 0.3%, DCM in 0.7%, ARVC in 0.3%, and thoracic aortic dilation in 0.3%. Among relatives completing follow-up, 3.3% had a cardiac event within 3 years and 7.2% had a cardiac event within 5 years.<sup>98</sup>
- 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.<sup>99</sup> 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.<sup>100</sup>

## 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.<sup>101</sup>
- GWASs also have been conducted with variation in electrocardiographic traits used 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.<sup>102</sup>
- A GWAS of T-peak-to-T-end interval on ECG, a predictor of increased arrhythmic risk, in the UK Biobank identified 32 genomic loci for resting T-peak-to-T-end interval, 3 for T-peak-to-T-end response to exercise, and 3 for T-peak-to-T-end response to recovery, but a GRS of these variants was not associated with arrhythmic risk.<sup>103</sup>

## 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 variants in 15 genes leading to 17 different subtypes of LQTS phenotype.<sup>104,105</sup> There is variability in presentation, therapeutic approach, and prognosis by subtype.
- Approximately 5% of sudden infant death syndrome cases and some cases of intrauterine fetal death could be attributable to LQTS.<sup>106</sup>
- Ancestry-specific LQTS variants exist: The S1103Y polymorphism in *SCN5A* is found in 13% of Black individuals and has been linked to lethal arrhythmias and SCD in Black individuals with HF.<sup>107,108</sup>
- 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.<sup>109</sup> 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.<sup>110</sup>

- 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%).<sup>111</sup>
- 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]).<sup>112</sup>
- Genetic testing for LQTS among 281 families had a diagnostic yield for genetic variants of 47%.<sup>113</sup>
- However, some studies have called into question whether previously identified LQTS genes are truly causative.<sup>114,115</sup> 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 association with acquired LQTS.
- GWASs have identified additional rare and common variants in genes associated with QT interval,<sup>114</sup> suggesting that individuals with long QT who are variant negative could have a polygenic inheritance.
- Drug-induced LQTS has emerged as a potential mechanism contributing to mortality and cardiac arrest in patients with COVID-19 infection. Many patients with COVID-19 infection have received drugs such as chloroquine, hydroxychloroquine, azithromycin, lopinavir, and ritonavir that have QT-prolonging effects.
- A randomized controlled multicenter trial of 665 patients with COVID-19 in Brazil treated with standard care, hydroxychloroquine alone or in combination with azithromycin, found a 14.6% incidence of QT interval prolongation >480 milliseconds in patients in the 2 active treatment groups versus 1.7% in the standard care group.<sup>116</sup> No patient developed TdP.
- A prospective survey of 119 patients with COVID-19 treated in 3 New York hospitals who received both chloroquine or hydroxychloroquine and azithromycin and 82 patients treated with chloroquine or hydroxychloroquine alone revealed significant increases in QTc. Patients receiving both drugs demonstrated significantly greater increases in QTc than patients receiving monotherapy. A peak QTc

>500 milliseconds was observed in 8.6% of patients receiving a single drug and 9.2% of patients receiving 2 drugs. There was no difference in QT prolongation according to sex. No patients in this series developed TdP.<sup>117</sup>

- A retrospective analysis of 91 hospitalized patients with COVID-19 in Connecticut treated with hydroxychloroquine and azithromycin found QTC prolongation >500 milliseconds in 14% on treatment. Almost half the patients with marked QTc prolongation were receiving other agents known to prolong the QT interval, most often propofol. Two patients developed VT: TdP in 1 patient and polymorphic VT leading to VF in the other.<sup>118</sup>
- A retrospective analysis of 415 hospitalized patients with COVID-19 infection treated with hydroxychloroquine and azithromycin found QTc prolongation >500 milliseconds in 21%, but no TdP was observed.<sup>119</sup>
- A retrospective cohort analysis of 170 patients in Wuhan China hospitalized with COVID-19 infection and evidence of myocarditis (elevated cardiac troponin I) found 6 patients with VT/VF, all of whom died. Patients treated with QT-prolonging agents had significantly longer QTc, but the increase in QTc was not associated with mortality independently.<sup>120</sup>
- A common ion channel genetic variant, p.Ser1103Tyr-SCN5A, which predisposes to QT prolongation and increased risk of TdP, is found almost exclusively in the Black population with a prevalence of 8%. This variant not only increases risk for drug-induced TdP but also has the ability to increase the risk for TdP in the presence of hypoxemia and acidemia resulting from an increase in the late Na current. This may explain part of the increased risk of OHCA in Black individuals and their increased mortality in the face of COVID infection.<sup>121</sup>

## 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. Variants in 5 ion channel genes (*SQT1–SQT5*) have been described.<sup>122</sup>
- Prevalence of a QTc interval <320 milliseconds in a population of 41 767 young, predominantly male Swiss conscripts was 0.02%,<sup>123</sup> which was identical to the prevalence from a Portugal sudden death registry.<sup>124</sup>
- 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%.<sup>125</sup> Short QT intervals were associated with male sex and Afro-Caribbean ethnicity.

- Prevalence of QT interval  $\leq 340$  milliseconds in 99380 unique patients  $\leq 21$  years of age at Cincinnati Children's Hospital between 1993 and 2013 was 0.05%.<sup>126</sup> Of these children, 15 of 45 (33%) were symptomatic.<sup>126</sup>

### 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.<sup>127</sup>

## 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.<sup>128</sup> Brugada syndrome is associated with variants in at least 12 ion channel–related genes.
- In a meta-analysis of 24 studies, prevalence was estimated at 0.4% worldwide, with regional prevalence of 0.9%, 0.3%, and 0.2% in Asia, Europe, and North America, respectively.<sup>129</sup> Prevalence was higher in males (0.9%) than in females (0.1%).<sup>130</sup>
- Among 678 patients with Brugada syndrome from 23 centers in 14 countries, patients whose first documented arrhythmic event was SCA had a mean age of 39 years (SD, 15 years), whereas age at the first documented arrhythmic event in patients with prophylactic defibrillator implantation was 46 years (SD, 13 years).<sup>131</sup>

### 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.<sup>132</sup>
- Variants in the *PKP2* gene that causes ARVC have been reported to cause an arrhythmogenic phenotype in the absence of overt structural disease<sup>133</sup> and may be implicated in Brugada syndrome.<sup>134</sup>
- 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.<sup>135</sup>

## Catecholaminergic Polymorphic VT

### 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). Variants in genes encoding RYR2 (*CPVT1*) are found in the majority of patients and result in a dominant pattern of inheritance.<sup>136</sup> Variants in genes encoding CASQ2 (*CPVT2*) are found in a small minority and result in a recessive pattern of inheritance. Variants have also been described in *KCNJ2* (*CPVT3*), *TRDN*, *ANK2*, and *CALM1*.<sup>136</sup>
- Prevalence of CPVT is estimated at 1:5000 to 1:10000, but this could be an underestimate because childhood cases were excluded.<sup>136</sup>
- Analysis of 171 probands with CPVT who were  $< 19$  years of age and 65 adult relatives described clinical presentations and prevalence of genotypes.<sup>137</sup> 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* (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.<sup>138</sup>
- Incidence of SCA in children with  $\geq 2$  CPVT gene variants was 11 of 15 (73%).<sup>139</sup> VT or exertional syncope occurred in 3 of the children (20%), and only 1 (7%) was asymptomatic.

## Arrhythmogenic RV Dysplasia/ARVC

- Arrhythmogenic RV dysplasia or ARVC 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*).<sup>140</sup>

### 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.<sup>141</sup>
- 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%).<sup>142</sup>

## Hypertrophic Cardiomyopathy

(Please refer to Chapter 22, 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.<sup>143</sup>
- Hospitalizations related to arrhythmias among patients with HCM increased 10.5% from 7784 in 2003 to 8380 in 2014 in the NIS.<sup>144</sup> Reported arrhythmias 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 in distinguishing HCM from secondary LVH in older patients, who were excluded from the analysis.<sup>145</sup>

## 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.<sup>146</sup>
- 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.<sup>146</sup>
- 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.<sup>147</sup>
- Among 11956 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%).<sup>148</sup>
- In an Italian public health screening project, 24% of 13016 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.<sup>149</sup>

### 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]).<sup>147</sup>
- Shocks from an automatic implantable cardioverter defibrillator occur more often and earlier in survivors of idiopathic VF with inferolateral early repolarization syndrome (HR, 3.9 [95% CI, 1.4–11.0];  $P=0.01$ ).<sup>150</sup>

## 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 premature ventricular contractions, and 5.5% of participants had nonsustained VT. Over follow-up, the highest quartile of ambulatory electrocardiographic premature ventricular contraction 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]).<sup>151</sup> Although premature ventricular contraction 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.

### Tetralogy of Fallot

- Patients with repaired TOF are known to be at risk for ventricular arrhythmias and SCD. However, the true incidence is not clear. Prevalence estimates from multicenter studies range from 1% to 14%.<sup>152–154</sup>
- A retrospective case-control study from 13 institutions containing the largest number of patients with TOF with VT or SCD to date identified risk factors (some noted earlier), including QRS duration ≥180 milliseconds, left or RV dysfunction, and age at surgical repair.<sup>155</sup>

### Cardiac Sarcoidosis

- Cardiac involvement in sarcoidosis is increasingly recognized as a cardiomyopathy with relatively high risk for sudden death attributable to ventricular tachyarrhythmias. Estimates of the prevalence of cardiac involvement in sarcoidosis vary widely, depending on the method of diagnosis, ranging from 3.7% to 54.9%.<sup>156</sup>
- A review of the NIS from 2012 to 2014 identified 46289 patients with diagnosis of sarcoidosis. VT was recognized in 2.29% of all patients with sarcoidosis versus 1.22% of control patients ( $P<0.001$ ). VF also was recognized significantly more frequently in patients with sarcoidosis: 0.25%

versus 0.21% ( $P < 0.001$ ). Prevalence of cardiac arrest in sarcoidosis patients was 0.72%.<sup>157</sup>

## Monomorphic VT

### Prevalence and Incidence

- Incidence of monomorphic VT in hospitalized patients with AMI decreased from 14.6% in 1986 to 1988 to 10.5% in 2009 to 2011.<sup>158</sup>
- Prevalence of sustained VT in patients with LV aneurysm after MI is reported at 10%.<sup>159</sup>
- Incidence of late (>48 hours) monomorphic VT after AMI in the GISSI-3 database was 1% by 6 weeks.<sup>160</sup> The presence of VT was associated with significantly increased total mortality attributed primarily to in-hospital pump failure and refractory VF.
- Monomorphic VT occurred in 9 of 342 patients (2.6%) at a median of 1 day (IQR, 0.25–4.75 days) after PCI for chronic total occlusion of a coronary artery.<sup>161</sup>
- 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.<sup>162</sup>

## Polymorphic VT/VF

### Prevalence and Incidence

- In the setting of AMI, the prevalence of polymorphic VT was 4.4%.<sup>163</sup>
- Incidence of VF in hospitalized patients with AMI decreased from 8.2% in 1986 to 1988 to 1.7% in 2009 to 2011.<sup>158</sup>

### Complications

- In the setting of AMI, polymorphic VT is associated with increased mortality (17.8%).<sup>163</sup>

## Torsade de Pointes

### Prevalence and Incidence

- Among 14 756 patients exposed to QT-prolonging drugs in 36 studies, 6.3% developed QT prolongation, and 0.33% developed TdP.<sup>164</sup>

### Risk Factors

- An up-to-date list of drugs with the potential to cause TdP is available at a website maintained by the University of Arizona Center for Education and Research on Therapeutics.<sup>165</sup>

## Awareness and Treatment

### (See Table 19-1)

- Median annual CPR training rate for US counties was 2.39% (25th–75th percentiles, 0.88%–5.31%)

according to training data from the AHA, the American Red Cross, and the Health & Safety Institute, the largest providers of CPR training in the United States.<sup>166</sup> 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.<sup>167</sup> 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,<sup>168</sup> 68% of citizens in Victoria, Australia,<sup>169</sup> 61.1% of laypeople in the United Kingdom,<sup>170</sup> and 49% of people in the Republic of Korea,<sup>171</sup> 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.<sup>172</sup>
- 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.<sup>170,171,173</sup> A total of 58% of Philadelphia respondents,<sup>173</sup> but only 2.1% of UK respondents,<sup>170</sup> 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.<sup>174</sup>
- 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.<sup>175</sup>
- Laypeople in the United States initiated CPR in 40.8% of OHCA in CARES 2020 data (Table 19-1).
- Layperson CPR rates in Asian countries range from 10.5% to 40.9%.<sup>176</sup>
- Layperson CPR among 4525 witnessed pediatric OHCA was 831 of 1669 (36.9%) for female patients versus 1336 of 2856 (46.8%) for male patients.<sup>177</sup>
- 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])<sup>178</sup> or in predominantly Hispanic neighborhoods (OR, 0.62 [95% CI, 0.44–0.89]) than in high-income White neighborhoods.<sup>179</sup>

- 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.<sup>180</sup>

## Mortality

### (See Tables 19-1, 19-3, and 19-5 and Chart 19-5)

- In 2019, primary-cause SCD mortality was 18 581, and any-mention SCD mortality in the United States was 370 494 (Table 19-5). The any-mention age-adjusted annual rate was 91.2 (95% CI, 90.9–91.5) SCDs per 100 000 population.<sup>181</sup>
- 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.<sup>7</sup>
- Survival after OHCA varied between US regions (4.2%–19.8%) in the ROC Epistry from 2011 to 2015.<sup>182</sup> 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.<sup>183</sup>
- Survival to hospital discharge after EMS-treated OHCA was 9.0% in the 2020 CARES registry, with variation between states reporting data (range, 4.6%–14.6%; Tables 19-1 and 19-3).
- 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.<sup>184</sup>
  - 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 19-5.

### OHCA: Adults

#### (See Tables 19-4 and 19-6)

- Survival to hospital discharge after EMS-treated OHCA was 9.0 % and survival to hospital discharge with good functional status was 7.0% on the basis of 124 088 adult cases in CARES for 2020 (Table 19-4).<sup>4</sup>
- Survival to hospital admission after EMS-treated nontraumatic OHCA in 2020 was 24.0% for all presentations, with higher survival rates in public places (36.5%) and lower survival rates in homes/residences (22.9%) and nursing homes (13.7%) in the 2020 CARES registry (Table 19-6).

- 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 154 177 patients hospitalized after OHCA in the NIS (2002–2013).<sup>185</sup>
- 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.<sup>186</sup>
- 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.<sup>24</sup>
- Survival to 30 days was lower for 2516 patients in nursing homes (1.7% [95% CI, 1.2%–2.2%]) than for 24 483 patients in private homes (4.9% [95% CI, 4.6%–5.2%]) in a national database in Denmark from 2001 to 2014.<sup>187</sup>
- Survival and neurological recovery after cardiac arrest are worse in White Hispanic, Black, and Asian patients compared to White patients.<sup>188</sup> The observed disparities were explained only in part by delays in onset of medical care. The findings suggest that people from underrepresented races may be more vulnerable than White people to adverse outcomes after cardiac arrest.
- Intraosseous administration of antiarrhythmic drugs during OHCA may be inferior to intravenous administration in a randomized trial of antiarrhythmic agents conducted by the ROC in patients with shock-refractory VF/VT.<sup>189,190</sup>
- Immediate coronary angiography versus standard of care in patients with OHCA and no STEMI was not associated with improved LV function in short-term measures, regardless of whether PCI was performed.<sup>191</sup> However, in a Korean prospective registry, high-risk patients who had early coronary angiography exhibited improved neurological function at 6 months, whereas low-risk patients showed no benefit.<sup>192</sup>
- Multiple methods have been examined to predict neurological recovery and overall survival early after resuscitation from OHCA. Several biomarkers, including higher levels of taurine<sup>193</sup> and neuron-specific enolase,<sup>194,195</sup> correlate with poorer outcomes.

### 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.<sup>43</sup>

### IHCA: Adults

#### (See Table 19-4 and Chart 19-7)

- Survival to hospital discharge was 22.4% of 33 874 adult patients with pulseless IHCA at 328 hospitals in GWTG 2020 data (Table 19-4 and Chart



19-7). Among survivors, 79.5% 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.<sup>196</sup>
- Unadjusted survival to 30 days after IHCA was 28.3% and survival to 1 year was 25.0% in 18 069 patients from 66 hospitals between 2006 and 2015 in the Swedish register of CPR.<sup>28</sup>
- 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 14 933 cases of IHCA from 2007 to 2014.<sup>197</sup>
- Mortality was lower among 348 368 patients with IHCA managed in teaching hospitals (55.3%) than among 376 035 managed in nonteaching hospitals (58.8%), even after adjustment for baseline patient and hospital characteristics (aOR, 0.92 [95% CI, 0.90–0.94]).<sup>198</sup>

### **OHCA: Children**

#### **(See Table 19-7)**

- 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 6.5% for 1366 children  $\leq 1$  year of age, 14.4% for 880 children 1 to 12 years of age, and 21.2% for 736 children 13 to 18 years of age in CARES 2020 data (Table 19-7).
- 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.<sup>199</sup>

### **IHCA: Children**

#### **(See Table 19-4)**

- Survival to hospital discharge after pulseless IHCA was 42.2% in 539 children 0 to 18 years of age and 28.9% in 160 neonates (0–30 days of age) per 2020 GWTG data (GWTG–Resuscitation, unpublished data, 2020; Table 19-4).
- 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.<sup>50</sup>

## **Complications**

### **(See Tables 19-6 and 19-7)**

- Survivors of cardiac arrest experience multiple medical problems related to critical illness, including

impaired consciousness and cognitive deficits (Tables 19-6 and 19-7).

- Functional impairments are associated with reduced function, reduced quality of life, and shortened life span.<sup>200,201</sup>
- 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.<sup>202,203</sup>
- 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.<sup>204</sup>
- 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%).<sup>205</sup> Subjective symptoms declined over time after SCA, although 10% to 22% had cognitive impairments at 12 months, with executive functioning being most affected.<sup>206</sup>
- Of 141 individuals who survived hospitalization after SCA, 41 (72%) returned to work by 12 months.<sup>205</sup>
- 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.<sup>207</sup>
- 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 of 714 days (SD, 1013 days).<sup>208</sup> 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.<sup>209</sup> 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.<sup>210</sup>
- Among 7321 patients with OHCA in Taiwan who survived to ICU admission, 281 (3.84%) had new-onset HF.<sup>211</sup> 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%]).<sup>212</sup> 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).<sup>213</sup>

### 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 the use of EMS affect results.<sup>214</sup>

- 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.<sup>215</sup> 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, reported SCD incidences of 37.94 and 36.2 per 100 000 for Han and Kazakh people, respectively.<sup>216</sup> 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.<sup>217</sup>
- Among 353 adults after IHCA in 6 Kenyan hospitals in 2014 to 2016, 16 (4.2%) survived to hospital discharge.<sup>218</sup>

**Table 19-1. Trends in Layperson Response and Outcomes for EMS-Treated OHCA, 2006 to 2020**

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
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	9.0
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	25.6
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	16.7
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	40.0	41.6	40.8
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	6.4	6.5	5.8
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	1.3

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.

\*Layperson-initiated CPR includes all locations and 9-1-1 responder-witnessed events.

†Layperson use of AED includes all locations and 9-1-1 responder-witnessed events.

Source: Data reported by ROC (ROC Investigators, unpublished data, July 7, 2016) and CARES.<sup>4</sup>

**Table 19-2. Differences in Bystander Interventions and Survival After OHCA, by Race, Ethnicity, and Sex, CARES, United States, 2020**

	Nontraumatic pathogenesis survival rates	Bystander intervention rates	
	Overall survival to hospital discharge	CPR	Public AED use
Total	11 419/127 376 (9.0%)	38 047/94 701 (40.2%)	1185/13 207 (9.0%)
American Indian/Alaska Native	48/503 (9.5%)	158/392 (40.3%)	7/68 (10.3%)
Asian	223/2916 (7.6%)	944/2271 (41.6%)	26/266 (9.8%)
Black/African American	2155/29 572 (7.3%)	6906/20 851 (33.1%)	203/2688(7.6%)
Hispanic/Latino	780/10 229 (7.6%)	3048/7970 (38.2%)	85/1123 (7.6%)
Native Hawaiian/Pacific Islander	58/583 (9.9%)	210/454 (46.3%)	8/72 (11.1%)
White	6402/64 947 (9.9%)	20 413/48 336 (42.2%)	660/6883 (9.6%)
Unknown	1753/18 626 (9.4%)	6368/14 427 (44.1%)	196/2107 (9.3%)
Male	7416/79 109 (9.4%)	24 598/60 703 (40.5%)	973/10 336 (9.4%)
American Indian/Alaska Native	22/276 (8.0%)	85/221 (38.5%)	4/44 (9.1%)
Asian	168/1845 (9.1%)	595/1465 (40.6%)	23/214 (10.7%)
Black/African American	1178/16 505 (7.1%)	3917/11 935 (32.8%)	162/2003 (8.1%)
Hispanic/Latino	539/6889 (7.8%)	2088/5500 (38.0%)	77/942 (8.2%)
Native Hawaiian/Pacific Islander	39/380 (10.3%)	134/292 (45.9%)	4/56 (7.1%)
White	4278/41 353 (10.3%)	13 583/31 863 (42.6%)	537/5391 (10.0%)
Unknown	1192/11 861 (10.0%)	4196/9427 (44.5%)	166/1686 (9.8%)
Female	4003/48 256 (8.3%)	13 443/33 987 (39.6%)	212/2870 (7.4%)
American Indian/Alaska Native	26/227 (11.5%)	73/171 (42.7%)	3/24 (12.5%)
Asian	55/1070 (5.1%)	348/805 (43.2%)	3/52 (5.8%)
Black/African American	977/13 065 (7.5%)	2987/8914 (33.5%)	41/685 (6.0%)
Hispanic/Latino	241/3339 (7.2%)	960/2469 (38.9%)	8/181 (4.4%)
Native Hawaiian/Pacific Islander	19/203 (9.4%)	76/162 (46.9%)	4/16 (25.0%)
White	2124/23 592 (9.0%)	6829/16 471 (41.5%)	123/1492 (8.2%)
Unknown	561/6760 (8.3%)	2170/4995 (43.4%)	30/420 (7.1%)

Bystander CPR rate excludes 9-1-1 responder–witnessed, nursing home, and health care facility arrests. Public AED use rate excludes 9-1-1 responder–witnessed, home/residence, nursing home, and health care facility arrests. Sex missing for 11 cases.

AED indicates automated external defibrillator, CARES, Cardiac Arrest Registry to Enhance Survival; CPR, cardiopulmonary resuscitation; and OHCA, out-of-hospital cardiac arrest.

Source: Data derived from CARES.<sup>4</sup>

**Table 19-3. Variation in EMS-Treated OHCA in Selected States, 2020**

	OHCA incidence			Nontraumatic pathogenesis survival rates		Bystander intervention rates	
	EMS-treated OHCA cases	Percent of population reporting data	Rate per 100 000 people	Overall survival to hospital discharge, %	Survival to hospital discharge if witnessed collapse and shockable rhythm, %	Layperson-initiated CPR, %	Public use of AED, %
United States	127 376	43.7	88.8	9.0	29.2	40.2	9.0
Alaska	474	82.9	78.2	10.1	27.0	72.0	9.7
California	19 908	61.0	82.6	7.9	29.1	41.8	7.6
Colorado	3347	92.0	63.1	13.1	33.2	40.1	7.0
Connecticut	1817	61.2	83.3	6.5	25.4	25.8	3.6
Delaware	1271	100.0	130.5	9.9	34.2	34.8	6.4
Hawaii	1296	100.0	91.5	9.4	29.4	45.2	5.2
Michigan	9290	84.2	110.4	7.1	27.4	36.2	8.3
Minnesota	3063	81.0	67.1	12.4	32.4	37.0	9.4
Mississippi	2306	78.4	98.9	6.2	24.7	42.4	7.9
Montana	571	85.5	62.5	10.2	31.9	49.6	6.3
Nebraska	694	52.8	67.9	14.6	33.1	49.1	16.3
North Carolina	7346	75.5	92.8	11.5	29.4	42.9	9.5
Oregon	2677	93.1	68.1	12.4	29.4	56.0	13.5
Pennsylvania	8516	72.3	92.0	8.0	22.8	35.8	10.3
Utah	1417	100.0	44.2	9.7	34.5	35.6	9.5
Vermont	517	100.0	82.9	10.3	24.2	53.8	6.2
Washington	4792	96.3	65.3	13.7	37.9	56.3	10.9
District of Columbia	956	100	135.5	4.6	31.7	28.0	5.3

Criteria for reporting: at least 50% population catchment in state; voluntarily reporting data. Utstein: witnessed by bystander and found in shockable rhythm. Bystander CPR rate excludes 9-1-1 responder-witnessed, nursing home, and health care facility arrests.

Public AED use rate excludes 9-1-1 responder-witnessed, home/residence, nursing home, and health care facility arrests.

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 2020 data from states with  $\geq 50\%$  population reporting data and voluntarily sharing data.<sup>4</sup>



**Table 19-4. Characteristics of and Outcomes for OHCA and IHCA, 2020**

	OHCA*		IHCA	
	Adults	Children†	Adults	Children
Survival to hospital discharge	9.0	12.5	23.3	42.6
Good functional status at hospital discharge	7.0	10.7	...	...
VF/VT/shockable	16.7	7.3	13.7	9.8
PEA	22.3	14.3	54.0	51.3
Asystole	52.9	68.1	24.3	28.5
Unknown	...	...	8.0	10.4
Public setting	15.1	12.2	...	...
Home	73.9	87.5	...	...
Nursing home	10.9	0.3	...	...
Arrest in ICU, operating room, or ED	...	...	56.2	86.6
Noncritical care area	...	...	43.8	13.4

Values are percentages.

CARES indicates Cardiac Arrest Registry to Enhance Survival; ED, emergency department; ellipses (...), data not available; EMS, emergency medical services; 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.

\*Inclusion criteria: An out-of-hospital cardiac arrest for which resuscitation is attempted by a 9-1-1 responder (CPR or defibrillation). This would also include patients who received an automated external defibrillator shock by a bystander before the arrival of 9-1-1 responders. Analysis excludes patients with missing hospital outcome (n=196).

†Stillborn neonates and perinatal newborns born without signs of life are not CARES cases and are not entered into the registry.

Source: OHCA data derived from CARES<sup>4</sup> and are based on 124 088 EMS-treated OHCA adult cases and 2982 EMS-treated OHCA child cases in 2020. IHCA data are from Get With The Guidelines (unpublished AHA tabulation) 2020 and are based on 33 874 pulseless adult IHCAs in 328 hospitals and 539 pulseless child IHCAs in 80 hospitals.

**Table 19-5. SCA Mortality, 2019 (ICD-10 I46.0, I46.1, I46.9, I49.0)**

Population group	No. of deaths as underlying cause, 2019, all ages	No. of deaths as any-mention cause, 2019, all ages
Both sexes	18 581	370 494
Males	10 130	193 922
Females	8451	176 572
NH White males	7610	137 889
NH White females	6263	123 771
NH Black males	1769	27 020
NH Black females	1614	26 845
Hispanic males	457	19 218
Hispanic females	365	17 050
NH Asian/Pacific Islander males	228	7899
NH Asian/Pacific Islander females	163	7333
NH American Indian/Alaska Native	84	2381

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.<sup>181</sup>

**Table 19-6. Outcomes of EMS-Treated Nontraumatic OHCA in Adults (>18 Years of Age), CARES, 2020**

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 (124 088)	24.0	9.0	7.0	62.9
Home/residence (91 754)	22.9	7.7	6.1	66.2
Nursing home (13 566)	13.7	3.7	1.6	73.1
Public setting (18 766)	36.5	18.2	15.7	50.0
Unwitnessed (61 637)	15.3	4.1	3.0	73.5
Bystander witnessed (46 325)	31.2	13.1	10.6	57.9
9-1-1 responder witnessed (16 120)	36.2	15.2	12.1	58.1
Shockable presenting rhythm (20 684)	43.4	25.6	22.6	40.9
Nonshockable presenting rhythm (103 392)	20.1	5.5	3.9	72.4
Layperson CPR (36 635)	25.8	11.0	9.5	57.3
No layperson CPR (55 047)	21.2	6.5	4.9	69.1

Values are percentages.

Inclusion criteria: An out-of-hospital cardiac arrest for which resuscitation is attempted by a 9-1-1 responder (CPR or defibrillation). This would also include patients who received an automated external defibrillator shock by a bystander before the arrival of 9-1-1 responders. Analysis excludes patients with missing hospital outcome (n=174).

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 124 088 adults in CARES.<sup>4</sup>

**Table 19-7. Outcomes of EMS-Treated Nontraumatic OHCA in Children, CARES, 2020**

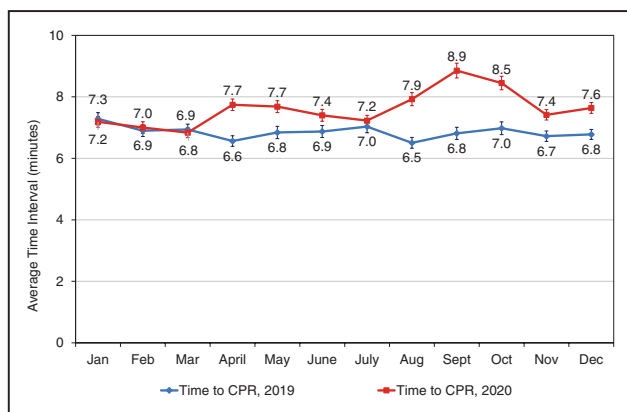
Age group (n)	Survival to hospital admission	Survival to hospital discharge	Survival with good neurological function (CPC 1 or 2)	In-hospital mortality*
<1 y (1366)	16.9	6.5	5.7	61.5
1–12 y (880)	36.7	14.4	11.6	60.7
13–18 y (736)	39.3	21.2	18.8	46.0

Values are percentages.  
 Inclusion criteria: An out-of-hospital cardiac arrest for which resuscitation is attempted by a 9-1-1 responder (CPR and/ or defibrillation). This would also include patients that received an AED shock by a bystander before the arrival of 9-1-1 responders. Analysis excludes patients with missing hospital outcome (n=17). Stillborn neonates and perinatal newborns born without signs of life are not CARES cases and are not entered into the registry.

CARES indicates Cardiac Arrest Registry to Enhance Survival; CPC, Cerebral Performance Category; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; and OHCA, out-of-hospital cardiac arrest.

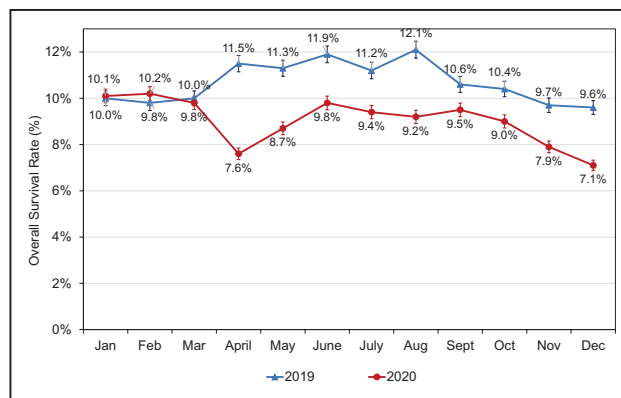
\*Percentage of patients admitted to hospital who died before hospital discharge.

Source: Data derived from CARES.<sup>4</sup>



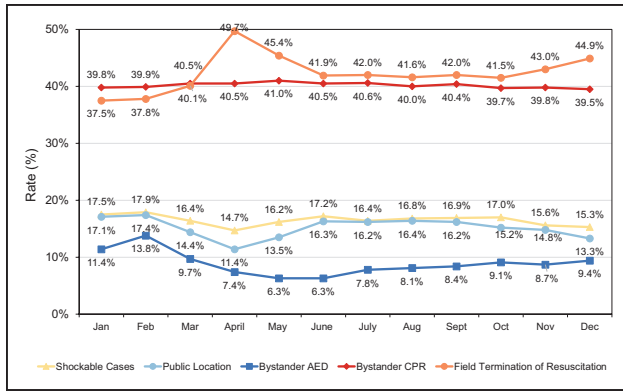
**Chart 19-1. Time to CPR, by month for OHCA, 2019 to 2020, CARES, United States.**

Bystander CPR rate excludes 9-1-1 responder-witnessed, nursing home, and health care facility arrests. Public AED use rate excludes 9-1-1 responder-witnessed, home/residence, nursing home, and health care facility arrests.  
 AED indicates automated external defibrillator; CARES, Cardiac Arrest Registry to Enhance Survival; CPR, cardiopulmonary resuscitation; and OHCA, out-of-hospital cardiac arrest. Source: Data derived from CARES.<sup>4</sup>



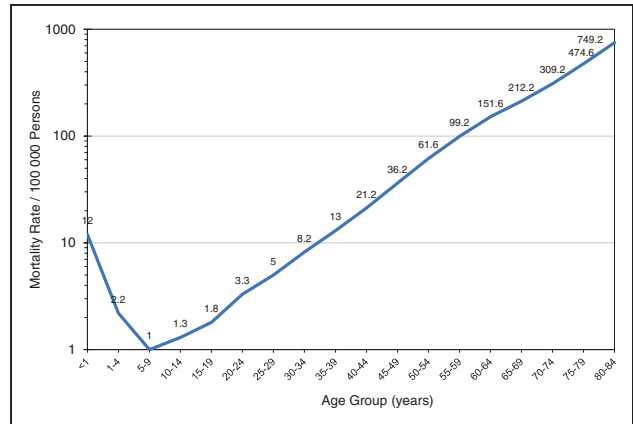
**Chart 19-2. Overall OHCA survival, by month, 2019 to 2020, CARES, United States.**

CARES indicates Cardiac Arrest Registry to Enhance Survival; and OHCA, out-of-hospital cardiac arrest. Source: Data derived from CARES.<sup>4</sup>



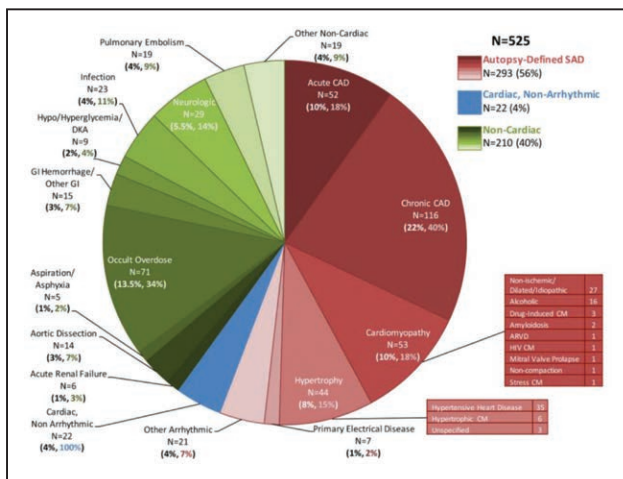
**Chart 19-3. OHCA, by month, 2020, CARES, United States.**

Bystander CPR rate excludes 9-1-1 responder-witnessed, nursing home, and health care facility arrests. Public AED use rate excludes 9-1-1 responder-witnessed, home/residence, nursing home, and health care facility arrests. Shockable rhythm includes VF, VT, or unknown shockable. AED indicates automated external defibrillator; CARES, Cardiac Arrest Registry to Enhance Survival; CPR, cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; VF, ventricular fibrillation; and VT, ventricular tachycardia. Source: Data derived from CARES.<sup>4</sup>



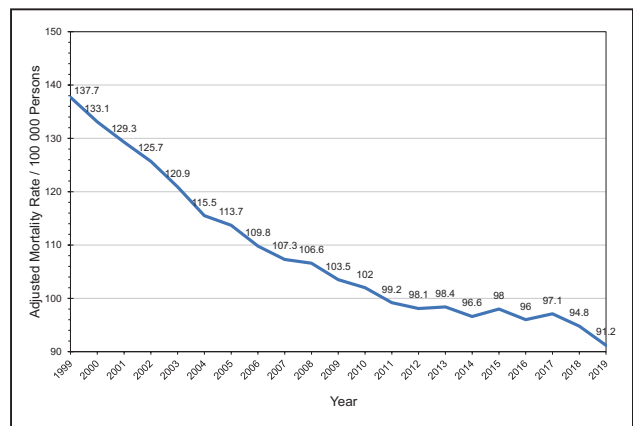
**Chart 19-5. Age-specific mortality rates for any mention of SCD, by age, United States, 2019.**

SCD indicates sudden cardiac death. Source: Data derived from Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research database.<sup>181</sup>



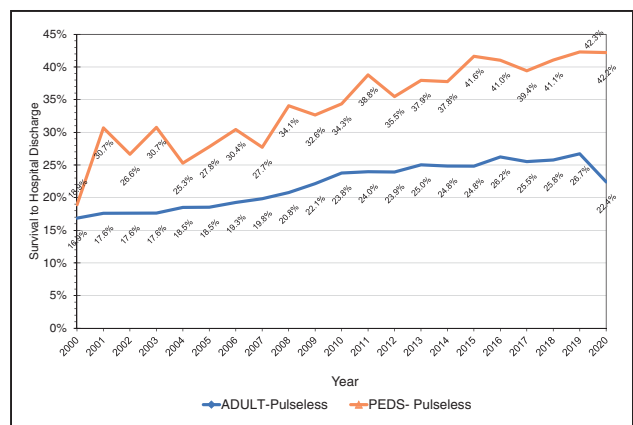
**Chart 19-4. Adjudicated causes of autopsied WHO-defined SCDs.**

Adjudicated causes of autopsied WHO-defined SCDs after review of comprehensive medical records, EMS records, complete autopsy, toxicology, and postmortem chemistries. Autopsy-defined SADs had no identifiable extracardiac (eg, pulmonary embolism, hemorrhage, lethal toxicology) or nonarrhythmic (tamponade, acute HF) cause of death. The first percent is of total WHO-defined SCDs; the second percent is of cause of death category. Overall, autopsy-defined SADs accounted for 56% of all WHO-defined SCDs, 4% were cardiac nonarrhythmic cause of death, and 40% were noncardiac cause of death. ARVD indicates arrhythmogenic right ventricular dysplasia; CAD, coronary artery disease; CM, cardiomyopathy; DKA, diabetic ketoacidosis; EMS, emergency medical service; GI, gastrointestinal; HF, heart failure; HIV, human immunodeficiency virus; SAD, sudden arrhythmic death; SCD, sudden cardiac death; and WHO, World Health Organization. Source: Adapted with permission from Tseng et al.<sup>39</sup> ©2018 American Heart Association, Inc.



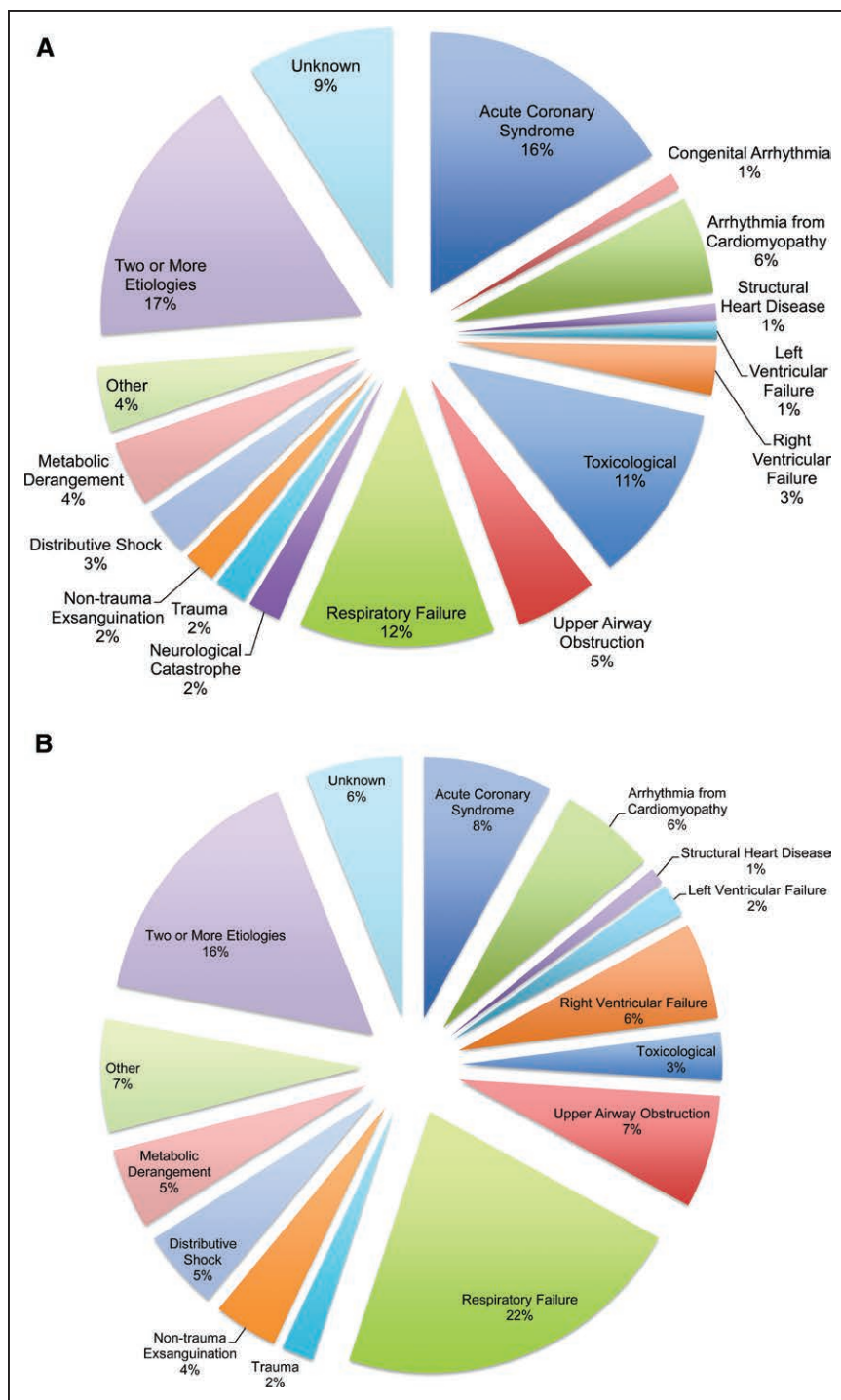
**Chart 19-6. Age-adjusted mortality rates for any mention of SCD, United States, 1999 to 2019.**

SCD indicates sudden cardiac death. Source: Data derived from Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>181</sup>



**Chart 19-7. Temporal trends in survival to hospital discharge after IHCA in adults and children in GWTG-Resuscitation from 2000 to 2020, United States.**

GW TG indicates Get With The Guidelines; IHCA, in-hospital cardiac arrest; and PEDS, pediatrics. Source: GW TG-Resuscitation; unpublished American Heart Association data.



**Chart 19-8. Detailed causes of OHCA and IHCA 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. IHCA indicates in-hospital cardiac arrest; and OHCA, out-of-hospital cardiac arrest. Source: Data derived from Chen et al.<sup>59</sup>

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## 20. SUBCLINICAL ATHEROSCLEROSIS

See Charts 20-1 through 20-4

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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, antihypertensives, lipid-lowering therapy) to prevent clinical manifestations of atherosclerosis such as MI, stroke, or PAD. Several modalities can be used for imaging atherosclerosis, including chest CT 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<sup>1</sup> and the 2019 CVD Primary Prevention Clinical Practice Guidelines,<sup>2</sup> 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, it is reasonable to use a CAC score in the decision to withhold, postpone, or initiate statin therapy.

### 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 20-1 through 20-3)

- 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).<sup>3</sup>

The 2022 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 2022. 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.

- 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.
- Chart 20-1 shows the prevalence of CAC by ethnicity and sex in adults 33 to 45 years of age. The prevalence of CAC was lower in Black versus White males but was similar in Black versus White females at these ages.
- 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.<sup>4</sup>
  - 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 a CAC prevalence that was 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.<sup>5</sup>
  - Overall, in the population (mean age, 58 years; 50% females), 85% of individuals were free of any CAC, and even in individuals >75 years of age, 65% remained free of CAC. These unique data indicate that coronary atherosclerosis typically can be avoided by maintaining a low lifetime burden of CAD risk factors.<sup>5</sup>
- In US adults who are free of CAC at baseline, subsequent development of CAC is common. In 3116 MESA participants (58±9 years of age; 63% females) who had no detectable CAC at baseline and were followed up over 10 years, 53%, 36%, and 8% of individuals had CAC >0, CAC >10, and CAC >100, respectively, at 10 years.<sup>6</sup> A rescanning interval of 3 to 7 years was suggested on the basis of age, sex, race and ethnicity, and diabetes.
- 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.<sup>7</sup>
  - 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 lipoprotein(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 PR of 1.59 (95% CI, 1.38–1.84).<sup>8</sup>
  - 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]).<sup>9</sup>
  - In 937 apparently healthy asymptomatic family members of individuals with premature ASCVD, high lipoprotein(a) levels were associated with CAC  $\geq$ 100 (OR, 1.79 [95% CI, 1.13–2.83]).<sup>10</sup>
  - In 140 patients with a CAC score of 1 to 999 who were treated with pitavastatin with or 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];  $P=0.04$ ).<sup>11</sup>
- The 10-year trends in CAC among individuals without clinical CVD in MESA were assessed (Chart 20-2).
  - The mean age at the baseline examination was 67 years; 47.4% were male. Detectable CAC was evaluated in White, Black, Hispanic, and Chinese participants, with  $>50\%$  prevalence at baseline.
  - Ten-year trends in CAC prevalence among the 4 racial and ethnic groups revealed a significant trend toward increased prevalence of CAC in Black participants but not in any other group (Chart 20-2). Among Black participants, the CAC PR (year 10 versus baseline) was 1.27 ( $P<0.001$  for test for trend).<sup>12</sup>
  - CAC severity was also evaluated at baseline and 10 years (Chart 20-3). 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  $\geq$ 400 decreased from 9.1% to 7.2% ( $P=0.11$ ).

### CAC and Incidence of ASCVD Events (CHD and Stroke)

#### (See Chart 20-4)

- CAC is associated with incident ASCVD events. When machine learning was used to assess predictors of cardiovascular events, CAC emerged as the strongest predictor of CHD and ASCVD events among 735 variables from imaging and noninvasive tests, questionnaires, and biomarker panels.<sup>13</sup>
- 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).<sup>14</sup>

- Chart 20-4 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  $\approx 4$  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).
- A very high CAC score  $\geq 1000$  is associated with a MACE rate of 3.4 per 100 person-years, which is similar to that in a stable secondary prevention population.<sup>15</sup> After adjustment for age, sex, and traditional cardiovascular risk factors, individuals with CAC  $\geq 1000$  had a 5-fold greater risk of CVD mortality compared with those with CAC=0.<sup>16</sup>
- 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.<sup>17</sup>
  - 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 1–99, 0.41%/y for CAC 100–399, and 0.70%/y for CAC  $\geq 400$ ).

### CAC and Incidence of HF, AF, and Noncardiovascular Outcomes

- 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]).<sup>18</sup>
- 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]).<sup>19</sup> The addition of CAC to a risk score yielded relative integrated discrimination improvement of 0.10 (95% CI, 0.061–0.15).
- Higher CAC burden has been associated with noncardiovascular outcomes.<sup>20</sup>
  - 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.

- In a study with a mean of 12.3 years of follow-up, cancer-related mortality was 1.55-fold higher in individuals who had CAC $\geq$ 1000 at baseline compared with those who had CAC=0 at baseline after adjustment for age, sex, and risk factors.<sup>16</sup>

### CAC Progression and Risk

- In MESA, 6778 participants showed annual CAC progression averaging 25 $\pm$ 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.<sup>21</sup>
- 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.<sup>22</sup>

### 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.<sup>23</sup>
- Schmidt et al<sup>24</sup> 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, 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%;  $P=1.8\times 10^{-7}$ ) 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.

## 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  $\geq$ 1 mm. Carotid ultrasound also can 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.<sup>2</sup>

### Risk Factors

- In a meta-analysis of 7645 individuals, carotid IMT increased from 723 $\pm$ 39  $\mu$ m in participants with normal BP to 779 $\pm$ 45  $\mu$ m in those with prehypertension and 858 $\pm$ 82  $\mu$ m in individuals with hypertension.<sup>25</sup>
- The association of inflammatory/immune response in atherosclerosis is highlighted by the association of granulocyte count with higher arterial calcification volume and risk of atherosclerotic CVD in a large population of elderly individuals.<sup>26</sup>
- Adverse risk factors in early childhood and young adulthood are implicated in the early development of atherosclerosis. In the Bogalusa Heart Study (mean age, 32 $\pm$ 3 years), carotid IMT was associated significantly and positively with WC, SBP, DBP, and LDL-C and 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.<sup>27</sup> 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.<sup>25</sup> Higher SBP and LDL-C and lower HDL-C in young adulthood also were associated with high carotid IMT. A large Finnish cohort study showed similar findings.<sup>28</sup>
- In 9388 US and Finnish individuals with longitudinal measurement of CVD risk factors and carotid IMT, CVH declined from childhood to adulthood and was associated with IMT thickening.<sup>29</sup>
- 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.<sup>30</sup>
- Two large, population-based prospective studies demonstrated the shared pathogenesis of atherosclerosis<sup>31,32</sup>:
  - In 1243 FHS participants (57 $\pm$ 9 years of age; 53% females), carotid stenosis  $\geq$ 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.<sup>31</sup>
  - 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 ( $\geq$ 0.81 mm) versus first quartile ( $<$ 0.62) was significantly associated with ESRD.<sup>32</sup>
- Sleep patterns and duration, which are associated with CVD, are associated with subclinical

atherosclerosis.<sup>33</sup> 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.<sup>33</sup>

- Sex and race differences have been demonstrated in carotid IMT. In 518 healthy Black and White males and females in the Bogalusa Heart Study, 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.<sup>27</sup> In MESA, Black people had the thickest carotid IMT (particularly common carotid) of all 4 ethnic groups, regardless of the presence of CAC.<sup>34</sup> Chinese participants had the lowest carotid IMT, in particular in the internal carotid, of the 4 ethnic groups. Common IMT and internal carotid IMT were greater in females and males who had CAC than in those who did not, regardless of ethnicity.

### Social Determinants of Carotid IMT and Vascular Disease

- The IMPROVE study of 3703 European people assessed 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.<sup>35</sup>
- In the biracial HANDLS study of 2270 adults, interaction analyses demonstrated a race×SES effect whereby individuals self-identified as Black race with high (rather than low) SES had higher carotid IMT and aortic stiffness than other groups, suggesting a group with greater subclinical CVD.<sup>36</sup>
- 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.<sup>37</sup>
- Although exposure to air pollution is associated with CVD, low levels of exposure were not associated with carotid IMT after adjustment for CVD risk factors and SES in 6103 participants in the Malmo Diet and Cancer study.<sup>38</sup>

### Risk Prediction

- A study from 3 population-based cohorts (ARIC, N=13907; 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.<sup>39</sup> 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.

- Carotid IMT has been associated with incident CVD in multiple large cohorts. In MESA, 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.<sup>40</sup> In MESA<sup>40</sup> and CHS participants,<sup>41</sup> the upper quartile and quintile, respectively, were associated with 2- to 3-fold increased risks for CVD, including MI and stroke. Among >13000 participants in ARIC, carotid IMT was associated with incident HF<sup>42</sup> and CHD and with carotid plaque was able to improve risk reclassification (0.742–0.755 [95% CI for difference in adjusted AUC, 0.008–0.017]).<sup>43</sup>
- 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 45828 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%).<sup>44</sup>
- The ability of carotid IMT to predict incident CVD events also might depend on data modeling or ultrasound sensitivity. 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%.<sup>45</sup>
- In the BiImage Study of 5808 asymptomatic US adults (mean age, 69 years; 56.5% females), increasing 3-dimensional carotid ultrasound plaque burden tertile was associated with an ≈2-fold risk for MACEs (cardiovascular death, MI, and ischemic stroke), and net reclassification improved significantly with carotid plaque burden (0.23).<sup>46</sup>

### 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).<sup>47</sup>
  - 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  $\geq$ 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.<sup>48</sup>
- 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.<sup>2,49–51</sup> 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.<sup>52</sup>
- In 4184 young to middle-aged asymptomatic individuals in the PESA cohort in whom carotid ultrasound and CAC were performed, elastic net machine-learning models identified a score based on age, HbA1c, TC/HDL, leukocyte volume, and hemoglobin predicting prevalent and progression of subclinical atherosclerosis and CVD risk.<sup>53</sup> This score was externally validated in the AWHs of similarly aged males.

## Genetics and 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.<sup>54–57</sup> 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.<sup>58</sup> 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  $\approx 160\,000$  individuals, suggesting a causal role between genetic predisposition to type 2 diabetes and ASCVD.<sup>59</sup>

- Combination of GWAS and proteomics has identified novel biomarkers of subclinical atherosclerosis, including circulating C-type lectin domain family 1 member B and platelet-derived growth factor receptor- $\beta$ .<sup>60</sup>

## Treatment: Healthy Lifestyle and Preventive Medications

- Optimal lifestyle habits in youth and adulthood are associated with lower subclinical atherosclerosis:
  - In overweight and obese children 6 to 13 years of age, greater nut consumption was independently associated with lower carotid IMT ( $\beta=0.135$  mm;  $P=0.009$ ).<sup>61</sup>
  - In a cohort of older females, a diet high in vegetables, particularly cruciferous vegetables, was associated with lower carotid IMT.<sup>62</sup> Consuming  $\geq 3$  servings of vegetables each day was associated with a  $\approx 5\%$  lower amount of carotid atherosclerosis compared with consuming <2 servings of vegetables.
  - In SWAN, healthier lifestyle, including self-reported abstinence from smoking, healthy diet, and PA, in females during midlife was associated with lower carotid IMT.<sup>63</sup> 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.<sup>64</sup>
- 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.
  - CAC identifies those most likely to benefit from statin treatment across the spectrum of risk profiles with an appropriate  $NNT_5$ : The estimated  $NNT_5$  for preventing 1 CVD event across dyslipidemia categories in the MESA cohort ranged from 23 to 30 in those with  $CAC \geq 100$ .<sup>65</sup> 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.<sup>66</sup>
  - Similarly, CAC testing has identified individuals who might derive the highest net benefit with aspirin therapy: In MESA, aspirin-naive participants <70 years of age who were not high risk for bleeding ( $n=3540$ ),  $CAC \geq 100$  and  $CAC \geq 400$  identified individuals with an  $NNT_5$  lower than the number needed to harm (for  $CAC \geq 100$ ,  $NNT_5=140$  versus  $NNH_5=518$ ).<sup>67</sup> In individuals



with CAC=0, the NNT<sub>5</sub> of 1 190 was much higher than the NNH<sub>5</sub> of 567. Similarly, in the Dallas Heart Study, among individuals at lower bleeding risk, CAC≥100 identified individuals who would tend to have net benefit, but only if 10-year ASCVD risk was ≥5%.<sup>68</sup> In individuals at higher bleeding risk, net harm from aspirin was observed regardless of CAC and ASCVD risk.

## 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.<sup>69</sup> 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.<sup>51</sup>

### Arterial Stiffness and CVD

- Arterial stiffness defined as pulse pressure ≥60 mm Hg conferred a 27% greater odds of in-hospital mortality after multivariable adjustment for comorbidities among 12 170 patients hospitalized with severe acute respiratory syndrome coronavirus 2 in the SEMI-COVID-19 network in Spain.<sup>70</sup>
- The association of arterial stiffness measured by PWV with CHD was assessed in the Rotterdam Study of 2835 elderly participants (mean age, 71 years).<sup>71</sup> 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%.<sup>72</sup>
- 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%;  $P<0.05$ ).<sup>73</sup>
- An analysis from the JHS suggested that peripheral arterial tonometry is associated with LVH.<sup>74</sup> In 440 Black participants (mean age, 59±10 years; 60% females) with peripheral arterial tonometry and

cardiac MRI evaluations, 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.<sup>75</sup>
  - In the ARIC–Neurocognitive and ARIC–PET studies, 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.<sup>76</sup>
  - 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 AD.<sup>77–81</sup>

### FMD and CVD

- In a meta-analysis of 13 studies involving 11 516 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.<sup>82</sup>

### Comparison of Measures of Subclinical Atherosclerosis

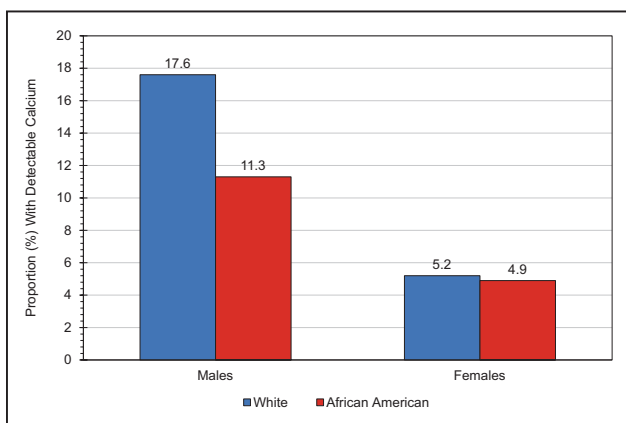
- A multimodal and multiterritorial approach to imaging of subclinical atherosclerosis in the PESA study showed that short-term (3-year) atherosclerosis progression is common (41.5%) in apparently healthy middle-aged males and females, as identified by peripheral 2-dimensional (26.4%) and 3-dimensional (21.3%) vascular ultrasound and CAC (11.5%).<sup>83</sup>
- CAC provides a particularly strong prognostic value in predicting CHD and CVD events among markers of subclinical atherosclerosis:
  - 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—was compared.<sup>84</sup> After 7.6 years of follow-up, CAC, ABI, high-sensitivity CRP, and family history were independently associated with incident CHD (HR, 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).

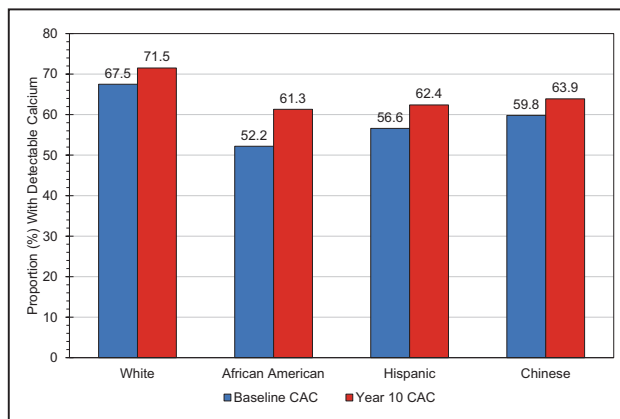
- Similar findings also were noted in the Rotterdam Study, in which, among 12 CHD risk markers, improvements in FRS predictions were most statistically and clinically significant with the addition of CAC scores.<sup>85</sup>
- In addition, in MESA, the values of 12 negative markers were compared for all and hard CHD and for all CVD events over the 10-year follow-up.<sup>86</sup> 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).

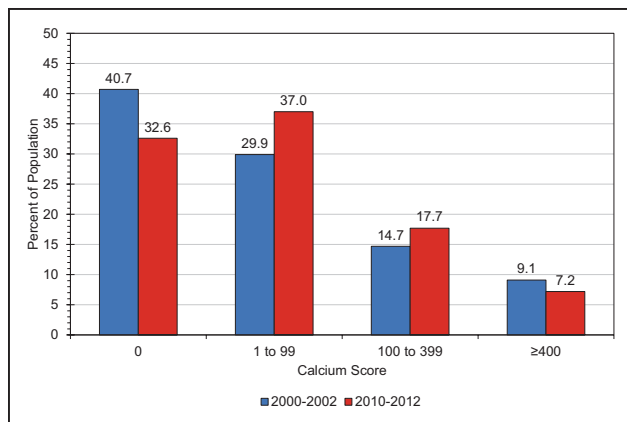
- The Pooled Cohort ASCVD Risk Estimator was compared with the FRS for prediction of subclinical atherosclerosis measured by carotid IMT and vascular dysfunction measured by carotid femoral PWV, central pulse pressure, and augmentation index in a cohort of 1231 individuals free of prevalent CVD.<sup>87</sup> 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 20-1. Prevalence (percent) of detectable CAC in the CARDIA study: US adults 33 to 45 years of age (2000–2001).** *P*<0.0001 across race-sex groups. CAC indicates coronary artery calcification; and CARDIA, Coronary Artery Risk Development in Young Adults. Source: Data derived from Loria et al.<sup>3</sup>



**Chart 20-2. 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.<sup>4,12</sup>

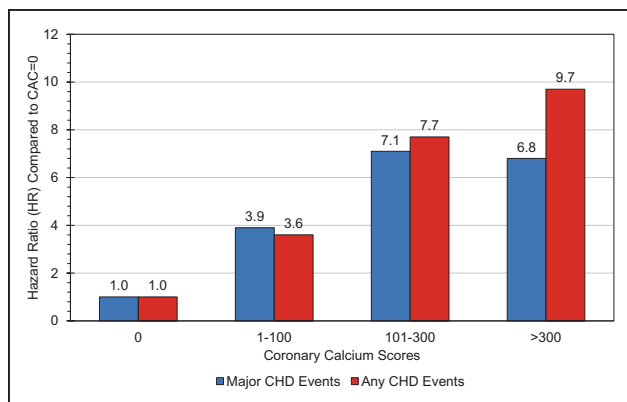


**Chart 20-3. Ten-year trends in severity of CAC in US individuals without clinical cardiovascular disease in MESA, baseline examination 2000 to 2002.**

Data adjusted to the average baseline age (67 years), sex (47% male), race and ethnicity (39% White, 28% Black, 21% Hispanic, and 12% Chinese), and scanner (electron-beam computed tomography vs other).

CAC indicates coronary artery calcification; and MESA, Multi-Ethnic Study of Atherosclerosis.

Source: Adapted from Bild et al.<sup>12</sup>



**Chart 20-4. 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.<sup>14</sup>

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## 21. CORONARY HEART DISEASE, ACUTE CORONARY SYNDROME, AND ANGINA PECTORIS

See Tables 21-1 through 21-3 and Charts 21-1 through 21-11

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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 21-1 and 21-2 and Charts 21-1 through 21-4)

- On the basis of data from NHANES 2015 to 2018,<sup>1</sup> an estimated 20.1 million Americans  $\geq 20$  years of age have CHD (Table 21-1). The prevalence of CHD was higher for males than females  $\geq 60$  years of age (Chart 21-1).
- Total CHD prevalence is 7.2% in US adults  $\geq 20$  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 21-1.
- 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  $\geq 18$  years of age.<sup>2</sup>
- According to data from NHANES 2015 to 2018 (unpublished NHLBI tabulation),<sup>1</sup> the overall prevalence for MI is 3.1% in US adults  $\geq 20$  years of age. Males have a higher prevalence of MI than females for all age groups except 20 to 39 years of age (Chart 21-2). MI prevalence is 4.3% for males and 2.1% for females. MI prevalence by sex and ethnicity is shown in Table 21-1.
- According to data from NHANES 2015 to 2018,<sup>1</sup> the overall prevalence of angina is 4.1% in US adults  $\geq 20$  years of age (Table 21-2).
- Data from the BRFSS 2019 survey indicated that 4.3% of respondents had been told that they

had had an MI. The highest prevalence was in West Virginia (6.6%), and the lowest was in the Colorado (2.5%) and Connecticut (2.5%; age adjusted; Chart 21-3).<sup>3</sup>

- In the same survey, in 2019, 3.9% of respondents had been told that they had angina or CHD. The highest prevalence was in Puerto Rico (6.6%) and West Virginia (6.2%), and the lowest was in Alaska (2.1%; age adjusted; Chart 21-4).<sup>3</sup>

#### Incidence

(See Charts 21-5 through 21-7)

- Approximately every 40 seconds, an American will have an MI (AHA computation based on incidence data from the ARIC study of the NHLBI<sup>4</sup>).
- On the basis of data tabulated by the NHLBI from the 2005 to 2014 ARIC study<sup>4</sup>:
  - Approximately 720 000 Americans will have a new coronary event (defined as first hospitalized MI or CHD death), and  $\approx 335$  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 21-5. Incidence of heart attacks or fatal CHD stratified by age, race, and sex is displayed in Chart 21-6.
- Incidence of MI by age, sex, and race in the NHLBI-sponsored ARIC study is displayed in Chart 21-7. Black males have a higher incidence of MI in all age groups.
- After adjustment for social determinants of health and cardiovascular risk factors, Black males and females have similar risk for fatal CHD (ARIC, 0.67 [95% CI, 0.36–1.24]; REGARDS, 1.00 [95% CI, 0.54–1.85]) but lower risk for nonfatal CHD (ARIC, 0.70 [95% CI, 0.51–0.97]; REGARDS, 0.70 [95% CI, 0.46–1.06]) compared with White males and females.<sup>5</sup>
- 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;  $P=0.002$ ).<sup>6</sup>

#### Secular Trends

- Among Medicare beneficiaries between 2002 and 2011, the rates of MI hospitalization declined from 1485 to 1122 per 100 000 person-years.<sup>7</sup>
  - 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).

The 2022 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 2022. 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.

- However, 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%.
- 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;  $P=0.02$ ).<sup>8</sup>

### Admissions and Mortality Trends

- An observational cohort analysis of Medicare beneficiaries hospitalized with MI (N=155 397) in a national MI registry between April 2018 and September 2019 showed that Black adults (compared with non-Black adults) had lower 30-day mortality rates in low-performing hospitals (OR: before the Hospital Readmission Reduction Program, 0.79 [95% CI, 0.63–0.97];  $P=0.03$ ; after the Hospital Readmission Reduction Program, 0.80 [95% CI, 0.68–0.95];  $P=0.01$ ) but not in high-performing hospitals.<sup>9</sup>
- The COVID-19 pandemic resulted in reductions in hospital admissions for MI. A multicenter study in Italy reported a 48% (95% CI, 45%–53%) reduction in MI admissions during 1 week in March 2020 compared with the same week the previous year.<sup>10</sup> This reduction was present for both STEMI (27% [95% CI, 22%–32%]) and NSTEMI (65% [95% CI, 60%–70%]).
- In England, AMI hospitalizations during the COVID-19 period (February 1–May 14, 2020; n=9325) declined >50% compared with the pre-COVID-19 period (February 1–May 14, 2019; n=20 310), with a corresponding increase in the incidence of OHCA (see Chapter 19 [Sudden Cardiac Arrest, Ventricular Arrhythmias, and Inherited Channelopathies]).<sup>11</sup> A similar multisite study in France observed a reduction in STEMI (IRR, 0.72 [95% CI, 0.62–0.85]) and NSTEMI (IRR, 0.64 [95% CI, 0.55–0.76]) comparing the 4 weeks before and after lockdown.<sup>12</sup>

### Social Determinants

- In an analysis of nationally representative longitudinal register data in Finnish adults (N=94 501) for the period of 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.<sup>13</sup> 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.
- 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).<sup>14</sup>

- 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%–13.8% for the most urban to most rural hospitals).<sup>15</sup>
- Among 3006 older adults in the SILVER-AMI study who were recruited across 94 hospitals in the United States, low emotional support, measured with the Medical Outcomes Study Social Support Survey, was associated with higher odds of mortality (OR, 1.43 [95% CI, 1.04–1.97]), whereas low informational support was associated with higher odds of readmission (OR, 1.22 [95% CI, 1.01–1.47]).<sup>16</sup>
- In a retrospective cohort study of Medicare fee-for-service patients (N=453 783) who were diagnosed with CAD, there was no significant difference in adherence to guideline-recommended care in practices that served the highest proportion of patients who were socioeconomically disadvantaged compared with practices serving the lowest proportion.<sup>17</sup> Yet, at the most socioeconomically disadvantaged-serving practices, patients had higher odds of being admitted for unstable angina (adjusted OR, 1.46 [95% CI, 1.04–2.05]) and higher 30-day mortality rates after AMI (aOR, 1.31 [95% CI, 1.02–1.68]). After additional adjustment for patient-level area deprivation index, these associations were attenuated (unstable angina aOR, 1.20 [95% CI, 1.02–1.68]; 30-day mortality after MI aOR, 1.31 [95% CI, 1.02–1.68]).

### Risk Prediction

- 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 (observed IR, 6.23 [95% CI, 5.31–7.31] versus predicted IR, 8.02; Hosmer-Lemeshow  $\chi^2=12.43$ ;  $P=0.01$ ).<sup>18</sup>
- 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 (observed [predicted] risks for baseline 10-year risk categories of <5%, 5%–7.5%, 7.5%–10%, and  $\geq 10\%$  were 3.8 [4.3], 7.1 [6.4], 8.3 [8.7], and 18.9 [18.7], respectively).<sup>19</sup>



- In 14 169 patients with ASCVD risk <5% and self-reported family history of CHD from the multicenter CAC Consortium followed up for ≈12 years, 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]).<sup>20</sup> 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 the model with traditional risk factors and 0.82 for the model adding CAC;  $P=0.03$ ).
- In a large competing-risk analysis among 66 363 adults from the CAC Consortium, participants with CAC >10 had higher risk of CHD death (aHR, 2.83 [95% CI, 2.07–3.86]) than those with CAC=0.<sup>21</sup> This risk was not significantly higher among adults <40 years but was significantly higher among adults >40 to 50 years of age (aHR, 2.97 [95% CI, 1.32–6.69]), 50 to 60 years of age (aHR, 5.08 [95% CI, 2.68–9.63]), 60 to 70 years of age (aHR, 1.89 [95% CI, 1.08–3.31]), and ≥70 years of age (aHR, 2.43 [95% CI, 1.33–4.46]) compared with their age counterparts with CAC=0.
- Among 66 636 asymptomatic adults in the CAC Consortium, those with extremely high CAC scores (≥1000) had higher adjusted risk of CVD (HR, 5.04 [95% CI, 3.92–6.48]), CHD (HR, 6.79 [95% CI, 4.74–9.73]), all-cause mortality (HR, 2.89 [95% CI, 2.53–3.31]), and cancer (HR, 1.55 [95% CI, 1.23–1.95]) than those with CAC=0.<sup>22</sup> Moreover, those with CAC ≥1000 had higher adjusted risk of CVD (HR, 1.71 [95% CI, 1.41–2.08]), CHD (HR, 1.84 [95% CI, 1.43–2.36]), all-cause mortality (HR, 1.51 [95% CI, 1.33–1.70]), and cancer (HR, 1.36 [95% CI, 1.07–1.73]) than those with CAC scores of 400 to 999.
- Among 16 289 adults (6526 males, 9763 females) in the HCHS/SOL, WC cut points of >102 cm in males (current joint interim statement criteria) and >97 cm (9 points above the joint interim statement criteria) in females provide optimal discrimination for CHD (evidence of prior MI from ECG or self-report of MI, angina, or coronary procedures).<sup>23</sup>
  - 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)<sup>1</sup>:
  - 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%).<sup>24</sup>
- 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];  $P<0.001$ ).<sup>25</sup>

### 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.<sup>26</sup>
- The first GWAS identified the now most consistently replicated genetic marker for CHD and MI in European-derived populations, on chromosome 9p21.3.<sup>27</sup> The frequency of the primary SNP is common (50% of the White population is estimated to harbor 1 risk allele, and 23% harbors 2 risk alleles).<sup>28</sup>
  - The 10-year HD risk for a male 65 years of age 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 female 40 years of age 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%.<sup>28</sup>
- 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.<sup>29</sup> Other

## 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 and ethnic breakdown from NHANES 2015 to 2018 is as follows (unpublished NHLBI tabulation)<sup>1</sup>:
  - 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 and 15.6% (SE, 1.2%) for females.

GWASs have identified at least 13 additional loci across the genome, implicating pathways in blood vessel morphogenesis, lipid metabolism, nitric oxide signaling, and inflammation.<sup>30</sup>

- Ancestry-specific GWASs have identified novel variants beyond those discovered in European cohorts. A large-scale GWAS of 25 892 cases and 142 336 controls of Japanese ancestry identified 8 new CAD susceptibility loci.<sup>31</sup>
- Genetic studies of CHD focused on the coding regions of the genome (exons) have identified additional genes and SNPs for CHD, including loss-of-function variants in *ANGPTL4* (angiopoietin-like 4), which is an inhibitor of lipoprotein lipase. These variants are associated with low plasma triglycerides and high HDL-C.<sup>32</sup>
- In a discovery analysis of common SNPs (minor allele frequency >5%) on an exome array, 6 new loci associated with CAD were identified, including SNPs on the *KCNJ13-GIGYF2*, *C2*, *MRV11-CTR9*, *LRP1*, *SCARB1*, and *CETP* genes.<sup>33</sup>
- 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.<sup>34</sup>
- 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];  $P=5.1 \times 10^{-3}$ ).<sup>35</sup>
- Genetic studies for CHD have focused primarily on the autosome; a study of X chromosome genetic variation in >500 000 individuals found common alleles on chromosome Xq23 to be strongly associated with lower TC, LDL-C, and triglycerides in both females and males and associated with a reduced odds for CHD and type 2 diabetes.<sup>36</sup> ORs for CHD and type 2 diabetes for each rs5942634-T allele, the lead cholesterol-lowering variant in chromosome Xq23, were 0.98 (95% CI, 0.96–0.99) and 0.97 (95% CI, 0.96–0.99), respectively.
- In a network mendelian randomization analysis, a 1-unit-longer genetically determined telomere length was associated with a lower risk of CHD in the CARDIo-GRAM Consortium (OR, 0.79 [95% CI, 0.65–0.97];  $P=0.016$ ) and the CARDIo-GRAMplusC4D 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.<sup>37</sup>
- 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, with ORs ranging from 0.73 to 2.76 for the minor allele.<sup>38</sup>

- Hematopoietic somatic variants (clonal hematopoiesis of indeterminate potential) that accumulate with age also have 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 that of noncarriers (95% CI, 1.4–2.7) and a risk of MI 4.0 times greater than that of noncarriers (95% CI, 2.4–6.7).<sup>39</sup> Clonal hematopoiesis of indeterminate potential itself has germline genetic determinants.<sup>40</sup>

### Clinical Utility of Genetic Markers

- Studies have shown that patients with early-onset MI have a higher proportion of very high polygenic GRS than of FH variants; for example, ≈2% carry a rare FH genetic variant, whereas ≈17% have a high polygenic risk score.<sup>41</sup>
- 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 (96.5±32.7 mg/dL versus 105.9±33.3 mg/dL;  $P=0.04$ ), which suggests the influence of GRS in risk prevention.<sup>42</sup>
- Even in individuals with high genetic risk, prevention strategies have added benefit. For example, in 4 studies across 55 685 participants, genetic and lifestyle factors were independently associated with CHD, but even in participants at high genetic risk, a favorable lifestyle was associated with a nearly 50% lower RR of CHD than an unfavorable lifestyle (HR, 0.54 [95% CI, 0.47–0.63]).<sup>43</sup>
- 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];  $P=0.0012$ ).<sup>44</sup>
- 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).<sup>45</sup>
- Studies suggest that addition of a GRS to a clinical model has only modest clinical utility in the general

population. In the UK Biobank with >350 000 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%).<sup>46</sup> In the ARIC and MESA studies, adding a GRS to the Pooled Cohort Equation did not significantly increase the C statistic in either cohort for prediction of incident CHD events (change in C statistic: ARIC, –0.001 [95% CI, –0.009 to 0.006]; MESA, 0.021 [95% CI, –0.0004 to 0.043]).<sup>47</sup>

- GRS derived in 1 ancestry may not perform well in other ancestries<sup>48</sup>; therefore, ancestry-specific GRSs are needed. For example, a new GRS for CAD derived and validated in South Asian individuals was created, which was associated with an OR per 1 SD of 1.58 (95% CI, 1.42–1.76).<sup>49</sup> This analysis did not compare performance with GRS derived in populations from different ancestries.

### Awareness, Treatment, and Control

#### Awareness of Warning Signs and Risk for HD

- In 2012, among female online survey participants<sup>50</sup>:
  - 21% responded that their doctor had talked to them about HD risk.
  - NH Black (36%) and Hispanic (34%) females had lower awareness than White females that HD/heart attack is the leading cause of death for females.
  - Hispanic females (12%) were less likely to report that their doctor ever discussed their risk of HD than White (22%) or Black (22%) females, and this increased with age from 6% (25–34 years of age) to 33% (≥65 years of age).
  - 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%.
- 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 professional had discussed HD and things they could do to take care of their heart.<sup>51</sup>
- 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 and ethnicity (White participants, 54.8%; Black

participants, 43.1%; Asian participants, 33.5%; Hispanic participants, 38.9%).<sup>52</sup>

- 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]).<sup>53</sup>

#### Time of Symptom Onset and Arrival at Hospital

- A retrospective analysis of the NHAMCS data from 2004 to 2011 that reviewed 15 438 hospital visits related to ACS symptoms suggested that Black individuals have a 30% longer waiting time than White individuals.<sup>54</sup>
- The timing of hospital admission influences management of MI. A study of the NIS database from 2000 to 2016 indicated that admission on a weekend (compared with a weekday) for MI was associated with a small but significantly reduced risk of coronary angiography (60% versus 59%;  $P<0.001$ ), particularly early coronary angiography (26% versus 21%;  $P<0.001$ ).<sup>55</sup> These differences did not result in clinically relevant increased mortality after multivariable adjustment (OR, 1.01 [95% CI, 1.00–1.01]).
- 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 (95% CI, 1.01–1.04) of in-hospital mortality.<sup>56</sup>
- In 2015, from the CathPCI registry, median door-to-balloon time for primary PCI for STEMI was 57 minutes.<sup>57</sup>
- In a European registry of high-volume PCI centers, the COVID-19 pandemic was associated with a significant increase in door-to-balloon and total ischemia times.<sup>58</sup> Door-to-balloon time >30 minutes was 57.0% in the period March to April 2020 compared with 52.9% in March to April 2019 ( $P=0.003$ ), and total ischemia time >12 hours was 11.7% in the 2020 period compared with 9.1% in 2019 ( $P=0.001$ ).
- In a meta-analysis including 57 136 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 14 261 patients from 8 studies (OR, 1.53 [95% CI, 1.13–2.06]).<sup>59</sup>

#### Operations and Procedures

- In 2014, an estimated 480 000 percutaneous transluminal coronary angioplasties, 371 000 inpatient bypass procedures, 1 016 000 inpatient diagnostic cardiac catheterizations, 86 000



carotid endarterectomies, and 351 000 pacemaker procedures were performed for inpatients in the United States (unpublished NHLBI tabulation using HCUP<sup>60</sup>).

### 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 MI (HR, 0.50 [95% CI, 0.31–0.82]) and repeat revascularizations (HR, 0.56 [95% CI, 0.41–0.75]).<sup>61</sup> CABG was associated with lower all-cause mortality, MI, or stroke (HR, 0.74 [95% CI, 0.56–0.98]) than PCI.<sup>62</sup>
- 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]).<sup>63</sup>
- In patients with left main CAD with low or intermediate complexity (SYNTAX scores  $\leq 32$ ), 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.<sup>64</sup>
- 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.<sup>65</sup>
- 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.<sup>66</sup>
- In 27 840 patients with STEMI transported by 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%;  $P=0.01$ ).<sup>67</sup>
- 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 ( $P=0.574$ ).<sup>68</sup>

- In a randomized trial including 5179 patients with stable coronary disease and moderate or severe ischemia, an initial invasive strategy did not reduce ischemic cardiovascular events or death compared with initial conservative strategy (risk difference,  $-1.8\%$  [95% CI,  $-4.7\%$  to  $1\%$ ] at 5 years).<sup>69</sup>

### 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.<sup>70</sup> 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];  $P<0.001$ ).
- 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.<sup>71</sup>
- 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.<sup>72</sup>
- In an analysis of the NIS, among patients  $\geq 70$  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.<sup>73</sup>
- Among Medicare fee-for-service beneficiaries, the total number of revascularization procedures performed peaked in 2010 and declined by  $>4\%/y$  through 2012.<sup>74</sup> 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.
- 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%).<sup>75</sup>
- 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.<sup>76</sup> A transradial approach also was 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.

### Cardiac Rehabilitation

- In the NCDR between 2009 and 2012, 59% of individuals were referred to cardiac rehabilitation after PCI, with significant site-specific variation.<sup>77</sup>
- 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.<sup>78</sup>
- 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 time initiation was 47.0 days (SD, 38.6 days), and 26.9% completed cardiac rehabilitation with  $\geq 36$  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  $\geq 5$  comorbidities.<sup>79</sup>
- In a randomized trial in patients undergoing cardiac rehabilitation after ACS with PCI, patients receiving digital health healthy lifestyle interventions had more weight loss at 90 days than the control group ( $-5.1\pm 6.5$  kg versus  $-0.8\pm 3.8$  kg [mean $\pm$ SD];  $P=0.02$ ) and a nonsignificant decrease in cardiovascular-related rehospitalizations and ED visits at 180 days (8.1% versus 26.6%; RR, 0.30 [95% CI, 0.08–1.10];  $P=0.054$ ).<sup>80</sup>

### Mortality

#### (See Table 21-1)

- On the basis of 2019 mortality data<sup>81</sup>:
  - CHD mortality was 360 900, and CHD any-mention mortality was 542 903 (Table 21-1).
  - MI mortality was 104 280. MI any-mention mortality was 144 050 (Table 21-1).
- From 2009 to 2019, the annual death rate attributable to CHD declined 25.2%, and the actual number of deaths declined 6.6% (unpublished NHLBI tabulation using CDC WONDER<sup>82</sup>).
- In 2019, CHD age-adjusted death rates per 100 000 were 124.9 for NH White males, 137.6 for NH Black males, and 91.4 for Hispanic males. For NH White females, the rate was 62.7; for NH Black females, it was 77.2; and for Hispanic females,

it was 49.0 (unpublished NHLBI tabulation using CDC WONDER<sup>82</sup>).

- In 2019, 78% of CHD deaths occurred out of hospital. According to US mortality data, 281 538 CHD deaths occurred out of hospital or in hospital EDs in 2019 (unpublished NHLBI tabulation using CDC WONDER<sup>82</sup>).
- The estimated average number of YLL because of an MI death was 16.1 in 2019 (unpublished NHLBI tabulation using CDC WONDER<sup>82</sup>).
- Approximately 35% of the people who experience a coronary event in a given year will die as a result of it, and  $\approx 14\%$  who experience an MI will die of it (unpublished NHLBI tabulation using ARIC Community Surveillance [2005–2014]).<sup>4</sup>
- 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.<sup>83</sup>
- In the CRUSADE study including 22 295 patients  $\geq 65$  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]).<sup>84</sup>
- An analysis of the multicenter NCDR Chest Pain–MI Registry reported that 30-day mortality among hospitalized patients with MI decreased from 6.6% to 5.0% in Black individuals and from 5.2% to 4.0% in non-Black individuals in the period of 2008 to 2016.<sup>9</sup>
- 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.<sup>85</sup>
- Other data indicate that the rapid increase in the population  $\geq 65$  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  $\geq 65$  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.<sup>86</sup>

### 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%).<sup>87,88</sup> 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.<sup>89</sup>
- 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.<sup>90</sup>
- 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.<sup>91</sup>
- Compared with ineligible individuals, participants in the Supplemental Nutrition Assistance Program have twice the risk of CVD mortality (HR, 2.00 [95% CI, 1.90–2.10]), which likely reflects differences in socioeconomic, environmental, and behavioral characteristics.<sup>92</sup>
- An analysis of the STS database, including 1 042 056 patients who underwent isolated CABG between 2011 and 2018, found that Black individuals had higher overall mortality than White individuals (OR, 1.11 [95% CI, 1.05–1.18]).<sup>93</sup> Likewise, odds of death were higher in females compared with males (OR, 1.26 [95% CI, 1.21–1.30]).
- A pooled analysis of 21 randomized PCI trials including 32 877 patients (28% females) found that female sex was an independent risk factor of MACEs (HR, 1.14 [95% CI, 1.01–1.30]) and ischemia-driven target lesion vascularization (HR, 1.23 [95% CI, 1.05–1.44]) but not all-cause or cardiovascular mortality (HR, 0.91 [95% CI, 0.75–1.09] and 0.97 [95% CI, 0.73–1.29], respectively).<sup>94</sup>
- 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.
- On the basis of pooled data from the FHS, ARIC, CHS, MESA, CARDIA, and JHS studies of the NHLBI (1995–2012), within 5 years after a first MI (unpublished NHLBI tabulation):
  - 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).<sup>75</sup> 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).<sup>75</sup> 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 SES 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]).<sup>95</sup>
- 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];  $P<0.001$ ).<sup>96</sup>
- 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 ( $P=0.84$ ).<sup>97</sup>

- 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];  $P<0.001$ ).<sup>98</sup>
- 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];  $P<0.001$ ).<sup>99</sup>
- Individuals with HF symptoms (New York Heart Association functional class  $\geq 2$ ) 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];  $P=0.03$ ).<sup>100</sup>
- The burden of rehospitalizations for AMI may be substantial. Among Medicare fee-for-service patients  $\geq 65$  years of age who were discharged alive after AMI in 2009 to 2014, the rate of 1-year recurrent AMI was 5.3% (95% CI, 5.27%–5.41%) with a median of 115 days (IQR, 34–230 days) of time from discharge to recurrent AMI.<sup>101</sup>
- 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.<sup>102</sup>
- 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.<sup>103</sup>

### 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  $\geq 45$  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  $\geq 75$  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  $\geq 45$  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  $\geq 75$  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  $\geq 45$  years of age, 4% of males and 7% of females.
  - At  $\geq 45$  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  $\geq 45$  years of age, 8.2 for males and 5.5 for females.
  - At  $\geq 45$  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 21-1 and Chart 21-8)

- From 2008 to 2018, the number of inpatient discharges from short-stay hospitals with CHD as the first-listed diagnosis decreased from 1 541 000 to 1 020 000 (Table 21-1).
- From 1997 through 2016, the number of hospital discharges for CHD was higher for males than for females (Chart 21-8).
- In 2018, there were 9 221 000 physician office visits for CHD (unpublished NHLBI tabulation using NAMCS<sup>104</sup>). In 2018, there were 997 000 ED visits with a primary diagnosis of CHD (unpublished NHLBI tabulation using HCUP<sup>60</sup>).
- 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.<sup>105</sup>
- In the CathPCI registry, a composite of use of evidence-based medical therapies, including aspirin, P2Y<sub>12</sub> 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<sub>12</sub> inhibitor use in eligible medically treated patients with AMI (56.7%), and use of aldosterone antagonists in patients with LV systolic dysfunction and either diabetes or HF (12.8%).<sup>75</sup>

### Cost

- The estimated direct cost of HD in 2017 to 2018 (average annual) was \$108.8 billion (MEPS,<sup>106</sup> unpublished NHLBI tabulation).
- The estimated direct and indirect cost of HD in 2017 to 2018 (average annual) was \$228.7 billion (MEPS,<sup>106</sup> 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.<sup>107</sup>
- 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.<sup>108</sup>
- 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.<sup>109</sup>
- 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.<sup>110</sup>
- 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  $\geq 65$  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 (\$61 16 for hospitalizations, \$1334 for outpatient hospital stays, and \$587 for ED visits).<sup>111</sup>
- 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.<sup>112</sup>

### Global Burden

(See Table 21-3 and Charts 21-9 and 21-10)

- The GBD 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020. (Data courtesy of the Global Burden of Disease Study 2020.) Globally, it was estimated that in 2020, 244.11 million (95% UI, 213.48–275.80 million) people lived with IHD, and it was more prevalent in males than in females (141.00 million [95% UI, 123.55–159.19 million] and 103.11 million [95% UI, 89.36–117.43 million] people, respectively). An estimated 8.95 million (95% UI, 8.26–9.50 million) deaths attributable to IHD occurred in 2020 (Table 21-3).
  - In 2020, age-standardized IHD mortality rates were highest in North Africa and the Middle East, Eastern Europe, and Central Asia (Chart 21-9).
  - In 2020, North Africa and the Middle East, Central and South Asia, and Eastern Europe had the highest age-standardized prevalence rates of IHD (Chart 21-10).
- Among 31 443 respondents  $\geq 50$  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.<sup>114</sup>

### Acute Coronary Syndrome

ICD-9 410, 411; ICD-10 I20.0, I21, I22.

- In 2018, there were 667 000 ACS principal diagnosis discharges. This estimate was derived by adding the principal diagnoses for MI (658 000) to those for UA (9000; unpublished NHLBI tabulation using HCUP<sup>60</sup>).
- When all listed discharge diagnoses in 2018 were included, the corresponding number of inpatient hospital discharges was 1 201 000 unique hospitalizations for ACS. Of the total, 1 181 000 were for MI alone, and 20 000 were for UA alone (HCUP<sup>60</sup> unpublished NHLBI tabulation).
- 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.<sup>115</sup>
- 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.<sup>116</sup>

- In a population-level study in Italy, the incidence rate of PCI for ACS reduced from 178 (before the COVID-19 outbreak) to 120 cases (after the COVID-19 outbreak) per 100 000 residents per year (IRR, 0.68 [95% CI, 0.65–0.70]).<sup>117</sup> Females (IRR, 0.60 [95% CI, 0.57–0.65]) had fewer PCIs for ACS than males (IRR, 0.70 [95% CI: 0.68–0.73]; *P* for interaction <0.011).

## Stable AP

### ICD-9 413; ICD-10 I20.1 to I20.9.

#### Prevalence

(See Table 21-2 and Chart 21-11)

- According to data from NHANES 2015 to 2018, the prevalence of AP among adults (≥20 years of age) is 4.1% (11.0 million adults; Table 21-2).

- On the basis of NHANES 2015 to 2018, the prevalence of AP increased with age from <1% among males and females 20 to 39 years of age to >10% among males and females ≥80 years of age (Chart 21-11).
- 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.<sup>118</sup>
- 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).<sup>119</sup>
- 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.<sup>120</sup>

**Table 21-1. 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, 2019, all ages	Mortality,* MI, 2019, all ages	Hospital discharges: CHD, 2018, 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	360 900	104 280	1 020 000
Males	11 000 000 (8.3%)	5 800 000 (4.3%)	610 000	470 000	213 364 (59.1%)†	61 695 (59.2%)†	
Females	9 100 000 (6.2%)	3 000 000 (2.1%)	445 000	335 000	147 536 (40.9%)†	42 585 (40.8%)†	
NH White males	8.7%	4.4%	520 000‡	...	167 340	48 465	...
NH White females	6.0%	2.0%	370 000‡	...	114 144	32 752	...
NH Black males	6.7%	3.9%	90 000‡	...	22 643	6 487	...
NH Black females	7.2%	2.3%	75 000‡	...	18 021	5 293	...
Hispanic males	6.8%	3.7%	...	...	15 166	4 475	...
Hispanic females	6.4%	2.1%	...	...	10 182	3 068	...
NH Asian males	5.0%	2.7%	...	...	6 095§	1 734§	...
NH Asian females	3.2%	0.7%	...	...	4 119§	1 184§	...
NH American Indian or Alaska Native	...	...	...	...	2 007	599	...

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 NH 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.<sup>1</sup> Percentages for racial and 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),<sup>4</sup> unpublished tabulation by NHLBI, extrapolated to the 2014 US population. Mortality: unpublished NHLBI tabulation using National Vital Statistics System.<sup>81</sup> Mortality for NH Asian people includes Pacific Islander people. Hospital discharges: unpublished NHLBI tabulation using Healthcare Cost and Utilization Project<sup>80</sup> (data include those inpatients discharged alive, dead, or status unknown).

**Table 21-2. AP\* in the United States**

Population group	Prevalence, 2015–2018, age ≥20 y	Hospital discharges, 2018, all ages
Both sexes	11 000 000 (4.1%)	15 000
Males	5 300 000 (4.2%)	
Females	5 700 000 (4.0%)	
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%	...

AP includes people who either answered “yes” to the question of ever having angina or angina pectoris or were diagnosed with Rose angina (the Rose questionnaire is administered only to survey participants >40 years of age).

AP indicates angina pectoris; ellipses (...), data not available; and NH, non-Hispanic.

\*AP is chest pain or discomfort that results from insufficient blood flow to the heart muscle. Stable AP is predictable chest pain on exertion or under mental or emotional stress. The incidence estimate is for AP without myocardial infarction.

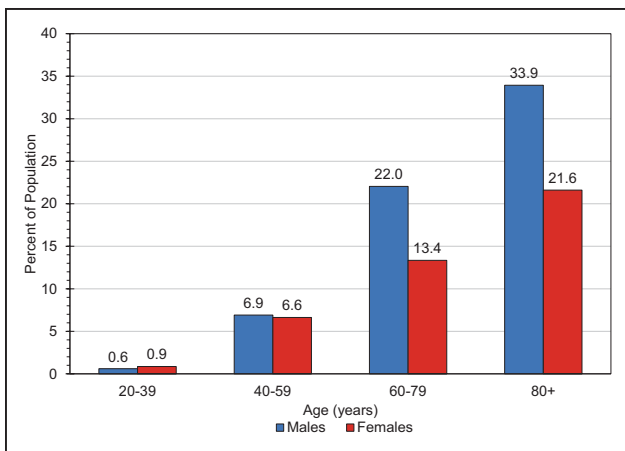
Sources: Prevalence: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES (National Health and Nutrition Examination Survey).<sup>1</sup> Percentages for racial and ethnic groups are age adjusted for US adults ≥20 years of age. Estimates from NHANES 2015 to 2018 were applied to 2018 population estimates (≥20 years of age). Hospital discharges: unpublished NHLBI tabulation using Healthcare Cost and Utilization Project<sup>60</sup>; data include those inpatients discharged alive, dead, or status unknown.

**Table 21-3. Global Mortality and Prevalence of IHD by Sex, 2020**

	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), 2020	8.95 (8.26 to 9.50)	244.11 (213.48 to 275.80)	4.90 (4.56 to 5.24)	141.00 (123.55 to 159.19)	4.04 (3.59 to 4.43)	103.11 (89.36 to 117.43)
Percent change in total number, 1990 to 2020	66.46 (57.69 to 75.51)	119.24 (116.87 to 121.70)	72.31 (59.21 to 85.97)	118.78 (116.43 to 121.12)	59.87 (48.02 to 71.90)	119.86 (116.46 to 123.26)
Percent change in total number, 2010 to 2020	21.28 (16.13 to 26.47)	34.85 (31.30 to 38.36)	21.92 (14.75 to 29.57)	33.47 (30.01 to 37.02)	20.52 (13.08 to 27.25)	36.78 (33.07 to 40.74)
Rate per 100 000, age standardized, 2020	112.37 (103.06 to 119.57)	2919.82 (2555.34 to 3296.62)	138.29 (128.18 to 147.75)	3617.05 (3179.09 to 4060.73)	90.10 (79.92 to 98.63)	2304.27 (1999.27 to 2621.41)
Percent change in rate, age standardized, 1990–2020	−29.94 (−33.23 to −26.48)	0.27 (−1.06 to 1.69)	−28.05 (−33.03 to −22.79)	−2.27 (−3.51 to −1.00)	−32.75 (−37.54 to −27.87)	2.09 (0.32 to 3.89)
Percent change in rate, age standardized, 2010–2020	−10.60 (−14.35 to −6.97)	1.80 (−0.72 to 4.30)	−9.82 (−14.78 to −4.69)	0.43 (−2.04 to 2.92)	−11.47 (−16.82 to −6.50)	3.39 (0.72 to 6.22)

IHD indicates ischemic heart disease; and UI, uncertainty interval.

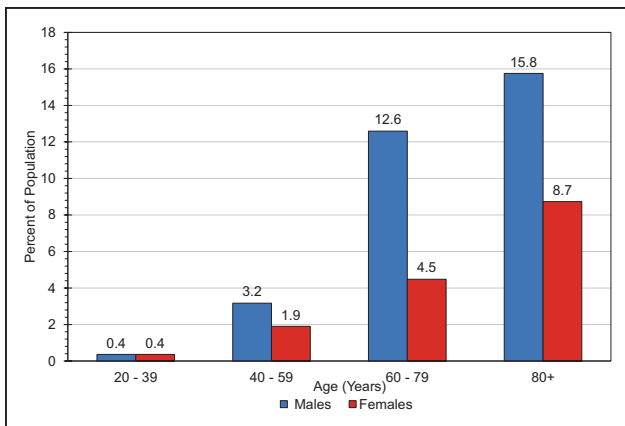
Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington.



**Chart 21-1. Prevalence of CHD, by age and sex, United States (NHANES, 2015–2018).**

CHD indicates coronary heart disease; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>1</sup>

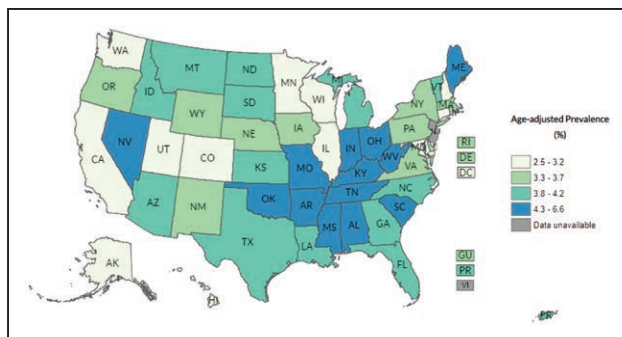


**Chart 21-2. Prevalence of MI, by age and sex, United States (NHANES, 2015–2018).**

MI includes people who answered “yes” to the question of ever having had a heart attack or MI.

MI indicates myocardial infarction; and NHANES, National Health and Nutrition Examination Survey.

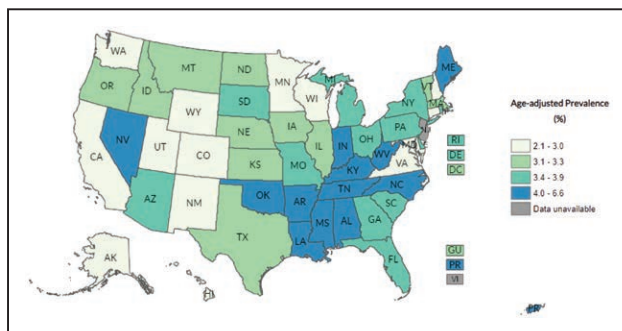
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>1</sup>



**Chart 21-3. “Ever told you had a heart attack (MI)?” Age-adjusted US prevalence, by state (BRFSS prevalence and trends data, 2019).**

Original chart has been modified to remove white space between map and legend. BRFSS indicates Behavioral Risk Factor Surveillance System; and MI, myocardial infarction.

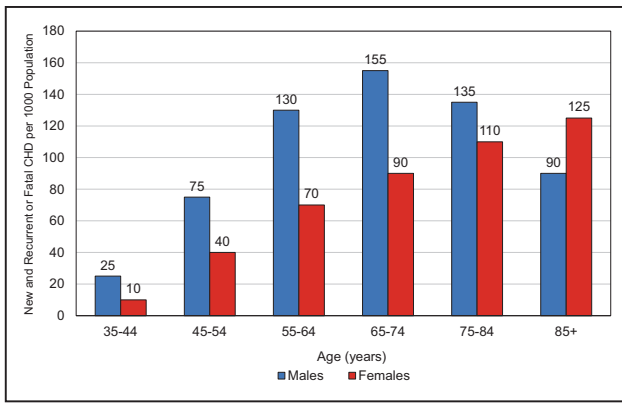
Source: BRFSS prevalence and trends data.<sup>3</sup>



**Chart 21-4. “Ever told you had angina or CHD?” Age-adjusted US prevalence, by state (BRFSS prevalence and trends data, 2019).**

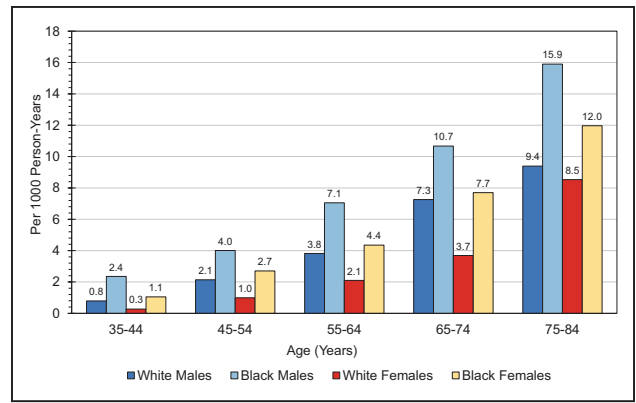
Original chart has been modified to remove white space between map and legend. BRFSS indicates Behavioral Risk Factor Surveillance System; and CHD, coronary heart disease.

Source: BRFSS prevalence and trends data.<sup>3</sup>



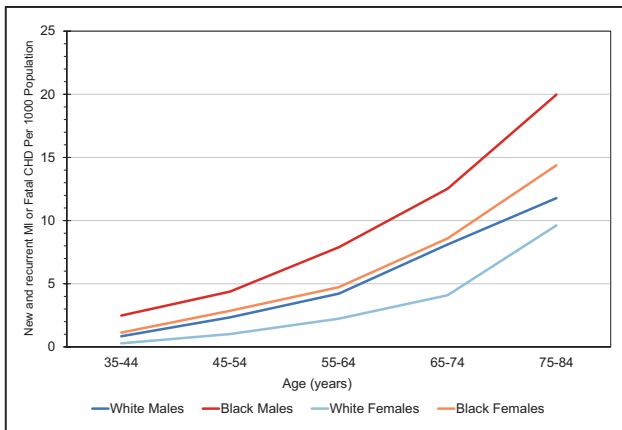
**Chart 21-5. Annual number of US adults per 1000 having diagnosed heart attack or fatal CHD, by age and sex (ARIC Surveillance, 2005–2014 and CHS).**

These data include MI and fatal CHD but not silent MI. ARIC indicates Atherosclerosis Risk in Communities; CHD, coronary heart disease; CHS, Cardiovascular Health Study; and MI, myocardial infarction. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using ARIC<sup>4</sup> and CHS.<sup>121</sup>



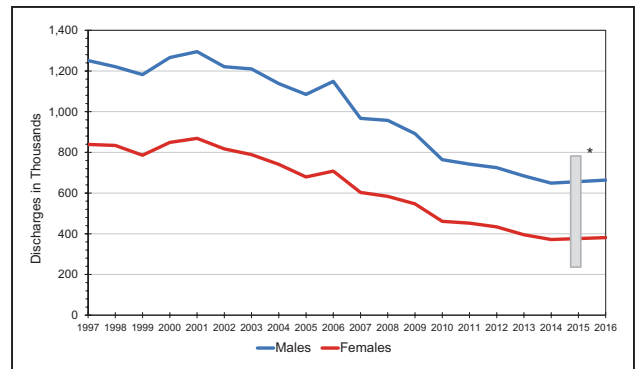
**Chart 21-7. Incidence of MI, by age, sex, and race, United States (ARIC Surveillance, 2005–2014).**

ARIC indicates Atherosclerosis Risk in Communities; and MI, myocardial infarction. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using ARIC.<sup>4</sup>



**Chart 21-6. Incidence of heart attack or fatal CHD, by age, sex, and race, United States (ARIC Surveillance, 2005–2014).**

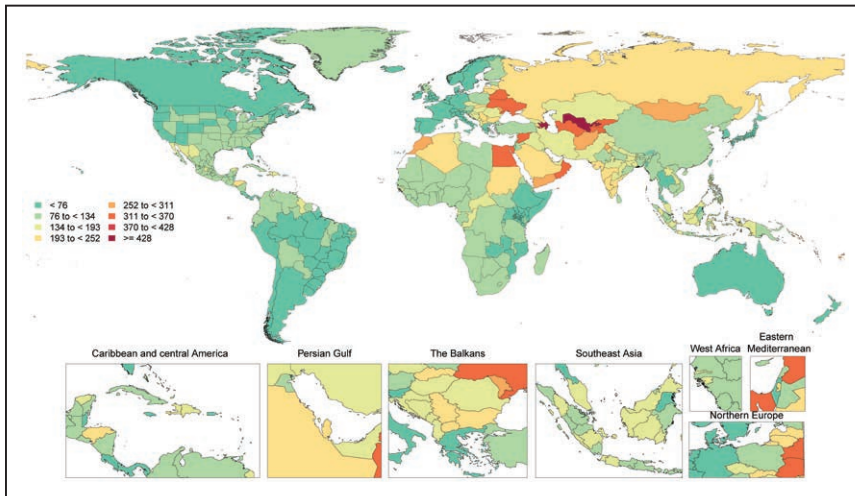
ARIC indicates Atherosclerosis Risk in Communities; CHD, coronary heart disease; and MI, myocardial infarction. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using ARIC.<sup>4</sup>



**Chart 21-8. Hospital discharges for CHD, by sex, United States (HCUP, 1997–2016).**

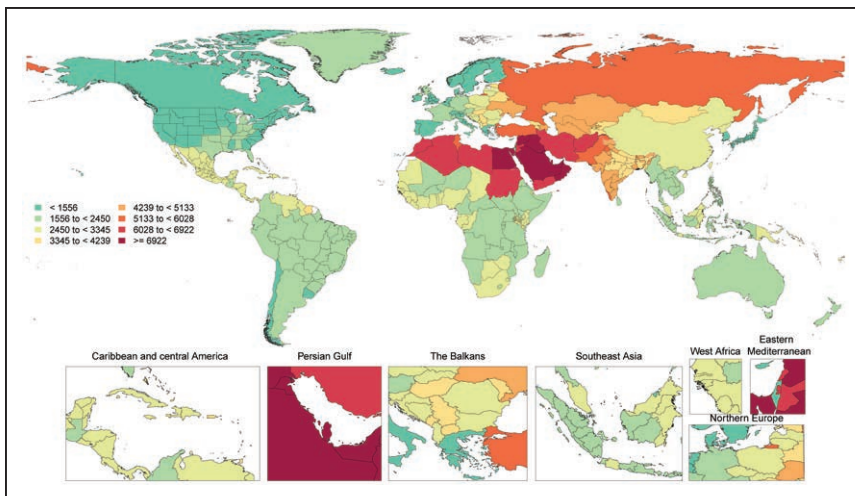
Hospital discharges include people discharged alive, dead, and status unknown. CHD indicates coronary heart disease; and HCUP, Healthcare Cost and Utilization Project. \*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the ninth 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.<sup>60</sup>





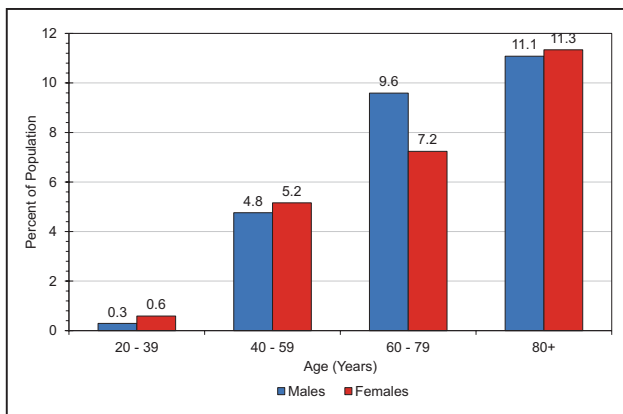
**Chart 21-9. Age-standardized global mortality rates of IHD per 100,000, both sexes, 2020.**

IHD indicates ischemic heart disease. Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>121</sup>



**Chart 21-10. Age-standardized global prevalence rates of IHD per 100,000, both sexes, 2020.**

IHD indicates ischemic heart disease. Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>121</sup>



**Chart 21-11. Prevalence of AP, by age and sex, United States (NHANES, 2015–2018).**

AP includes people who either answered “yes” to the question of ever having angina or angina pectoris or were diagnosed with Rose angina. AP indicates anginal pectoris; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>1</sup>

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## 22. CARDIOMYOPATHY AND HEART FAILURE

See Tables 22-1 and 22-2 and Charts 22-1 through 22-4

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### Cardiomyopathy

#### ICD-9 425; ICD-10 I42.

2019: Mortality—20 444. Any-mention mortality—42 341.

Cardiomyopathy diagnoses account for a substantial number of inpatient and outpatient encounters annually. According to 2018 HCUP data<sup>1</sup> for inpatient hospitalizations, cardiomyopathy was the principal diagnosis for 18 000, and it was included among all-listed diagnoses for 1 101 000.

#### Hypertrophic Cardiomyopathy

- The prevalence of unexplained LVH has been estimated at 0.2% and up to 1.4% in the community.<sup>2</sup>
- Of people with HCM, ≈30% to 60% are estimated to have sarcomere variants detectable on genetic testing<sup>3</sup>; conversely, not all people with sarcomere variants manifest clinical HCM because of incomplete penetrance, even among members of the same family (see the Family History and Genetics section for more details).<sup>4</sup>
- The Sarcomeric Human Cardiomyopathy Registry studied 4591 patients with HCM, contributing >24 000 person-years of follow-up, and observed a higher mortality rate in patients with HCM compared with unaffected individuals of a similar age in the US general population: 20 to 29 years of age, 0.39% versus 0.09% ( $P<0.05$ ); 40 to 49 years of age, 0.66% versus 0.28% ( $P=0.09$ ); and 60 to 69 years of age, 3.99% versus 1.33% ( $P<0.01$ ). 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 (cumulative incidence, 77% [95% CI, 72%–80%] by 60 years of age versus 32% [95% CI, 29%–36%] by 70 years of age, respectively).

The 2022 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 2022. 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.

Adverse events were also higher in patients with versus without pathogenic sarcomere variants (HR, 1.98 [95% CI, 1.72–2.28]. AF (HR, 2.41 [95% CI, 1.98–2.94]) and HF (HR, 2.03 [95% CI, 1.68–2.45]) accounted for a substantial proportion of the adverse events, despite typically not manifesting until years to decades after the initial diagnosis.<sup>5</sup>

#### Dilated Cardiomyopathy

- Commonly recognized causes of chronic DCM are variants in a diverse group of genes inherited in an autosomal dominant fashion with age-dependent penetrance and variable clinical expression (see the Family History and Genetics section for more details).<sup>6</sup> 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 the Peripartum Cardiomyopathy section).<sup>7,8</sup> 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 the LV Function section).<sup>9,10</sup>

#### 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.<sup>11</sup> Accordingly, worldwide and in the United States, females with Black ancestry appear to have highest risk, especially females with Nigerian (1 per 100 live births) and Haitian (1 per 300 live births) background.<sup>12–14</sup>
- 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 ( $P_{\text{trend}}<0.001$ ), likely related to rising average maternal age and prevalence of PPCM risk factors such as obesity, hypertension, pregnancy-related hypertension, and diabetes.<sup>15</sup> Stratified by race and ethnicity, incidence of PPCM was lowest in Hispanic females (3.6 per 10 000 live births) and highest in Black females (22.8 per 10 000 live births). 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).<sup>15</sup>
- Genetic analyses suggest that ≈15% of individuals with PPCM have rare truncating variants in genes also linked to idiopathic DCM. The majority of these are truncating variants in *TTN*, which encodes the sarcomeric protein titin, and truncating variants in *TTN* in females with PPCM are associated with lower EF after 1-year of follow-up.<sup>16</sup>

- Global mortality from PPCM is 9% and is lower in developed (4%) than developing (14%) countries; in addition, a high prevalence of women of African descent was positively correlated with mortality (weight correlation coefficient, 0.29 [95% CI, 0.13–0.52]).<sup>17</sup>
- In most cases of PPCM (50%–80%), LVEF recovers to at least near-normal ( $\geq 50\%$ ) function and often within 6 months.<sup>18–21</sup> However, an initial LVEF  $< 30\%$ , LV end-diastolic dimension  $\geq 6.0$  cm, Black race, and initial presentation  $> 6$  weeks after delivery are associated with lower LVEF at 1 year.<sup>16</sup>

### Youth

- Since 1996, the Pediatric Cardiomyopathy Registry has collected data on children with cardiomyopathy in New England and central southwestern states.<sup>22</sup>
  - 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 ( $P=0.02$ ), in boys (1.32) than in girls (0.92) ( $P<0.001$ ), and in New England (1.44) than in the central Southwest (0.98;  $P<0.001$ ).
- The annual incidence of HCM in children is  $\approx 4.7$  per 1 million (95% CI, 4.1–5.3), with higher incidence in New England (5.9 per 1 million [95% CI, 4.8–7.2]) than in the central Southwest region (4.2 per 1 million [95% CI, 3.5–4.9]) and in boys (5.9 per 1 million [95% CI, 5.0–6.9]) than in girls (3.4 per 1 million [95% CI, 2.8–4.2]).<sup>23</sup> Approximately 9% progress to HF and 12% to SCD over a median follow-up of 6.5 years.<sup>24</sup> Chapter 18 (Disorders of Heart Rhythm) provides statistics on sudden death. Data from the NIS indicate that hospitalization is more likely with increasing age (OR, 5.59 [95% CI, 2.03–15.37]) for  $\geq 10$  years of age versus 1–9 years of age) and in Black individuals compared with White individuals (OR, 2.78 [95% CI, 1.19–6.47]).<sup>25</sup>
- The annual incidence of DCM in children is  $\approx 0.57$  per 100 000 (95% CI, 0.52–0.63), with a higher incidence in boys than girls (0.66 versus 0.47;  $P<0.001$ ) and in Black children than White children (0.98 versus 0.46;  $P<0.001$ ). Commonly recognized causes include myocarditis (46%) and neuromuscular disease (26%).<sup>26</sup> The 5-year incidence rate of SCD is 3% at the time of DCM diagnosis.<sup>27</sup>
- 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.<sup>28</sup>
- Data from the Childhood Cancer Survivor Study cohort of 14 358 survivors of childhood or adolescent cancers showed a 5.9-fold (95% CI, 3.4–9.6) increased risk for HF compared with siblings,<sup>29</sup>

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 22-1 and Charts 22-1 and 22-2)

- The GBD 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020. (Data courtesy of the Global Burden of Disease Study 2020.)
  - In 2020, there were 0.37 million (95% UI, 0.33–0.41 million) deaths estimated for cardiomyopathy and myocarditis, a decrease of 0.95% (95% UI, –6.03% to 4.03%) since 2010 (Table 22-1).
  - The highest age-standardized death rates in 2020 estimated for cardiomyopathy and myocarditis were in Eastern Europe (Chart 22-1).
  - Globally, there were 6.11 million (95% UI, 5.02–7.22 million) prevalent cases of cardiomyopathy and myocarditis and an age-standardized prevalence rate of 76.92 (95% UI, 63.29–91.56) per 100 000 (Table 22-1).
  - Age-standardized prevalence of cardiomyopathy and myocarditis was highest in eastern and southern sub-Saharan Africa and tropical Latin America (Chart 22-2).

### Heart Failure

**ICD-9 428; ICD-10 I50. For hospital discharges, ICD-10 I50, I11.0, I13.0, I13.2, I09.81.**

2019: Mortality—86 177. Any-mention mortality—377 599.

2018: Hospital discharges—1 250 000.

### Prevalence

(See Table 22-2 and Chart 22-3)

- On the basis of data from NHANES 2015 to 2018,  $\approx 6.0$  million Americans  $\geq 20$  years of age had HF (Table 22-2), which is increased from  $\approx 5.7$  million according to NHANES 2009 to 2012 (NHLBI unpublished tabulation using NHANES<sup>31</sup>). The breakdown of HF prevalence by age and sex is shown in Chart 22-3.
- Prevalence of HF is projected to increase by 46% from 2012 to 2030, affecting  $> 8$  million people  $\geq 18$  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.<sup>32</sup>

### Incidence

(See Table 22-2)

- According to ARIC Community Surveillance data, the incidence of HF in people  $\geq 55$  years of age in



the United States was  $\approx 1\,000\,000$  in 2014, with slightly more new-onset cases seen in females than in males (Table 22-2).

- 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  $\approx 21$  per 1000 population after 65 years of age.<sup>33</sup>
- 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.<sup>34</sup>
- Data from Olmsted County, Minnesota, indicate that the age- and sex-adjusted incidence of HF declined substantially, from 315.8 per 100 000 in 2000 to 219.3 per 100 000 in 2010, with a greater rate reduction for HF<sub>rEF</sub> (−45% [95% CI, −33% to −55%]) than for HF<sub>pEF</sub> (−27.9% [95% CI, −12.9% to −40.3%]).<sup>35</sup>
- In the NCDR PINNACLE, 1 in 6 patients with HF<sub>rEF</sub> developed worsening HF within 18 months of diagnosis and 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 the 2-year mortality rate was 22.5%.<sup>36</sup>
- In MESA, Black individuals had the highest risk of developing future HF, followed by Hispanic, White, and Chinese American individuals (incidence rates, 4.6, 3.5, 2.4, and 1.0 per 1000 person-years, respectively); higher risk reflected differential prevalence of hypertension, diabetes, and low SES.<sup>37</sup> Black individuals also had the highest proportion of incident HF not preceded by MI (75%).<sup>37</sup>

### 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<sup>38</sup>; however, 5-year mortality for those with HF did not decline from 2000 to 2010 and remained high (52.6% overall; 24.4% for those 60 years of age and 54.4% for those 80 years of age).<sup>35</sup>

### Lifetime Risk

- Because most forms of HF present in older age, lifetime risk for HF in the community is high given the aging of the population. Data from the NHLBI-sponsored Chicago Heart Association Detection Project in Industry, ARIC, and CHS cohorts have indicated<sup>33</sup>:
  - 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 mmHg compared with <120/90 mmHg and a doubling of risk for BMI  $\geq 30$  kg/m<sup>2</sup> compared with BMI <25 kg/m<sup>2</sup>.<sup>39–41</sup>

### HF Subtypes: HF<sub>pEF</sub>, HF<sub>mrEF</sub>, and HF<sub>rEF</sub>

- Among 4 community-based cohorts, including CHS, FHS, PREVEND, and MESA, incidence rates by HF subtype were as follows: 34.9 HF<sub>rEF</sub> cases, 26.9 HF<sub>pEF</sub> cases, and 6.7 HF<sub>mrEF</sub> cases per 10 000 person-years. After HF onset, all-cause mortality rates were 459 events per 10 000 person-years among those with HF<sub>rEF</sub>, 394 events per 10 000 person-years in individuals with HF<sub>pEF</sub>, and 497 events per 10 000 person-years in those with HF<sub>mrEF</sub>.<sup>39</sup>
- In FHS, secular trends across 2 decades (1990–1999 and 2000–2009) showed similar incidence of overall HF but declining incidence for HF<sub>rEF</sub> (IRR, 0.80 [95% CI, 0.69–0.93]) and increasing incidence for HF<sub>pEF</sub> (IRR, 1.53 [95% CI, 1.30–1.79]).<sup>40</sup>
- Data from patients admitted with HF between 2005 to 2009 in the AHA GWG-HF registry demonstrate a prevalence of 46% HF<sub>pEF</sub>, 8.2% HF<sub>mrEF</sub>, and 46% HF<sub>rEF</sub>, with similar 5-year mortality across the HF subgroups in risk-adjusted survival analysis.<sup>41</sup>

### Risk Factors

- Traditional cardiometabolic 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<sup>42</sup>: 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.<sup>43</sup>
- Racial differences in risks for HF persist, as shown in the Health ABC Study<sup>44</sup>: the PAR of HF attributable to modifiable risk factors (elevated SBP, fasting glucose level, LVH, CHD, and smoking) was 68% (95% CI, 55%–77%) among Black people versus 49% (95% CI, 35%–60%) among White people. 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).<sup>44</sup>
- Risk factors differ by HF subtype: among 4 community-based studies (CHS, FHS, PREVEND, MESA)<sup>45</sup>:
  - Older age was more strongly associated with incident HF<sub>pEF</sub> (subdistribution HR, 1.91 [95% CI,



1.78–2.06] versus 1.69 [95% CI, 1.59–1.81] per 10-year age increase in HFpEF versus HFrEF respectively;  $P$  for equality=0.02).

- In contrast, the following risk factors were more strongly associated with incident HFrEF: male sex (subdistribution HR, 1.87 [95% CI, 1.63–2.16] in HFrEF versus 0.91 [95% CI, 0.79–1.05] in HFpEF;  $P$  for equality<0.0001), previous MI (subdistribution HR, 2.70 [95% CI, 2.25–3.24] in HFrEF versus 1.30 [95% CI, 1.02–1.67] in HFpEF;  $P$  for equality<0.0001), LVH (subdistribution HR, 2.08 [95% CI, 1.60–2.69] in HFrEF versus 1.16 [95% CI, 0.84–1.60] in HFpEF;  $P$  for equality=0.009), and left bundle-branch block (subdistribution HR, 3.65 [95% CI, 2.62–5.09] in HFrEF versus 1.30 [95% CI, 0.81–2.09] in HFpEF;  $P$  for equality=0.0008).
- Dietary and lifestyle factors also affect HF risk. Among 20900 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. Men adhering to none of the 6 lifestyle factors had a lifetime risk of HF of 21% (95% CI, 17%–26%), whereas men adhering to  $\geq 4$  desirable factors had a lifetime risk of 10% (95% CI, 8%–12%).<sup>46</sup>
- 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. Specifically, the lifetime risk of HF among those with 5 to 7 ideal components in middle age was 12% (95% CI, 9%–15%), whereas those with 0 ideal components had a lifetime risk of 45% (95% CI, 35%–52%).<sup>47</sup>

### 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 (HR, 2.33 [95% CI, 1.43–3.78] and 1.32 [95% CI, 1.01–1.71], respectively).<sup>48</sup>
  - 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 (HR, 1.81 [95% CI, 1.01–3.48]).<sup>49</sup>
  - In race and 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.<sup>9</sup>

- Among Black 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.<sup>50</sup> Furthermore, individuals in JHS with reduced EF (<50%) and low-normal EF ( $\geq 50$ , <55%) had a higher rate of incident HF hospitalization compared with those with normal EF (HR, 1.58 [95% CI, 1.04–2.38];  $P<0.05$ ).<sup>51</sup>
- 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.<sup>52</sup>

### Family History and Genetics

- In the multigenerational FHS, HF in at least 1 parent was associated with a higher prevalence of asymptomatic LV systolic dysfunction (5.7% versus 3.1%,  $P$ [adjusted for age, sex, height]=0.046) and greater risk of incident HF (age- and sex-adjusted 10-year incidence rate, 2.72% [95% CI, 1.80%–4.11%] versus 1.62% [95% CI, 1.10%–2.39%]; age- and sex-adjusted HR, 1.72 [95% CI, 1.13–2.61];  $P=0.01$ ).<sup>53</sup>
- Several GWASs have been conducted to identify common variations associated with cardiomyopathy and HF in the general population, albeit with modest results, highlighting a small number of putative loci, including *HSPB7*<sup>54–56</sup> and *CACNB4*.<sup>57</sup> In a GWAS of >47 000 cases and >930 000 controls, 11 HF loci were identified, all of which have known relationships with other CVD traits.<sup>58</sup>
- Genetic variation within subjects with HF may influence outcomes, with a locus on chromosome 5q22 associated with mortality in patients with HF.<sup>59</sup> A large meta-analysis of >73 000 subjects identified 52 loci associated with myocardial mass.<sup>60</sup>

### HCM and DCM

- HCM and familial DCM are the most common mendelian cardiomyopathies, with estimated genetic testing diagnostic yield of 30% to 60% and 10% to 40%, respectively,<sup>3</sup> with autosomal dominant or recessive transmission, in addition to X-linked and mitochondrial inheritance.<sup>61</sup>
- HCM is a monogenic disorder with primarily autosomal dominant inheritance and is caused by 1 of hundreds of variants in >30 genes that encode primarily components of the sarcomere, with variants in *MYH7* and *MYBPC3* (cardiac

myosin-binding protein C) being the most common.<sup>3,62</sup> A variant is identifiable in 30% to 60% of cases of familial HCM.

- Given the heterogeneous nature of the underlying genetics, manifestation of the disease is highly variable, even in cases for which the causal variant has been identified.<sup>63</sup> Among clinically unaffected individuals with pathogenic sarcomere variants discovered as part of cascade testing, 46% developed HCM over 15 years of follow-up.<sup>64</sup>
- Familial DCM accounts for up to 50% of cases of DCM, with a prevalence of 1 in 2500, but it is likely underestimated.<sup>65</sup> Familial DCM often displays an age-dependent penetrance.<sup>66</sup> Up to 40% of cases have an identifiable genetic cause.<sup>3</sup>
- Missense and truncating variants in the titin gene have been linked to autosomal dominant cardiomyopathy,<sup>67</sup> as well as to DCM, with incomplete penetrance in the general population.<sup>67</sup> Analysis of sequence data in 7855 cases with cardiomyopathy and >60 000 controls revealed the variance in penetrance of putative disease variants, which further highlights the challenges in clinical interpretation of variation in mendelian disease genes.<sup>68</sup>

### Treatment

- Mortality declines have been attributed primarily to evidence-based approaches to treat HF<sub>rEF</sub> and the implementation of treatment with neurohormonal blockade, coronary revascularization, implantable cardioverter defibrillators, and cardiac resynchronization therapies.<sup>69</sup>
- Initiation of contemporary guideline-directed medical therapy for HF<sub>rEF</sub> (quadruple therapy with angiotensin receptor neprilysin inhibitors,  $\beta$ -blockers, mineralocorticoid receptor antagonists, and sodium glucose cotransporter-2 inhibitors) is estimated to reduce the hazard of cardiovascular death or HF hospitalization by up to 62% (HR, 0.38 [95% CI, 0.30–0.47]) compared with limited conventional therapy, resulting in estimated 1.4 to 6.3 additional years alive.<sup>70</sup>
- Contemporary evidence from the CHAMP-HF registry demonstrates significant gaps in use and dose of guideline-directed medical therapy for HF<sub>rEF</sub>. Specifically, among eligible patients, 27% were not prescribed angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitors, 33% were not prescribed  $\beta$ -blockers, and 67% were not prescribed mineralocorticoid antagonists.<sup>71</sup>

### Mortality

#### (See Table 22-2)

- Survival after HF onset has improved, although not evenly 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.<sup>72</sup> 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 ( $P<0.05$ ).<sup>73</sup>

- 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, respectively, compared with White females.<sup>34</sup>
- 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  $\approx 1$  in 8 deaths in 2019 has HF mentioned on the death certificate (unpublished NHLBI tabulation).<sup>74</sup>
- Hospitalizations of children with advanced HF in congenital HD have increased, but overall hospital mortality has improved.<sup>75</sup>
- In 2019, HF was the underlying cause in 86 177 deaths (40 101 males and 46 076 females; Table 22-2). Table 22-2 shows the numbers of these deaths coded for HF as the underlying cause.
- The number of underlying causes of deaths attributable to HF was 52.8% higher in 2019 (86 177) than it was in 2009 (56 410; unpublished NHLBI tabulation using NVSS<sup>74</sup>).
- In 2019, the overall any-mention age-adjusted death rate for HF was 92.3 per 100 000, with variation across racial and ethnic groups. In males, the rates were 115.3 for NH White males, 123.3 for NH Black males, 48.5 for NH Asian or Pacific Islander males, 99.2 for NH American Indian or Alaska Native males, and 71.5 for Hispanic males. In females, the respective rates were 82.7 for NH White females, 88.9 for NH Black females, 34.2 for NH Asian or Pacific Islander females, 70.0 for NH American Indian or Alaska Native females, and 50.6 for Hispanic females (unpublished NHLBI tabulation using CDC WONDER<sup>76</sup>).
- 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.<sup>77</sup>
- Patients with HF have been recognized as susceptible to severe COVID-19. Among patients with HF admitted with COVID-19, 24.2% died in-hospital compared with 2.6% of patients admitted with acute HF in a large multicenter, all-payer US database.<sup>78</sup>

### Health Care Use: Hospital Discharges/Ambulatory Care Visits

(See Table 22-2)

- In 2018, there were 3 267 000 physician office visits with a primary diagnosis of HF (NAMCS,<sup>79</sup> unpublished NHLBI tabulation). In 2018, there were 1 404 000 ED visits for HF (HCUP,<sup>1</sup> unpublished NHLBI tabulation). In 2018, there were 1 250 000 principal diagnosis hospital discharges for HF (HCUP,<sup>1</sup> unpublished NHLBI tabulation).
- Data from the 2005 to 2014 ARIC Community Surveillance study have shown:
  - HF hospitalization rates are increasing over time, with average annual percentage change ranging from 1.9% (95% CI, 0.7%–3.1%) in White women to 4.3% (95% CI, 2.7%–5.9%) in Black females from 2005 to 2014. This increase in HF hospitalizations is driven largely by HFpEF events. For example, the annual percentage change among Black females was 8.2% (95% CI, 5.2%–11.3%) for HFpEF and 2.0% (95% CI, –0.7% to 4.7%) for HFrEF.<sup>80</sup>
  - 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.<sup>81</sup>
- 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.<sup>81</sup> Among Medicare beneficiaries, the overall HF hospitalization rate declined substantially from 1998 to 2008 but at a lower rate for Black males,<sup>72</sup> and the temporal trend findings were uneven across states.
- In the BIOSTAT-CHF Study, inpatients with symptomatic HF had higher rates of death or HF hospitalization than outpatients with symptomatic HF (33.4 versus 18.5 per 100 person-years).<sup>82</sup>
- In the GWTG-HF Registry, only 1/10th of eligible patients with HF received cardiac rehabilitation referral at discharge after hospitalization for HF.<sup>83</sup>
- Among Medicare Part D coverage beneficiaries, HF medication adherence (angiotensin-converting enzyme 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.<sup>84</sup>

### Race and Ethnicity

- In the ARIC Community Surveillance study, 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) compared with White

individuals (21 per 1000 White males, 15 per 1000 White females).<sup>80</sup>

- In the ARIC Community Surveillance study:<sup>81</sup>
  - 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%).
- Hispanic individuals hospitalized with HF were significantly younger than NH White individuals but with higher prevalence of diabetes, hypertension, and overweight/obesity. Hispanic individuals with HFpEF (but not HFrEF) also had an adjusted 45% lower in-hospital mortality risk.<sup>86</sup>
- Data from the Health and Retirement Study from 1998 to 2014 show racial and ethnic differences in hospitalization trajectories over 24 months after HF diagnosis.<sup>87</sup> Compared with NH males, Hispanic males have declines in hospitalization rates after initial diagnosis (Hispanic×time, –0.52 [95% CI, –0.99 to –0.05]) but increases in hospitalizations in later stages of disease (Hispanic×time<sup>2</sup>, 0.06 [95% CI, 0.00–0.12]). Among females, Black individuals had significantly more hospitalizations throughout the follow-up period compared with other groups (5.8 total hospitalizations in Black individuals versus 4.7 in White individuals versus 4.7 in Hispanic individuals; unadjusted *P* for ANOVA across all race groups <0.001).

### Noncardiovascular Hospitalizations

- 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.<sup>88</sup>
- Rates of HF rehospitalization or cardiovascular death were greatest for those previously hospitalized for HF compared with those never hospitalized regardless of subtype, including those with LVEF >40% (HR, 1.59 [95% CI, 1.32–1.91]) and LVEF ≤40% (HR, 1.56 [95% CI, 1.38–1.76]).<sup>89</sup>
- 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.<sup>35</sup>

## Orthotopic Heart Transplantation and Mechanical Circulatory Support Device Placement in the United States

(See Chart 22-4)

### Heart Transplantation

- According to United Network for Organ Sharing data from 1988 to 2020, a total of 79 562 heart transplantations were performed, with the annual number of transplantations more than doubling over this period from 1676 to 3658.<sup>90</sup> Of the 3658 recipients in 2020:
  - The primary diagnosis was cardiomyopathy (59.3%), CAD (23.0%), congenital HD (8.9%), and retransplantation (3.3%).
  - A ventricular assist device was present in 34.5% at the time of transplantation.

See Chapter 27 (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.<sup>91</sup>
- 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.<sup>92</sup>
- In the NIS data, outcomes after HF admission are similar in patients with history of heart transplantation compared with those without prior transplantations.<sup>93</sup>

### Mechanical Circulatory Support

- 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.<sup>94</sup>
- 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.<sup>95</sup>
- 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.<sup>94</sup>

- 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 22-4).<sup>94</sup> 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%.<sup>94</sup>
- 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.<sup>96</sup>
- 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 length of stay and cost (see also the Cost section).<sup>97</sup>
- In a meta-analysis of 8 studies (7957 patients total) comparing mortality rates in patients treated with heart transplantation and 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; and 1.49 [95% CI, 0.48–4.66] for transplantation versus destination therapy LVAD).<sup>98</sup>
- 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 (subdistribution HR, 1.57 [95% CI, 1.15–2.16]), although access to transplantation was not different.<sup>99</sup>
- Among Medicare beneficiaries undergoing LVAD implantation, 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.<sup>100</sup>

### **LVAD and Orthotopic 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.<sup>101</sup>
- 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;  $P=0.01$ ).<sup>102</sup>
- In a study of 111 patients with ventricular assist devices, SES was not associated with adverse prognosis or complications after implantation ( $P>0.05$  for SES measures, including income, insurance status, race, patient location, and marital status).<sup>103</sup>
- In the United Network for Organ Sharing database of 18085 patients who had heart transplantation performed at 102 centers, Black individuals 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];  $P=0.002$ ).<sup>104</sup> Compared with White and Hispanic individuals, a higher proportion of Black individuals were treated at centers with higher-than-expected mortality, which persisted after adjustment for insurance type and education level.

## **Cost**

### **Overall Costs**

The overall cost of HF continues to rise. See Chapter 28 (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.<sup>32</sup> Projections suggest that by 2030 the total cost of HF will increase by 127%, to \$69.8 billion, amounting to  $\approx$ \$244 for every US adult.<sup>32</sup>
- The cost-effectiveness of implantable cardioverter defibrillators varies by annual cardiac mortality rate and sudden versus nonsudden death ratio. At a rate of 12%, the cost-effectiveness is \$36000 per QALY gained if the ratio of SCD to nonsudden cardiac death is 4 and \$116000 if the ratio

is 0.25.<sup>105</sup> In this context, the benefit might not be as great in those with high overall 1-year mortality (eg,  $\geq 75$  years of age, New York Heart Association functional class III, LVEF  $\leq 20\%$ , BNP  $\geq 700$  pg/mL, SBP  $\leq 120$  mm Hg, AF, diabetes, chronic lung disease, and CKD).<sup>106,107</sup>

- 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.<sup>108</sup>

### **Costs Associated With Mechanical Circulatory Support**

- 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 decreased markedly from the pulsatile LVAD (before 2008) to the continuous-flow LVAD (2008–2011) eras.<sup>109</sup> The mean cost of LVAD-related hospitalization increased from \$194380 in 2005 to \$234808 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 €100000 per QALY.<sup>110</sup>
- 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 LVADs, 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.<sup>111</sup>
- In a Markov model analysis, LVADs in patients with non-inotrope-dependent HF improved quality of life, at a substantial increase in costs, attributable mostly 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 \$209400 per QALY gained and \$597400 per life-year gained. Moreover, those results were sensitive to readmission rates and outpatient care costs.<sup>112</sup>
- On the basis of NIS data from 2009 to 2014, regional differences across the United States were noted in length of stay and cost after ventricular assist device implantation: In the Northeast, median length of stay was 32 days and median cost was \$192604; in the South, median length of stay was 27 days and median cost was \$198884; and in the West, median length of stay was 29 days and median cost was \$246292.<sup>97</sup>

## 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).<sup>113</sup> 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. For example, the prevalence of hypertension was high across all regions, with highest age- and sex-adjusted prevalence of 35% in Eastern and Central Europe and 33% in sub-Saharan Africa. In contrast, IHD prevalence in HF is highest in Europe and North America and rare in sub-Saharan Africa (unadjusted prevalence >50% in Western high-income and Eastern and Central Europe regions compared with <10% in sub-Saharan Africa).<sup>114</sup>
- 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.<sup>113</sup>
- In the INTER-CHF cohort study, both cause of HF and mortality after HF diagnosis varied by geographic region. The main cause of HF was attributed to IHD in 56% of cases in Southeast Asia, 50% of cases in the Middle East, 46% of cases in India, 45% of cases in China, 25% in South America, and 20% in Africa. When 1-year all-cause mortality among individuals with HF was examined, geographic variation was observed with multivariable-aHR of 3.8 (95% CI, 2.6–5.5) for Africa, HR of 2.9 (95% CI, 1.9–4.3) for India, HR of 2.6 (95% CI, 1.7–3.9) for Southeast Asia, HR of 1.3 (95% CI, 0.9–1.9) for the Middle East, and HR of 0.7 (95% CI, 0.4–1.1) for China compared with South America as the referent group.<sup>115</sup>

**Table 22-1. Global Prevalence and Mortality of Cardiomyopathy and Myocarditis, by Sex, 2020**

	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), 2020	0.37 (0.33 to 0.41)	6.11 (5.02 to 7.22)	0.23 (0.20 to 0.25)	3.41 (2.81 to 4.04)	0.14 (0.12 to 0.17)	2.70 (2.23 to 3.22)
Percent change in total number, 1990–2020	43.01 (29.79 to 55.73)	59.95 (53.96 to 66.69)	57.86 (42.26 to 74.64)	61.68 (55.04 to 68.81)	24.56 (10.88 to 37.41)	57.81 (51.84 to 64.72)
Percent change in total number, 2010–2020	−0.95 (−6.03 to 4.03)	18.24 (15.58 to 21.14)	−1.07 (−7.37 to 5.36)	17.23 (14.36 to 20.43)	−0.76 (−6.61 to 5.54)	19.54 (16.56 to 22.98)
Rate per 100 000, age standardized, 2020	4.69 (4.15 to 5.11)	76.92 (63.29 to 91.56)	6.20 (5.53 to 6.85)	88.75 (73.37 to 104.96)	3.32 (2.73 to 3.81)	65.88 (54.01 to 78.66)
Percent change in rate, age standardized, 1990–2020	−37.21 (−42.14 to −32.33)	−7.07 (−11.11 to −3.50)	−31.01 (−36.65 to −24.75)	−6.25 (−10.08 to −2.95)	−45.57 (−51.30 to −40.75)	−7.90 (−12.50 to −3.75)
Percent change (%) in rate, age standardized, 2010–2020	−23.86 (−27.57 to −20.17)	−1.40 (−3.11 to 0.19)	−22.81 (−27.35 to −18.16)	−2.48 (−4.45 to −0.71)	−25.15 (−29.40 to −20.44)	−0.08 (−2.33 to 1.96)

UI indicates uncertainty interval.

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington.

**Table 22-2. HF in the United States**

Population group	Prevalence, 2015–2018, age ≥20 y	Incidence, 2014, age ≥55 y	Mortality, 2019, all ages*	Hospital discharges, 2018, all ages	Cost, 2012†
Both sexes	6 000 000 (2.1%) [95% CI, 1.8%–2.4%]	1 000 000	86 177	1 250 000	\$30.7 billion
Males	3 400 000 (2.5%)	495 000	40 101 (46.6%)‡		...
Females	2 600 000 (1.7%)	505 000	46 076 (53.5%)‡		...
NH White males	2.4%	430 000§	32 335	...	...
NH White females	1.4%	425 000§	37 679	...	...
NH Black males	3.6%	65 000§	4721	...	...
NH Black females	3.3%	80 000§	5146	...	...
Hispanic males	2.4%	...	2066	...	...
Hispanic females	1.7%	...	2222	...	...
NH Asian males	1.9%	...	755	...	...
NH Asian females	0.7%	...	812	...	...
NH American Indian or Alaska Native	...	...	342	...	...

HF includes people who answered “yes” to the question of ever having congestive heart failure. 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; 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.

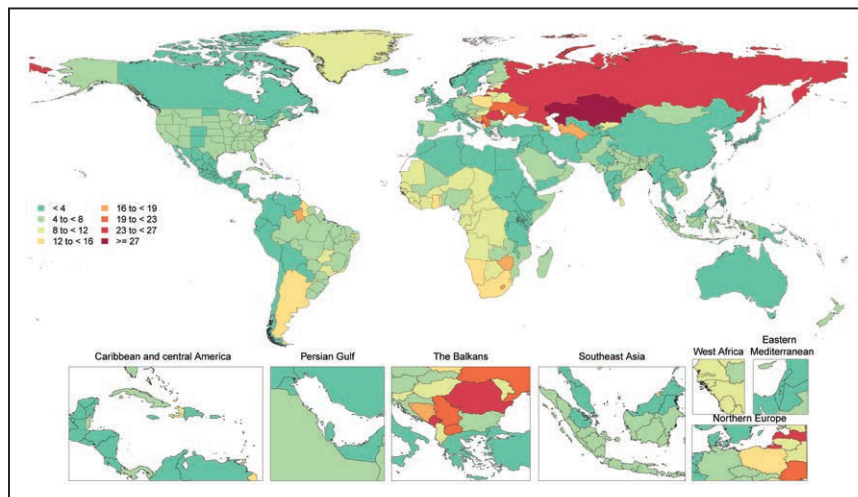
†Cost data are from Heidenreich et al.<sup>32</sup>

‡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.

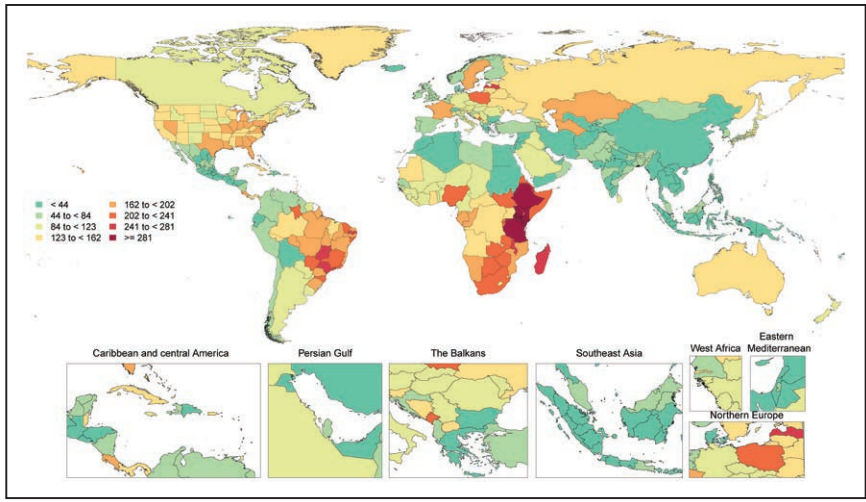
||Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander people.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey.<sup>31</sup> 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.<sup>116</sup> Mortality: Unpublished NHLBI tabulation using National Vital Statistics System.<sup>74</sup> Mortality for NH Asian people includes Pacific Islander people. Hospital discharges: Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project (data include those inpatients discharged alive, dead, or status unknown).<sup>1</sup>



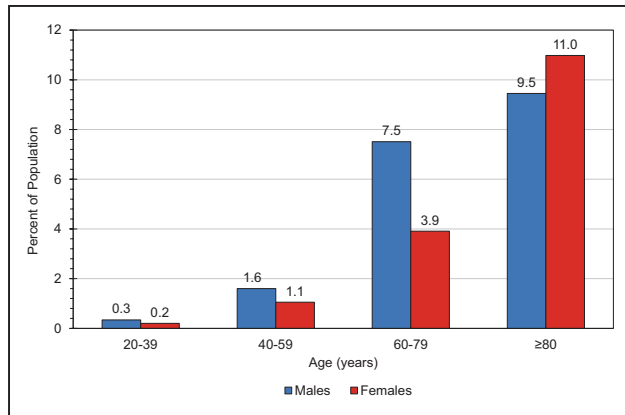
**Chart 22-1. Age-standardized global mortality rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2020.**

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease website.<sup>117</sup>

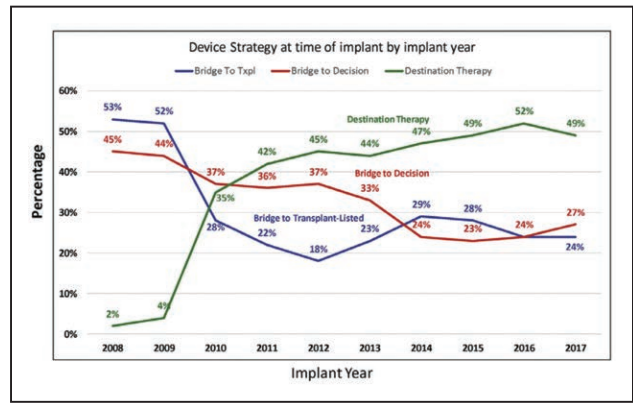


**Chart 22-2. Age-standardized global prevalence rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2020.**

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease website.<sup>117</sup>



**Chart 22-3. 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.<sup>31</sup>



**Chart 22-4. 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=18 359). Txpl indicates transplantation. Source: Reprinted from Kormos et al<sup>34</sup> with permission from the Society of Thoracic Surgeons. Copyright © 2019 Society of Thoracic Surgeons. Published by Elsevier Inc on behalf of the International Society for Heart and Lung Transplantation.

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## 23. VALVULAR DISEASES

See Tables 23-1 through 23-5 and Charts 23-1 through 23-7

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Mortality and any-mention mortality in this section are for 2019 and based on unpublished NHLBI tabulations using the NVSS and CDC WONDER.<sup>1,2</sup> Mortality is the number of deaths in 2019 for the given underlying cause according to *ICD-10*. Prevalence data are for 2016 and 2017. Hospital discharge data are from HCUP<sup>3</sup> (2018); data included are for inpatients discharged alive, dead, or status unknown. Hospital discharge data for 2018 are based on *ICD-10* codes.

### Valvular HD

#### *ICD-9 424; ICD-10 I34 to I38.*

2019: Mortality—24 192. Any-mention mortality—54 030.  
2018: Hospital discharges—132 000.

#### Prevalence

- In 2500 individuals  $\geq 65$  years of age from a primary care population screened with transthoracic echocardiography<sup>4</sup>:
  - The prevalence of previously undiagnosed, predominantly mild valvular HD was 5.1%.
  - The prevalence of undiagnosed moderate or severe valvular HD was 6.4%.
- 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%. Regurgitant lesions of moderate or greater severity were present in 2.4% of the population, and stenotic lesions of moderate or greater severity were present in 0.2%.<sup>5</sup>

#### 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 individuals  $\geq 65$  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.<sup>6</sup> Incidences of aortic regurgitation (incidence rate, 20.2 versus 10.8), aortic stenosis (incidence rate, 37.8 versus 24.2), and MR (incidence rate, 21.3 versus 16) were higher in males, who were also more frequently diagnosed at an earlier age (70 years versus 76 years). Mitral stenosis incidence was higher in females (incidence rate, 2.3 versus 1.5).<sup>6</sup>

### Aortic Valve Disorders

#### *ICD-9 424.1; ICD-10 I35.*

2019: Mortality—16 119. Any-mention mortality—35 766.  
2018: Hospital discharges—101 000.

#### Prevalence

- Prevalence of aortic stenosis by echocardiography was 4.3% among individuals  $\geq 70$  years of age in the Icelandic AGES-Reykjavik cohort.<sup>7</sup>
- 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%).<sup>8</sup>

#### 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.<sup>9</sup>
- In the Norwegian Tromsø study, the incidence of new aortic stenosis was 4.9 per 1000 per year, with the initial mean age of participants being 60 years.<sup>10</sup>
- 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).<sup>11</sup>

#### 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.<sup>12</sup>
- The pooled prevalence of all AS in the elderly was 12.4% (95% CI, 6.6%–18.2%), and the prevalence of severe AS was 3.4% (95% CI, 1.1%–5.7%).<sup>12</sup>

The 2022 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 2022. 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.

- In the Icelandic AGES-Reykjavik study alone, in both males and females, the prevalences for severe AS, defined as an aortic valve area index of  $<0.6 \text{ cm}^2/\text{m}^2$ , in the groups  $<70$ , 70 to 79, and  $\geq 80$  years of age were 0.92%, 2.4%, and 7.3%, respectively. Projections suggest a doubling in prevalence among those with severe aortic stenosis who are  $\geq 70$  years of age by 2040 and a tripling by 2060.<sup>7</sup>

### 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  $P<0.001$ ).<sup>11</sup>
- In the Copenhagen General Population Study, among 108 275 individuals, the risk of developing aortic stenosis was particularly high if BMI was  $\geq 35.0 \text{ kg}/\text{m}^2$  (HR, 2.6 [95% CI, 2.0–3.5]).<sup>13</sup>

### Genetics and Family History

- Bicuspid aortic valve is thought to be highly heritable, with estimates from 47% to as high as 89%.<sup>14,15</sup> Bicuspid aortic valve has been linked to variants of *NOTCH1*, *GATA5*, *GATA4*, *GATA6*, and *SMAD6*.<sup>16–20</sup>
- 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.<sup>21</sup>
- A GWAS in 6942 individuals identified a SNP located in an intron of the lipoprotein (a) gene that was significantly associated with the presence of aortic calcification (OR per allele, 2.05), circulating lipoprotein(a) levels, and the development of aortic stenosis.<sup>22</sup>
- A GWAS meta-analysis of 51 15 cases and 354 072 controls identified *IL6*, *ALPL*, and *NAV1* as susceptibility genes for calcific aortic valve stenosis,<sup>23</sup> adding to knowledge from previous GWASs and transcriptome studies of aortic valve stenosis that have established several loci, including *LPA*, *PALMD*, and *TEX41*.<sup>22,24–26</sup>
- 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.<sup>27</sup>

### Awareness, Treatment, and Control (See Chart 23-1)

- The annual volume of TAVR has increased each year since 2011.<sup>28</sup> After the US FDA approval of TAVR for low-risk patients in 2019, the TAVR volume exceeded all forms of SAVR ( $n=72\,991$  versus  $n=57\,626$ ).<sup>28</sup> From 2011 through 2018, extreme-risk and high-risk patients remained the largest cohort undergoing TAVI, but in 2019, intermediate-risk patients were the largest cohort, and the low-risk patients with a median of 75 years of age increased to 8395, comprising 11.5% of all patients with TAVI.
- Despite the increase in TAVR procedures, the percentage of Black individuals undergoing TAVR was 3.98% compared with 92.82% among White individuals in the STS/ACC TVT Registry.<sup>28,29</sup>
- The 276 316 patients with TAVR who entered the STS/ACC TVT Registry between 2011 to 2019 demonstrated<sup>28</sup>:
  - Decreased expected risk of 30-day operative mortality (STS Predicted Risk of Mortality score) from 7.2% to 2.5%.<sup>28</sup>
  - From 2018 data, overall 1-year mortality decreased to 12.6%, with mortality differing according to risk group and intermediate-risk patients experiencing in-hospital, 30-day, and 1-year mortality about half that of high- and extreme-risk patients.<sup>28</sup>
  - Overall in-hospital and 30-day stroke decreased to 1.6% and 2.3%, respectively, by 2019.
  - Incidence of permanent pacemaker implantation at 30 days had been stable over time at 10.8% but lower than 12% in 2015.<sup>28</sup>
- 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.<sup>30</sup> Over the same period (2011–2016), the number of SAVR procedures remained relatively stable at  $\approx 10\,000$  per year, a lower number than for TAVR (Chart 23-1). In the same European registry, mortality decreased continuously, with overall in-hospital mortality being similar for TAVR and SAVR (2.6% versus 2.9%, respectively;  $P=0.19$ ) in 2016 despite the higher risk profile in patients undergoing TAVR (Chart 23-1).
- 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%;  $P=0.0009$ ).<sup>31</sup>

### High-Risk Patients

- 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 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];  $P=0.76$ ).<sup>32</sup>
  - 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).<sup>33</sup> In the 5-year follow-up of this study, there were similar mid-term survival and stroke rates in high-risk patients after TAVR (55.3% all-cause mortality, 12.3% major stroke) or SAVR (55.4% all-cause mortality, 13.2% major stroke rates).<sup>34</sup>

### Intermediate-Risk Patients

- 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.<sup>35</sup>
- 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) group and SAVR group, respectively (HR, 1.09 [95% CI, 0.95–1.25];  $P=0.21$ ).<sup>36</sup> Overall, these findings demonstrate that TAVR is a noninferior alternative to SAVR in patients with severe aortic stenosis at intermediate surgical risk.<sup>36,37</sup>

### Low-Risk Patients

- In 1000 patients with severe aortic stenosis at low surgical risk randomized in the PARTNER 3 trial 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).<sup>38</sup>

- Similar results were obtained in the Evolut Low Risk trial using a self-expanding valve in low-risk patients with severe aortic stenosis.<sup>39</sup> 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.<sup>40</sup>
- 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 than in SAVR (RR, 3.16 [95% CI, 1.61–6.19]; heterogeneity  $P=0.60$ ,  $I^2=0\%$  at 2 years).<sup>41</sup>
- 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;  $P=0.02$ ).<sup>42</sup>

### Mortality

- With the use of ICD-10 data coded from 1999 to 2009, there were 146304 aortic valve disease deaths 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.<sup>43</sup>
- In 145 asymptomatic patients with 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;  $P=0.003$ ).<sup>44</sup>
- 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  $52\pm 4\%$  in males versus  $35\pm 6\%$  in females ( $P=0.01$ ).<sup>45</sup> Nevertheless, females have a significantly higher RR of death in tertiary and

surgical referral cohorts, with an age-adjusted relative risk of death of 1.63 (95% CI, 1.40–1.89) for females versus 1.34 (95% CI, 1.22–1.47) for males ( $P=0.026$ ).<sup>45</sup> The risk of death is independently associated with aortic regurgitation ( $P\leq 0.04$ ).

### Complications

- In a cohort of 416 community-based participants from Olmsted County, Minnesota, with bicuspid aortic valve followed up for a mean of 16 years (SD, 7 years)<sup>46</sup>:
  - The incidence of aortic dissection in individuals  $\geq 50$  years of age at baseline was 17.4 (95% CI, 2.9–53.6) cases per 10 000 patient-years.
  - The incidence of aortic dissection in individuals  $\geq 50$  years of age with a bicuspid valve and a baseline aortic aneurysm was 44.9 (95% CI, 7.5–138.5) cases per 10 000 patient-years.
  - The incidence of aortic aneurysm in the remaining participants without baseline aortic aneurysm was 84.9 (95% CI, 63.3–110.9) cases per 10 000 patient-years, for an age-aRR of 86.2 (95% CI, 65.1–114) compared with the general population.
- There are complications associated with valvular interventions, both percutaneous and surgical. In a meta-analysis of RCTs of TAVR versus SAVR, TAVR was significantly associated with a lower risk of acute kidney injury (RR, 0.27 [95% CI, 0.13–0.54];  $P=0.0002$ ), new-onset AF (RR, 0.26 [95% CI, 0.18–0.39];  $P<0.00001$ ), and life-threatening or disabling bleeding (RR, 0.35 [95% CI, 0.22–0.55];  $P<0.00001$ ) but a higher risk of moderate to severe paravalvular leak (RR, 4.40 [95% CI, 1.22–15.86];  $P=0.02$ ) and permanent pacemaker insertion (RR, 2.73 [95% CI, 1.41–5.28];  $P=0.003$ ).<sup>47</sup>
- 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];  $P<0.005$ ).<sup>48</sup>

### Cost

- In the 3110 intermediate-risk patients with AS treated with TAVR or SAVR in the PARTNER 2 trial and 1078 patients treated with TAVR using the SAPIEN 3 valve in the PARTNER S3i registry, procedural costs were estimated from measured resource use, from linkage of trial data with Medicare claims, or by linear regression models for unlinked patients.<sup>49</sup>
- Index procedure costs were more than \$20 000 higher with both XT-TAVR and SAPIEN 3 valves as a result of the higher cost of the TAVR valve

implantation compared with SAVR.<sup>49</sup> However, the higher procedure costs associated with TAVR were offset by significant reductions in other costs, especially by reductions in total length of stay. 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 (differences of 4.5 and 6.3 days with XT-TAVR and SAPIEN 3 valve, respectively;  $P<0.001$  compared with SAVR for both comparisons).<sup>49</sup>

- TAVR also reduced the need for rehabilitation services at discharge and was associated with improved 1-month quality of life. TAVR had higher index admission and projected lifetime costs than SAVR (differences of \$11 260 and \$17 849 per patient, respectively). However, TAVR was estimated to provide a lifetime gain of 0.32 QALYs (0.41) with 3% discounting. Lifetime incremental cost-effectiveness ratios were \$55 090 per QALY gained and \$43 114 per life-year gained. On the basis of sensitivity analyses, a reduction in the initial cost of TAVR by  $\approx$ \$1650 was expected to lead to an incremental cost-effectiveness ratio of  $<$ \$50 000 per QALY gained.<sup>49</sup>
- 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.<sup>50</sup>
- In patients undergoing TAVR at low surgical risk in the Danish health care system, the incremental cost-effectiveness ratios (range, 334 200–904 100 Danish kroner per QALY gained) were all below the country-specific willingness to pay of 1.13 million Danish kroner.<sup>51</sup>

### Global Burden (See Table 23-1)

- The global burden of calcific aortic valve disease is shown in Table 23-1.

### Mitral Valve Disorders

#### ICD-9 424.0; ICD-10 I34.

2019: Mortality—2673. Any-mention mortality—6387.

2018: Hospital discharges—29 000.

Primary MR includes Carpentier functional classification system 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).

### Prevalence

- A systematic review by de Marchena et al<sup>52</sup> found that in the US population, the prevalence of MR according to Carpentier type 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

### 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.<sup>53–55</sup>

### Genetics and Family History

- Among 3679 young to middle-aged Third Generation participants in the FHS with available parental data, 49 (1%) had mitral valve prolapse.<sup>56</sup> 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*.<sup>57–61</sup>
- An exome sequencing study identified potential associations between variants in known cardiomyopathy genes (*DSP*, *HCN4*, *MYH6*, *TMEM67*, *TRPS1*, and *TTN*) and mitral valve prolapse.<sup>62</sup>
- 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  $P<0.05$ ).<sup>63</sup> 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.<sup>63</sup>

### Awareness, Treatment, and Control

#### (See Table 23-2 and Charts 23-2 through 23-4)

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 (564 patients (56% male; median age, 83 years) commercially treated with the MitraClip percutaneous mitral valve repair device showed the following<sup>64</sup>: 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%.<sup>65</sup>
- 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 23-2) from 2503 procedures in 2015 to 7230 in 2018.<sup>66</sup> Use of MitraClip procedures has also increased in Asia, although at a slower pace (Chart 23-3 and Table 23-2), with the highest increase seen in Japan from 18 procedures in 2011 to 439 procedures in 2018.
- The role of MitraClip in secondary MR has been investigated in 2 published randomized clinical trials with divergent results that may be related to differences in sample characteristics, sample size, duration of follow-up, and primary end point (Chart 23-4).<sup>67–69</sup>
  - 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 to severe or severe secondary MR who were symptomatic (New York Heart Association functional class II–IV) despite optimal medical therapy and cardiac resynchronization therapy.<sup>68</sup> With MitraClip, there was a significant reduction in the primary end point of rehospitalization for 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];  $P<0.001$ ).

- 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.<sup>70</sup>
- In patients with severe chronic MR secondary to ischemic cardiomyopathy undergoing CABG surgery, survival rates were not significantly different without and with mitral valve repair (1-, 5-, and 10-year survival: 88%, 75%, and 47% versus 92%, 74%, and 39%, respectively;  $P=0.6$ ).<sup>71</sup> 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];  $P=0.81$ ).<sup>72</sup> However, repairing mitral valve along with CABG yields improvement in postoperative residual MR (standard mean differences, 0.28 [95% CI, 0.10–0.46];  $P<0.01$ ) and LVEF (standard mean difference, 4.22 [95% CI, –6.48 to –1.97];  $P<0.0001$ ) in patients with significant ischemic MR.<sup>73</sup>
- 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.<sup>74</sup>

### Mortality

- With the use of data from Mayo Clinic electronic health records and the Rochester Epidemiology Project to identify all cases of moderate or severe isolated MR diagnosed during a 10-year period in the community setting in Olmsted County, Minnesota, at 15 years of follow-up, females with no or mild MR had better survival than males (87% versus 77%; aRR, 0.82 [95% CI, 0.76–0.89]). In contrast, in individuals with severe MR, females had worse survival than males (60% versus 68%; aRR, 1.13 [95% CI, 1.01–1.26]). Survival 10 years after surgery was similar in females and males (77% versus 79%;  $P=0.14$ ).<sup>74</sup>
- 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).<sup>75</sup>

### 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<sup>76</sup>; however, females had fewer complications (flail leaflet occurred in 2% versus 8% in males and severe regurgitation in 10% versus 23%; all  $P<0.001$ ). 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  $82\pm 1\%$ ,  $70\pm 4\%$ , and  $57\pm 3\%$ , respectively ( $P<0.0001$ ).<sup>77</sup>

### Cost

- Lifetime costs, life-years, QALYs, and incremental cost per life-year and QALYs gained were estimated for patients receiving MitraClip therapy compared with standard of care for primary MR.<sup>78</sup> 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 (2013 Canadian 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 to 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 incremental cost-effectiveness ratio of \$40 361 per life-year and \$55 600 per QALY gained.<sup>79</sup>

### Global Burden (See Table 23-3)

- The global burden of degenerative mitral valve disease is shown in Table 23-3.

### Pulmonary Valve Disorders

#### ICD-9 424.3; ICD-10 I37.

2019: Mortality—17. Any-mention mortality—65.

- Pulmonic valve stenosis is a relatively common congenital defect, occurring in  $\approx 10\%$  of children with congenital HD.<sup>80</sup> Among 44 neonates with critical pulmonic stenosis who underwent balloon pulmonic 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.<sup>81</sup>
- 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.<sup>82</sup>

- The most common cause of severe pulmonic regurgitation is iatrogenic, resulting from surgical valvotomy/valvectomy or balloon pulmonary valvuloplasty performed for RV outflow tract obstruction as part of TOF repair.<sup>83</sup> Transcatheter pulmonic valve implantation of either a Melody or a SAPIEN valve is effective and relatively safe,<sup>83–85</sup> with serious complications occurring in only 3 patients (1 died and 2 required surgical intervention in a study using the NIS database, which included 57 transcatheter pulmonic valve implantation procedures performed in 2012).<sup>86</sup> 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.<sup>87</sup>
- 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.<sup>88</sup> 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.

2019: Mortality—67. Any-mention mortality—224.

- 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.<sup>89</sup> 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 mmHg; HR, 1.32 [95% CI, 1.05–1.62] for pulmonary artery systolic pressure ≤40 mmHg) 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%).<sup>89</sup>
- 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];  $P<0.001$ ).<sup>90</sup>

- 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%.<sup>91</sup>
- Outcomes of transcatheter tricuspid valve interventions were analyzed in 317 high-risk patients with severe tricuspid regurgitation from the international Trivalve registry.<sup>92</sup> 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%;  $P<0.0002$ ).

## Rheumatic Fever/Rheumatic HD

### ICD-9 390 to 398; ICD-10 I00 to I09.

2019: Mortality—3647. Any-mention mortality—7495.

2018: 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.<sup>93</sup>

#### Subclinical Disease

- The prevalence of subclinical or latent rheumatic HD among children is estimated by echocardiography and can be classified as definite or borderline.<sup>94</sup> 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.<sup>95–98</sup>
- 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.<sup>99–102</sup>
- 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%).<sup>103</sup>

- 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.<sup>104</sup>

### Awareness, Treatment, and Control

- REMEDY is a prospective registry of 3343 patients with rheumatic HD from 25 hospitals in 12 African countries, India, and Yemen.<sup>105</sup> This 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 one-quarter of these had therapeutic international normalized ratios.
- 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%]).<sup>106</sup>

### Mortality

#### (See Table 23-4)

- In the United States in 2019, mortality attributable to rheumatic fever/rheumatic HD was 3647 for all ages (2368 females and 1279 males; Table 23-4).
- 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.<sup>107</sup>
- 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 23-4). Recent declines in mortality have been slowest in the South compared with other regions.<sup>107</sup>

### 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.<sup>105</sup> 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.<sup>108</sup>
- 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.<sup>109</sup>

- The PAR of rheumatic HD for maternal mortality may approach 10% in sub-Saharan Africa.<sup>110</sup>

### Global Burden of Rheumatic HD

#### (See Charts 23-5 through 23-7)

- The age and sex distributions of the subjects in the REMEDY study are shown in Chart 23-5. Rheumatic HD was twice as common among females, a finding consistent with prior studies across a variety of populations.<sup>105</sup>
- 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.<sup>111</sup> 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.<sup>108</sup>
- The GBD 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020. (Data courtesy of the Global Burden of Disease Study 2020.)
  - In 2020, there were 0.39 million (95% UI, 0.33–0.46 million) deaths estimated for rheumatic HD, a decrease of 1.54% (95% UI, –12.05% to 9.72%) from 2010 to 2020.
  - There was substantial geographic heterogeneity in age-standardized mortality estimated for rheumatic HD, with the highest rates in South Asia and Oceania (Chart 23-6).
  - The number of prevalent cases of rheumatic HD in 2020 was 54.23 million (95% UI, 43.53–66.92 million), an increase of 16.57% (95% UI, 15.38%–17.92%) compared with 2010.
  - Rheumatic HD age-standardized prevalence was highest in sub-Saharan Africa and parts of Latin America (Chart 23-7).

### Infective Endocarditis

#### ICD-9 421.0; ICD-10 I33.0.

2019: Mortality—1584. Any-mention mortality—3474.

2018: Hospital discharges—13 000.

### Prevalence and Incidence

#### (See Table 23-5)

- In 2011, there were 47 134 cases of IE and valve replacement in the United States (Table 23-5).
- 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.<sup>113</sup>



- 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.<sup>114</sup>

### 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 decade from 2000 to 2011 and a corresponding decrease in streptococcal endocarditis (32% to 17%) over the same time period.<sup>115</sup>
- 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 (73% vs. 63%;  $P<0.01$ ).<sup>116</sup>
- Data from the NIS (2000–2011) 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<sup>117</sup> (change in slope of *S epidemidis* per 1 000 000 US population between 2000 to 2007 and 2007 to 2011, 1.00 [95% CI, –0.40 to 2.53];  $P=0.13$ ).<sup>118</sup> These findings from referral centers were corroborated by a community-based review of adults in Olmsted County, Minnesota, where 51 cases of IE were documented between 2007 and 2013 with no significant difference in incidence of IE during the study period ( $P=0.222$ ), although incidence was significantly higher in males and those of older age ( $P<0.001$ ).<sup>113</sup>
- 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<sup>119</sup> 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%];  $P=0.7$ ).

### 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  $1.1\pm 0.4\%$  (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.
- There was a higher incidence of IE in patients with mitral valve prolapse and moderate, moderate to severe, or severe MR (289.5 cases per 100 000 person-years [95% CI, 108.7–771.2];  $P=0.02$  compared with trivial, mild, or mild to moderate MR) and in patients with a flail mitral leaflet (715.5 cases per 100 000 person-years [95% CI, 178.9–2861.0];  $P=0.02$  compared with no flail mitral leaflet).<sup>120</sup>
- Among 20 006 patients in the IE After TAVI International Registry, the incidence of IE after TAVI was 1.1% per person-year (95% CI, 1.1%–1.4%) with an in-hospital mortality rate of 36% (95% CI, 30.0%–41.9%).<sup>121</sup> In the SwissTAVI Registry, IE after TAVI occurred most frequently in the early period (<100 days, 2.59 events per 100 person-years) and was most commonly caused by *Enterococcus* species (30.1% of cases).<sup>122</sup>
- Antibiotic prophylaxis is currently not recommended for bicuspid aortic valve and mitral valve prolapse.<sup>117</sup> 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 those at low or moderate risk (50% and 47.2% versus 30.6%; both  $P<0.01$ ) and had complications similar to those of patients in the high-risk group.<sup>123</sup>

### 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.<sup>124</sup>
- 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];  $P=0.40$ ).<sup>125</sup> Longer-term

outcomes in this trial showed that after a median follow-up of 3.5 years, the primary composite end point had occurred in 38.2% patients in the intravenous group and 26.4% in the oral antibiotic group (HR, 0.64 [95% CI, 0.45–0.91]).<sup>126</sup>

### Mortality

- According to the GBD 2020 study, the age-standardized death rate of endocarditis in 2020 was 0.93 (95% UI, 0.82–1.05) per 100 000.<sup>112</sup>
- 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]).<sup>127</sup>
- In-hospital and 1-year mortality rates for patients with cardiac devices 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]).<sup>114</sup>
- 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.<sup>128</sup>

### 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%.<sup>129</sup> 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;  $P=0.003$ ).<sup>129</sup>
- 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%;  $P=0.58$ ).<sup>129</sup>

### Heart Valve Procedure Costs

- In 2014, for heart valve procedures<sup>130</sup>:
  - The mean inflation-adjusted cost per hospitalization in 2014 dollars was \$51 896 compared with \$56 426 in 2010 and \$44 609 in 2000.
  - The number of discharges for which heart valve surgery was the principal operating room procedure was 110 915, which was an increase from 98 101 in 2010 and 79 719 in 2000.
- Total inflation-adjusted national cost in 2014 dollars (in millions) was \$5756, which was an increase from the mean cost (in millions) of \$5541 in 2010 and \$3550 in 2000.<sup>130</sup>

**Table 23-1. Global Mortality and Prevalence of Nonrheumatic Calcific Aortic Valve Disease, by Sex, 2020**

	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), 2020	0.14 (0.12 to 0.16)	13.03 (11.25 to 14.75)	0.06 (0.05 to 0.06)	7.14 (6.19 to 8.11)	0.08 (0.07 to 0.09)	5.89 (5.05 to 6.70)
Percent change in total number, 1990–2020	150.22 (129.10 to 168.97)	177.65 (163.36 to 193.79)	137.35 (119.43 to 155.92)	186.21 (171.82 to 203.03)	160.40 (133.41 to 180.34)	167.94 (151.21 to 186.54)
Percent change in total number, 2010–2020	38.78 (34.63 to 42.57)	32.81 (28.68 to 37.12)	40.93 (35.97 to 46.00)	34.89 (30.25 to 39.87)	37.27 (32.42 to 41.56)	30.36 (25.75 to 35.27)
Rate per 100 000, age standardized, 2020	1.93 (1.60 to 2.12)	161.29 (139.84 to 182.58)	2.01 (1.78 to 2.16)	197.47 (171.55 to 223.75)	1.83 (1.47 to 2.06)	131.13 (112.56 to 149.04)
Percent change in rate, age standardized, 1990–2020	0.87 (–6.18 to 7.05)	22.21 (15.67 to 29.80)	2.04 (–4.73 to 8.61)	23.29 (17.01 to 31.07)	0.92 (–7.77 to 7.61)	19.46 (12.11 to 27.90)
Percent change in rate, age standardized, 2010–2020	–3.34 (–5.75 to –1.00)	–1.50 (–4.53 to 1.67)	–1.10 (–4.09 to 1.90)	–0.20 (–3.64 to 3.48)	–4.58 (–7.50 to –1.69)	–2.98 (–6.37 to 0.61)

UI indicates uncertainty interval.

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington.

**Table 23-2. MitraClip Milestones in the Asia-Pacific Region**

Country	Date of first implantation	Site of first implantation	Type of MR indicated	Reimbursement
Australia	March 23, 2011	Sir Charles Gairdner Hospital	FMR, DMR	No
Singapore	April 14, 2011	National Heart Centre Singapore	FMR, DMR	No
Malaysia	December 14, 2011	Institut Jantung Negara	FMR, DMR	No
Hong Kong	July 18, 2012	Hong Kong Adventist Hospital	FMR, DMR	No
Indonesia	February 23, 2013	Medistra Hospital	FMR, DMR	No
Brunei	February 25, 2014	Gleneagles Jerudong Park Medical Centre	FMR, DMR	No
New Zealand	March 22, 2014	Braemar Hospital: Midland Cardio-Vascular Services	FMR, DMR	No
Philippines	May 23, 2014	St. Luke's Medical Center	FMR, DMR	No
Vietnam	September 21, 2014	Bach Mai Hospital	FMR, DMR	No
Thailand	October 12, 2015	Central Chest Institute of Thailand	FMR, DMR	No
Taiwan	May 1, 2016	Taipei Veterans General Hospital	FMR, DMR	No
Pakistan*	September 17, 2017	Rawalpindi Institute of Cardiology	FMR, DMR	No
Japan	April 2, 2018	Sendai Kousei Hospital	FMR, DMR	Yes
India*	November 26, 2018	Fortis Escorts Heart Institute	FMR, DMR	No

DMR indicates degenerative mitral regurgitation; FMR, functional mitral regurgitation; and MR, mitral regurgitation.

\*Special access.

Source: Data derived from Wong et al.<sup>131</sup>

**Table 23-3. Global Prevalence and Mortality of Nonrheumatic Degenerative Mitral Valve Disease, 2020**

	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), 2020	0.04 (0.03 to 0.04)	15.27 (14.25 to 16.40)	0.01 (0.01 to 0.02)	9.66 (9.00 to 10.40)	0.02 (0.02 to 0.03)	5.61 (5.26 to 5.99)
Percent change in total number, 1990–2020	57.64 (45.18 to 70.97)	114.53 (108.69 to 119.86)	66.09 (51.83 to 83.01)	123.21 (116.64 to 129.20)	52.98 (37.24 to 69.97)	101.08 (95.52 to 106.34)
Percent change in total number, 2010–2020	30.13 (24.85 to 35.21)	29.77 (25.98 to 31.63)	35.22 (28.55 to 42.53)	31.67 (27.24 to 34.15)	27.25 (20.53 to 33.61)	26.62 (24.02 to 28.51)
Rate per 100 000, age standardized, 2020	0.48 (0.41 to 0.53)	186.90 (174.55 to 200.36)	0.42 (0.36 to 0.47)	264.71 (247.02 to 284.37)	0.52 (0.43 to 0.59)	124.73 (116.85 to 133.06)
Percent change in rate, age standardized, 1990–2020	−32.20 (−36.74 to −27.04)	−4.59 (−6.94 to −2.41)	−28.01 (−33.33 to −21.90)	−4.91 (−7.29 to −2.58)	−34.01 (−39.73 to −26.95)	−8.42 (−10.70 to −6.07)
Percent change in rate, age standardized, 2010–2020	−5.56 (−9.23 to −1.98)	−4.09 (−6.86 to −2.71)	−1.29 (−5.64 to 3.33)	−3.86 (−7.10 to −1.98)	−7.05 (−11.97 to −2.23)	−5.62 (−7.55 to −4.18)

UI indicates uncertainty interval.

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**Table 23-4. Rheumatic Fever/Rheumatic HD in the United States**

Population group	Mortality, 2019: all ages*	Hospital discharges, 2018: all ages
Both sexes	3647	26 000
Males	1279 (35.1%)†	
Females	2368 (64.9%)†	
NH White males	1006	...
NH White females	1899	...
NH Black males	130	...
NH Black females	208	...
Hispanic males	81	...
Hispanic females	136	...
NH Asian or Pacific Islander males	53‡	...
NH Asian or Pacific Islander females	104‡	...
NH American Indian or Alaska Native	22	...

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<sup>1</sup>; data represent underlying cause of death only. Hospital discharges: Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project<sup>2</sup>; data include those inpatients discharged alive, dead, or status unknown.

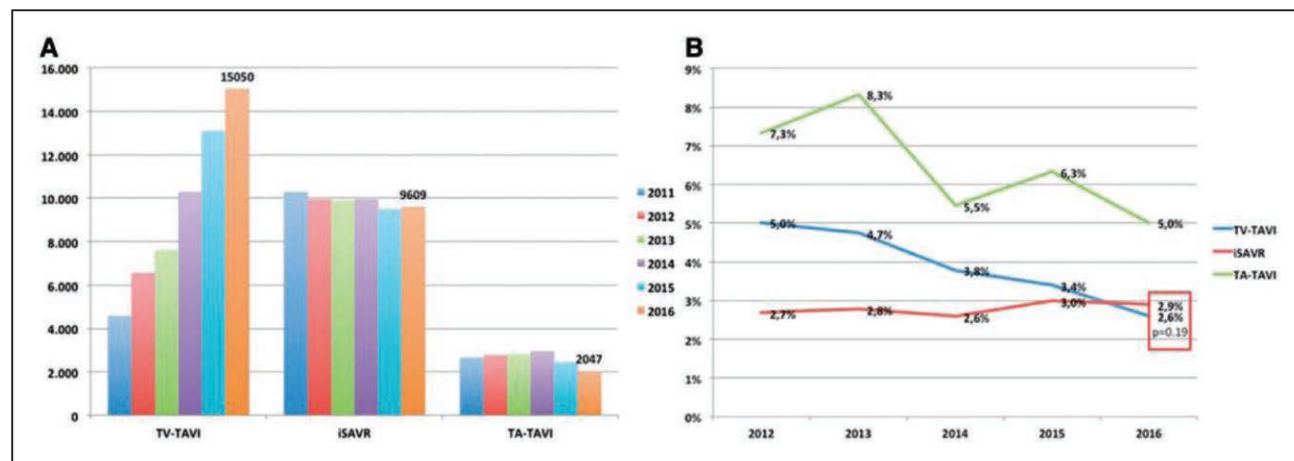
**Table 23-5. Incidence of IE and Valve Replacement, United States, 2000 to 2011**

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<sup>18</sup> with permission from the American College of Cardiology Foundation. Copyright © 2015 American College of Cardiology Foundation.

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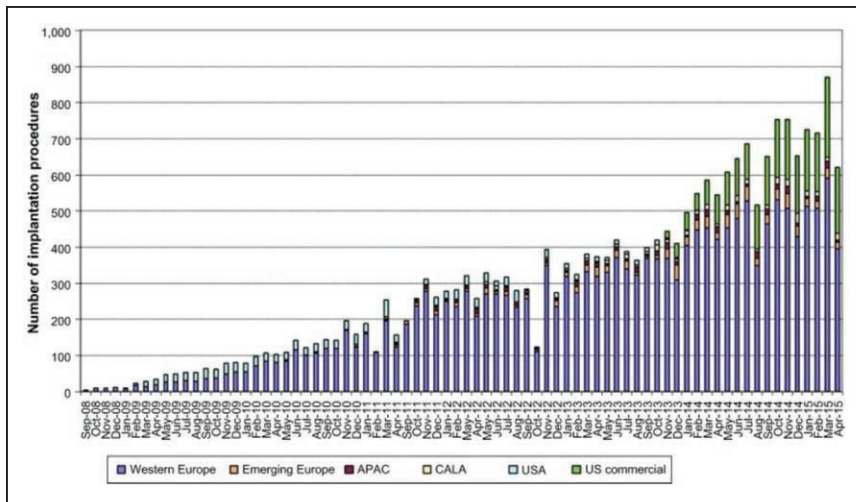


**Chart 23-1. Number of TAVI and SAVR procedures performed and in-hospital mortality according to type of procedure, Germany, 2011 to 2016.**

**A**, Number of TAVI and SAVR procedures. **B**, In-hospital mortality. iSAVR indicates isolated surgical aortic valve replacement; SAVR, surgical aortic valve replacement; TA, transapical; TAVI, transcatheter aortic valve implantation; and TV, transvascular.

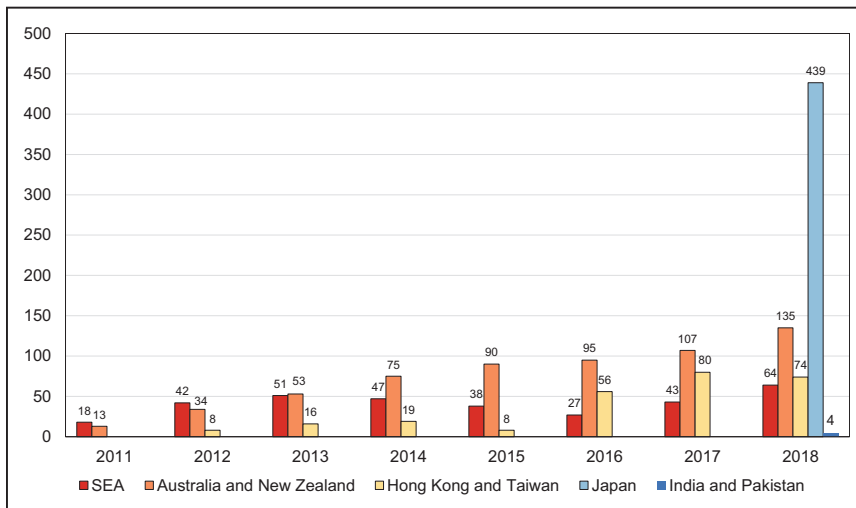
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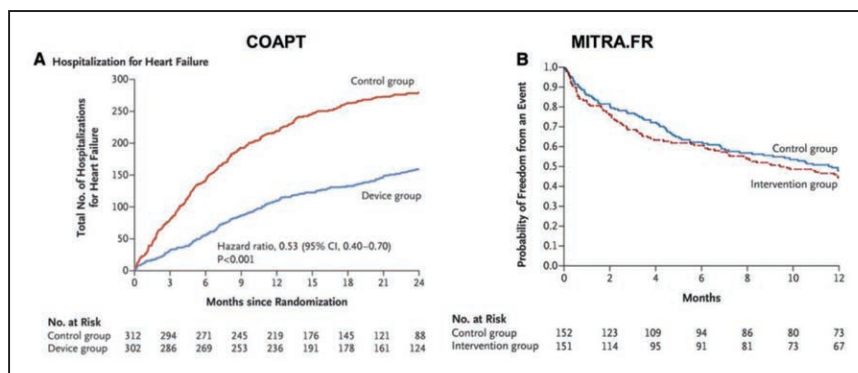
**Chart 23-2. Worldwide experience with the MitraClip procedure from September 2008 until April 2015.**

As of 2021, more than 100 000 patients have been treated worldwide. APAC indicates Asia-Pacific; and CALA, Caribbean and Latin America. Source: Figure courtesy of Abbott Laboratories. Abbott, Abbott A, and MitraClip are trademarks of Abbott or its related companies. Reproduced with permission of Abbott, © 2021. All rights reserved.



**Chart 23-3. Asia-Pacific MitraClip cases, 2011 to 2018.**

SEA indicates Southeast Asia (Singapore, Malaysia, Indonesia, Brunei, Philippines, Vietnam, Thailand). Source: Data derived from Wong et al.<sup>131</sup>

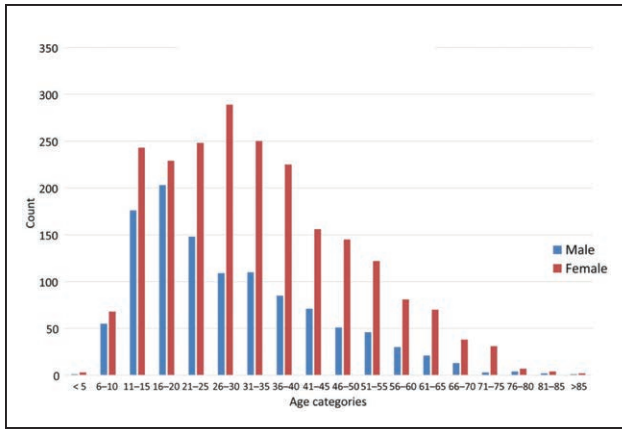


**Chart 23-4. Comparison of primary outcomes after MitraClip implantation for secondary mitral regurgitation in the COAPT and MITRA-FR trials.**

**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.

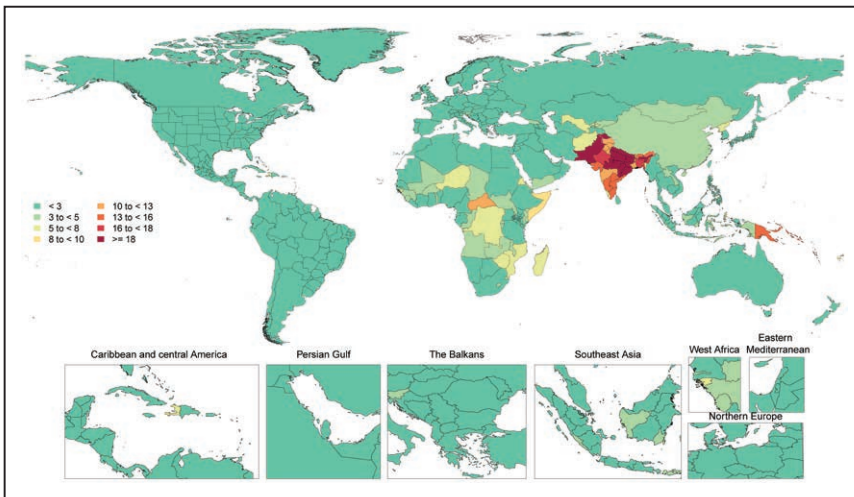
Source: **A**, Reprinted from Stone et al<sup>68</sup> with permission from the Massachusetts Medical Society. Copyright © 2018 Massachusetts Medical Society. **B**, Reprinted from Obadia et al<sup>69</sup> with permission from the Massachusetts Medical Society. Copyright © 2018 Massachusetts Medical Society.



**Chart 23-5. Age and sex distribution of 3343 subjects with rheumatic HD participating in the REMEDY study, 2010 to 2012.**

HD indicates heart disease; and REMEDY, Global Rheumatic Heart Disease Registry.

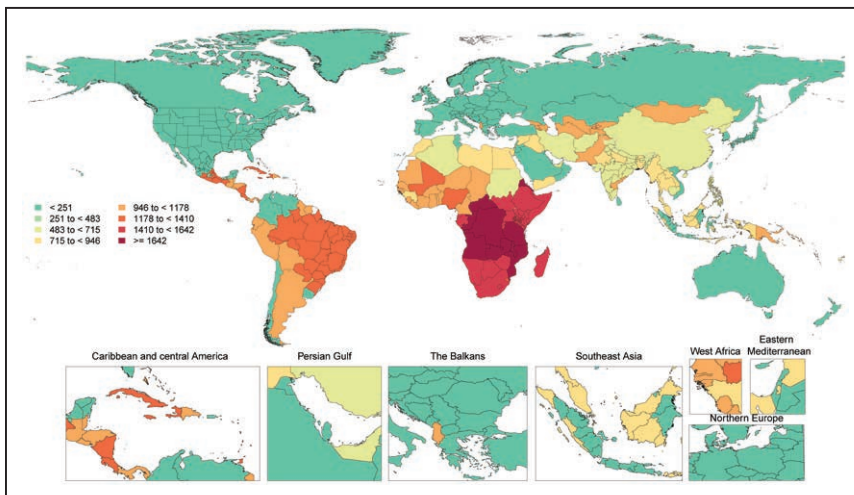
Source: Reprinted from Zühlke et al<sup>105</sup> with permission of the European Society of Cardiology. Copyright © 2014, The Authors. Published by Oxford University Press on behalf of the European Society of Cardiology.



**Chart 23-6. Age-standardized global mortality rates of rheumatic HD per 100 000, both sexes, 2020.**

HD indicates heart disease.

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease website.<sup>132</sup>



**Chart 23-7. Age-standardized global prevalence rates of rheumatic HD per 100 000, both sexes, 2020.**

HD indicates heart disease.

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease website.<sup>132</sup>

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## 24. VENOUS THROMBOEMBOLISM (DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM), CHRONIC VENOUS INSUFFICIENCY, PULMONARY HYPERTENSION

See Charts 24-1 through 24-3

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[Click here to return to the Abbreviations](#)

In this chapter, 2019 mortality data come from unpublished NHLBI tabulations using the NVSS<sup>1</sup> and CDC WONDER.<sup>2</sup> Hospital discharge data, from 2017, come from unpublished NHLBI tabulations using the HCUP.<sup>3</sup>

### Pulmonary Embolism

**ICD-9 415.1; ICD-10 I26.**

2019: Mortality—8615. Any-mention mortality—37 571.

2018: Hospital discharges—190 000 (principal diagnosis), 389 000 (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.**

2019: Mortality—3147. Any-mention mortality—17 730.

2018: Hospital discharges—86 000 (principal diagnosis), 626 000 (all-listed diagnoses).

### Venous Thromboembolism

#### Incidence

(See Charts 24-1 and 24-2)

- VTE includes both PE and DVT. In 2018, there were an estimated  $\approx$ 389 000 cases of PE (HCUP NIS<sup>3</sup>; Chart 24-1),  $\approx$ 626 000 cases of DVT (HCUP NIS<sup>3</sup>; Chart 24-2), and  $\approx$ 1 015 000 total VTE cases in the United States (US population was 327 million in

2018); these estimates used the all-listed diagnoses hospitalization data and assumed that 30% of DVTs were treated in an outpatient setting.

- In 2018, there were 217 000 ED visits with a principal diagnosis of DVT (unpublished NHLBI tabulation using HCUP<sup>3</sup>).
- Data from >1.8 million outpatient surgeries in the United States between 2005 and 2016 found an incidence of 0.19% postoperative VTE.<sup>4</sup> As expected, vascular interventions showed higher VTE rates after surgery (0.85%).
- The CHS cohort found a higher VTE incidence in Black individuals compared with White individuals (HR, 1.81 [95% CI, 1.20–2.73]), although this is intensified by SES in the REGARDS cohort (Black individuals in the southeast versus Black individuals in the rest of the United States, *P* for interaction=0.01).<sup>5</sup>
- VTE incidence was high during the COVID-19 pandemic, varying between 14.1% (95% CI, 11.6%–16.9%) and 31% (95% CI, 24.3%–39.2%) in hospitalized populations according to several meta-analyses.<sup>6–9</sup> PE incidence was 16.5% (95% CI, 11.6%–22.9%), and DVT incidence was 14.8% (95% CI, 8.5%–24.5%). Patients admitted to the ICU had 2- to 3-fold higher incidence of VTE than those who did not need intensive care (PE: pooled incidence, 24.7% [95% CI, 18.6%–32.1%] versus 10.5% [95% CI, 5.1%–20.2%], respectively; DVT: pooled incidence, 21.2% [95% CI, 11.1%–36.8%] versus 7.4% [95% CI, 3.2%–16.2%]).<sup>10</sup> It is important to note most COVID-19 studies have issues related to selection bias attributable to the severity of the condition of the population admitted in most high-volume tertiary care centers.

#### Lifetime Risk

- The 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 variant, 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.<sup>11</sup>

#### Secular Trends

(See Charts 24-1 and 24-2)

- The HCUP NIS (Chart 24-1) shows increasing numbers of hospitalized cases for PE from 1996 to 2016. Focusing on all-listed diagnoses (Chart 24-2), the number of hospitalized DVT cases also increased from 2005 to 2016, probably driven by an increase in VTE diagnosis that might overstate changes in VTE incidence. Improvements in VTE screening, as predictive scores, wider access to imaging tests for specific conditions,<sup>12–15</sup> and other factors (eg, outpatient management of  $\approx$ 35% of

The 2022 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 2022. 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.

DVT cases<sup>16</sup> and a smaller portion of PE cases,<sup>17,18</sup> misdiagnosis of VTE events, and failure to ascertain fatal PEs because of low autopsy rates), could lead to underestimation of VTE incidence.

- 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.<sup>19</sup> 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.<sup>20–23</sup>
- Hospitalized patients are at particularly high risk of VTE; a 2019 publication demonstrated that asymptomatic DVT was associated with a greater risk of death among acutely ill hospitalized patients (HR, 2.31 [95% CI, 1.52–3.51]).<sup>24</sup>
- Independent VTE risk factors, beyond the provoking factors noted above, include increasing age (HR, 2.67 per decade [95% CI, 2.45–2.91]); obesity (HR, 1.43 [95% CI, 1.35–1.50]); family history or personal history of thrombosis; indwelling central venous catheter or transvenous pacemaker; prior superficial vein thrombosis; infection; autoimmune disease as both cutaneous (HR, 1.39 [95% CI, 1.10–1.78]) and systemic lupus erythematosus (HR, 3.32 [95% CI, 2.73–4.03]); inherited or acquired thrombophilia; kidney disease (HR, 1.54 [95% CI, 1.15–2.06]); AF; neurological disease with leg paresis; sickle cell anemia and sickle cell trait (HR for PE, 2.05 [95% CI, 1.12–3.76]); and long-distance travel (pooled RR, 2.8 [95% CI, 2.2–3.7]).<sup>25–30</sup>
- Presence of HF was associated with a 3-fold greater VTE risk (HR, 3.13 [95% CI, 2.58–3.80]) in a 2019 publication from the ARIC study. The association was present for both HFpEF and HFrEF.<sup>31</sup>
- Use of testosterone therapy was also associated with doubling of VTE risk in males with and without evidence of hypogonadism.<sup>32</sup> 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.<sup>33,34</sup> In one of the meta-analyses, cigarette smoking was associated with provoked but not with unprovoked VTE events.<sup>33</sup>
- Among females, VTE risk is elevated among those using estrogen-based contraceptives, hormone therapy, or infertility treatment.<sup>35</sup>
- 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.<sup>36</sup> An analysis in the GARFIELD-VTE study population showed that, in pregnant women with VTE, the classic risk factors present were obesity, hospitalization, prior surgery, family history of VTE, and diagnosis of thrombophilia. In addition, there was a lower likelihood of PE.<sup>37</sup>

### Family History and Genetics

- VTE is highly heritable, estimated to be 47% for males and 40% for females from an analysis of 881 206 full-sibling pairs and 95 198 half-sibling pairs in the Swedish Multi-Generation Register.<sup>38</sup>
- FVL is the most common inherited thrombophilia in populations of European descent (prevalence, 5.2%) but is rare in African (1.2%) and Asian (0.45%) populations.<sup>39</sup> In ARIC, ≈5% of White and <1% of Black people were heterozygous carriers of FVL, and lifetime risk of VTE was 17.1% in individuals with the FVL genetic variant.<sup>11</sup> 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.<sup>40</sup>
- Antithrombin deficiency is a rare variant that is associated with greatly increased risk of incident VTE (OR, 14.0 [95% CI, 5.5–29.0]).<sup>41</sup> A bayesian meta-analysis found that for childbearing females with this variant, VTE risk was 7% in the antepartum period and 11% postpartum.<sup>42</sup>
- Whole-exome sequencing of a panel of 55 thrombophilia genes in 64 patients with VTE identified a probable disease-causing genetic variant or variant of unknown significance in 39 of 64 individuals (60.9%).<sup>43</sup>
- More common genetic variants associated with VTE have a lesser risk of VTE than rare variants and include non-O blood group, prothrombin 20210A, and sickle cell disease and trait.<sup>44</sup> GWASs have identified additional common genetic variants associated with VTE risk, including variants in *F5*, *F2*, *F11*, *FGG*, and *ZFPM2*.<sup>45</sup> 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.<sup>46</sup>
- 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.<sup>47,48</sup>



## 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 use of direct oral anticoagulants.<sup>49</sup>
- Addressing VTE prevention in critically ill patients, 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 ( $P=0.74$ )<sup>50</sup> 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 ( $P=0.98$ ).<sup>51</sup>
- Even in patients at high risk for VTE, there is no net benefit in extended thromboprophylaxis compared with inpatient only strategy ( $P=0.18$  for VTE and  $P=0.43$  for bleeding).<sup>52,53</sup>
- After DVT diagnosis, anticoagulants consistently reduced both VTE and DVT recurrence by 66% and 75%, respectively.<sup>54</sup> When oral anticoagulation is contraindicated or ineffective, inferior vena cava filter can be used, but its routine use is not recommended because there is no reduction in recurrent PE when combined with anticoagulants versus oral anticoagulation alone (RR, 2.0 [95% CI, 0.51–7.89]).<sup>49,55</sup>
- Systemic thrombolysis did not result in a reduction in all-cause mortality ( $P=0.56$ ), lowering the risk of PTS (RR, 0.66 [95% CI, 0.53–0.81]) at the cost of higher bleeding rate (RR, 2.23 [95% CI, 1.41–3.52]).<sup>56,57</sup> Furthermore, percutaneous pharmacomechanical catheter-directed thrombolysis also showed no benefit for mortality ( $P=0.83$ ), PTS ( $P=0.56$ ), or recurrent PE ( $P=0.09$ ).<sup>58,59</sup>
- In patients with cancer, thromboprophylaxis reduces any VTE and DVT by half (RR, 0.51 [95% CI, 0.32–0.81] and 0.53 [95% CI, 0.33–0.87], respectively), with no increase in major bleeding incidence ( $P=0.15$ ).<sup>60</sup> In those who had DVT, a US cohort analysis found a substantial improvement in PE-free survival in those who underwent vena cava filter placement (HR, 0.69 [95% CI, 0.64–0.75]) regardless of the underlying neoplasm.<sup>61</sup>

## Mortality

### See Chart 24-3

- Among Medicare beneficiaries with DVT, the 30-day mortality rate was 5.1% and the 1-year mortality rate was 19.6% in 2010.<sup>62</sup> These rates were similar to those in 1999 (5.0% and 21.5%, respectively).

- The Computerized Registry of Patients with Venous Thromboembolism registry, a database from 26 countries (including the United States) and  $\approx 100\,000$  patients, found a 30-day mortality of 2.56% for distal DVT, 3.35% for proximal DVT, and 5.33% for PE (Chart 24-3).<sup>63</sup>
- In patients with COVID-19, a meta-analysis observed a 74% overall increase in mortality after VTE.<sup>64</sup> When stratified by disease severity, the OR for mortality in ICU was 2.63 (95% CI, 1.49–4.67) and for patients in mechanical ventilation was 3.14 (95% CI, 1.97–5.02).<sup>65</sup>
- During pregnancy, a VTE event is associated with a higher risk of preterm birth (OR, 2.4 [95% CI, 1.67–3.46]) and stillbirth (OR, 5.07 [95% CI, 3.12–8.24]).<sup>66</sup> Furthermore, PE is an important contributor to maternal mortality, being responsible for  $\approx 9\%$  of pregnancy-associated deaths.<sup>67</sup>
- Asymptomatic DVTs diagnosed with compression ultrasound were associated with a 3-fold increased risk (HR, 2.87 [95% CI, 1.48–5.57]) of short-term all-cause mortality in patients with acute medical illness relative to those with no evidence of DVT.<sup>68</sup>

## Complications

- VTE is a chronic disease with episodic recurrence.
  - A Cochrane meta-analysis found a 9% VTE recurrence within 3 months in patients without treatment. Even under short-term anticoagulation, the rate of VTE recurrence was 13.5% in studies with up to 24 months of follow-up.<sup>64</sup>
  - In a French cohort including patients with no cancer,  $\approx 20\%$  presented with recurrent VTE. Independent predictors of recurrence were first unprovoked VTE and family history of DVT after a mean of 7 years of follow-up.<sup>69</sup>
- Bleeding is a major potential complication of the use of anticoagulant therapy to treat VTE. Data from a group of phase III RCTs suggest that use of direct oral anticoagulants instead of warfarin for VTE primary treatment could further reduce bleeding risk (pooled RR, 0.60 [95% CI, 0.41–0.88] for major bleeding).<sup>70</sup>
- 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. Even under anticoagulation, 2 pooled analyses found incidences of 45% in the short term<sup>71</sup> and up to 70% in the long term (follow-up  $>5$  years).<sup>56</sup> In this context, direct oral anticoagulant drugs appear to prevent PTS (OR, 0.46 [95% CI, 0.33–0.63]).<sup>71</sup>
- CTEPH affects  $\approx 4\%$  of patients with PE within 2 years of their initial PE event.<sup>72</sup> One-, 3-, and 5-year mortality in patients who did not undergo

pulmonary endarterectomy was 9%, 25%, and 31%, respectively.<sup>73</sup>

### Costs

- The incremental direct medical cost (US \$2014) per case among 1-year survivors of acute VTE is estimated at \$12 000 to \$15 000, and the cost of complications, including recurrent VTE, PTS, CTEPH, and anticoagulation-related adverse events, is estimated 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.<sup>74</sup>
- In a registry of 3 million patients who underwent cardiac surgery, an additional mean cost of \$13 000 was observed among those with postoperative VTE diagnosis.<sup>75</sup>

## Chronic Venous Insufficiency

### ICD-10 I87.2.

2019: Mortality—42. Any-mention mortality—664.

### Prevalence

- Data from Edinburgh Vein Study estimated that in 1999 >25 million people in the United States were affected by CVI. Of these, ≈6 million have venous stasis ulcers. CVI is predominantly prevalent in females (3:1 ratio) and in White populations (55%).<sup>76</sup>
- Pain is the most common symptom (29%), followed by swelling, heaviness, fatigue, and cramping. Spider veins are seen in 7%, and varicosities and skin changes are seen in 4% each. Stasis ulcer is present in 1% of all patients with CVI.<sup>77</sup>
- A study including 636 US health care workers (median age, 42 years; 93% women) found a high prevalence of CVI, with presence of varicose veins in 20% of the participants.<sup>78</sup>
- 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.<sup>79</sup> Approximately 4% of patients with DVT experience venous stasis ulcers.<sup>80</sup>

### Incidence

- In a Spanish registry covering 5.8 million people, the CVI incidence was 3.37 per 1000 person-years (95% CI, 3.31–3.43), increasing with age: 0.61 per 1000 person-years in those <30 years of age and up to 10.95 per 1000 person-years in those ≥80 years of age. Women presented ≈2.5-fold more CVI incidence than men (4.77 and 1.95 per 1000 person years, respectively). The venous stasis ulcer incidence was 0.23 per 1000 person-years (95% CI, 0.21–0.24).<sup>81</sup>

### Risk Factors

- The prevalence of moderate CVI increases with advancing age (OR per decade, 1.59 [95% CI,

1.26–2.00] and 1.43 [95% CI, 1.25–1.64] in males and females, respectively), family history (OR, 2.87 [95% CI, 1.81–4.55] and 2.34 [95% CI, 1.77–3.10] in males and females, respectively), hernia surgery (OR, 1.85 [95% CI, 1.09–3.14]), obesity (OR, 1.32 per 10-kg increase [95% CI, 1.12–1.56]), number of births, and presence of flat feet in females and is less likely in those with hypertension.<sup>82</sup> Risk factors for more severe CVI include smoking in males (OR, 2.24 [95% CI, 1.11–4.54]) and leg injury in females (OR, 1.67 [95% CI, 1.14–2.44]). Inflammation, endothelial dysfunction, and blood coagulation disorders are thought to predispose to CVI.<sup>83</sup>

- PTS, a subset of CVI, has specific risk factors that can be identified at the time of or after DVT: recurrent ipsilateral DVT (OR, 6.30 [95% CI, 1.5–26.9]), obesity (OR, 2.63 [95% CI, 1.47–4.70]), CKD (OR, 2.21 [95% CI, 1.45–3.39]), active cancer (OR, 3.66 [95% CI, 2.30–5.84]), more extensive DVT, poor quality of anticoagulation, ongoing symptoms or signs of DVT 1 month after diagnosis, and elevated D-dimer at 1 month.<sup>79,84,85</sup>
- Using data from 762 patients with DVT, Rabinovich et al<sup>86</sup> developed a clinical prediction model for PTS. High-risk predictors were index DVT in the iliac vein, BMI of ≥35 kg/m<sup>2</sup>, and moderate to severe Villalta score (PTS severity) at DVT diagnosis (OR, 5.9 [95% CI, 2.1–16.6] for PTS if Villalta score ≥4).
- 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]).<sup>87</sup>

### Family History and Genetics

- Varicose veins are more likely to occur in the setting of a positive family history, consistent with a heritable component. Heritability of varicose veins and CVI has been estimated at 17%.<sup>88</sup>
- Although a number of genes have been implicated,<sup>89</sup> to date, no causal association has been proved.<sup>90</sup> GWASs in >400 000 individuals established 12 candidate loci for varicose veins in individuals with European ancestry, highlighting the SNPs *CASZ1*, *PIEZO1*, *PPP3R1*, *EBF1*, *STIM2*, *HFE*, *GATA2*, *NFATC2*, and *SOX9*.<sup>91</sup>

### 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 assessed with the Varicose Vein Questionnaire was better after laser ablation (effect size, –2.86 [95% CI, –4.49 to –1.22]) or surgery (effect size, –2.60 [95% CI, –3.99 to –1.22]) than after foam sclerotherapy.<sup>92</sup> The success of

these procedures is critically compromised according to the progressive increase in weight, especially in those with a BMI  $\geq 35$  kg/m<sup>2</sup>.<sup>93</sup>

- 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.<sup>94</sup> Individualized therapy was noninferior to standard duration of therapy of 24 months (OR, 1.06 [95% CI, 0.78–1.44]). 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 ( $P=1.00$ ).<sup>95</sup>
- Oral phlebotonics may contribute to reducing edema (pooled RR, 0.70 [95% CI, 0.60–0.78]), pain (pooled RR, 0.63 [95% CI, 0.48–0.83]), swelling (pooled RR, 0.63 [95% CI, 0.50–0.80]), and paresthesia (pooled RR, 0.67 [95% CI, 0.50–0.88]). In addition, there is likely to be a slight improvement in trophic changes (pooled RR, 0.87 [95% CI, 0.81–0.95]).<sup>96</sup>

## Pulmonary Hypertension

### ICD-10 I27.0, I27.2.

2019: Mortality—8549. Any-mention mortality—27 574.

#### Incidence

- In the United States, PH accounted for 0.8% of all ED visits from 2011 to 2015, with a high hospitalization rate (87% of all patients with PH in the ED).<sup>97</sup>
- PH incidence is somewhat higher in females than males,<sup>98</sup> and women have at least 3-fold more prevalence of PAH (female-to-male ratio in the PHC registry, 3.0:1.0; REVEAL registry, 4.8:1.0; and the Mayo registry, 3.2:1.0).<sup>99</sup>
- 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<sup>100</sup> 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.
  - 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): prevalence is estimated at 6.6 to 26.0 per million adults and incidence at 1.1 to 7.6 per million adults annually.<sup>101</sup>

- WHO group 2 PH (left-sided HD): prevalence and incidence are difficult to estimate but most likely would track with HF prevalence rates.<sup>101</sup>
- WHO group 3 PH (lung disease or hypoxia): prevalence and incidence are difficult to estimate but likely would track with lung disease prevalence.<sup>101</sup>
- WHO group 4 PH (CTEPH and other pulmonary obstructions): prevalence ranges from 1.0% to 8.8% among those with PE.<sup>101</sup> 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.<sup>102</sup>
- WHO group 5 PH (multifactorial mechanisms): when it accompanies sickle cell disease, prevalence is 6% to 10% and increases with advancing age. When it accompanies thalassemia, prevalence is 2.1%.<sup>103</sup>

#### Secular Trends

- In the United States, data from HCUP NIS show an upward trend in hospitalizations for PH between 1993 and 2015 in both principal and all-listed diagnoses.<sup>3</sup>

#### 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.<sup>104</sup>
- In a study of 772 consecutive patients with PE without major comorbidities such as cancer, the risk factors for CTEPH were unprovoked PE (OR, 18 [95% CI, 1.8– $>100$ ]), hypothyroidism (OR, 8.7 [95% CI, 2.1–34.0]), symptom onset  $>2$  weeks before PE diagnosis (OR, 6.9 [95% CI, 2.5–19.0]), and RV dysfunction on CT or echocardiography (OR, 5.9 [95% CI, 1.8–19]). 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%).<sup>105</sup> 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 (HR, 1.19 [95% CI, 1.04–1.36] per 1–kg/m<sup>2</sup> increase).<sup>106</sup>

#### 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.<sup>107</sup>

- A Japanese family study identified *BMP2* (bone morphogenetic protein receptor type 2) as a risk factor for PAH.<sup>108</sup> GWASs in >11 000 individuals have identified risk loci for PAH, including *SOX17* and *HLA-DPA1/DPB1*.<sup>109</sup>
- Exome sequencing in 2572 individuals and case-control gene-based association analyses in 1832 cases and 12 771 controls identified candidate risk genes for idiopathic PAH, including *KLK1*, *GGCX*, and *GDF2*.<sup>110</sup>

### Treatment

- As nonpharmacological therapy, exercise-based rehabilitation programs have shown improvements in 6MWD (+60 m [95% CI, 30–90]) and  $\dot{V}O_{2\text{peak}}$  (+2.41 mL·kg<sup>-1</sup>·min<sup>-1</sup> [95% CI, 1.38–3.44]).<sup>111</sup>
- Clinical guidelines<sup>112</sup> and consensus statements<sup>113</sup> guide PH management. The FDA has approved several medications for group 1 PH (PAH); most of these medications do not have approval for treatment in other PH groups (II–V). The PAH drugs act through vasodilation, platelet aggregation inhibition, or antiproliferative effects on vascular smooth muscle cells by 3 main drug classes: phosphodiesterase type 5 inhibitors, endothelin receptor antagonists, and prostacyclin (prostacyclin analogs or prostacyclin receptor agonists).
- Phosphodiesterase 5 inhibitors showed a clear benefit in 6MWD (+48 m [95% CI, 40–56]), WHO functional class (OR 8.59 [95% CI, 3.95–18.72]), and mortality (OR, 0.22 [95% CI, 0.07–0.68]).<sup>114</sup> Endothelin receptor antagonists improve 6MWD (+25 m [95% CI, 17–33]) and WHO functional class (OR, 1.41 [95% CI, 1.16–1.70]) without a statistically significant reduction in mortality (OR, 0.78 [95% CI, 0.58–1.07]).<sup>115</sup> Therefore, clinical guidelines advise the association of these 2 classes as the initial oral treatment.
- Intravenous prostacyclin exhibited improvements in WHO functional class (OR, 14.96 [95% CI, 4.76–47.04]), 6MWD (+91 m [95% CI, 59–124]), and mortality (OR, 0.29 [95% CI, 0.12–0.69]).<sup>116</sup> However, serious adverse events may occur in 12% to 25% of cases, including sepsis, hemorrhage, pneumothorax, and PE.

### Mortality

- 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.<sup>117</sup>
- Mortality rates also vary according to WHO functional class. A meta-analysis including 10 studies

found a 1-, 2-, and 3-year survival for patients with PAH in WHO functional class I/II of 93.3%, 85.5%, and 78.4%, respectively. However, in patients with worse functional class (WHO functional class III/IV), the survival rates were 81.2% at year 1, 66.7% at year 2, and 54.8% at year 3.<sup>118</sup>

- Among group 1 PH in WHO functional class I/II, a post hoc analysis including PHIRST and TRIUMPH participants found that those who achieved 6MWD  $\geq$ 440 m had a better prognosis (HR, 0.225 [95% CI, 0.098–0.519]).<sup>119</sup> 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 (AUC, 0.693 [95% CI, 0.646–0.739]).<sup>120</sup>
- In sickle cell disease–related PH, the 5-year survival rate in 1 study was 63% with and 83% without PH.<sup>121</sup>
- An international prospective registry that included 679 patients with CTEPH estimated that the 3-year survival was 89% with and 70% without pulmonary thromboendarterectomy.<sup>122</sup>
- In the United States, patients with PH admitted to the hospital presented a high in-hospital mortality (4.2% versus 2.6% for all other patients). Furthermore, the mortality risk increases according to the age group, reaching a 10-fold risk in those  $\geq$ 80 years of age.<sup>97</sup>

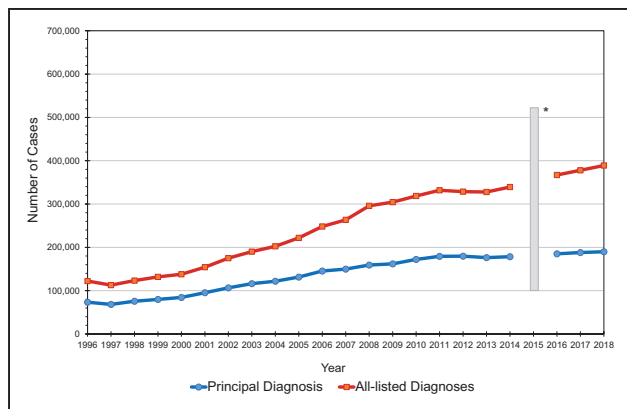
### Costs

- Health care costs associated with PH are substantial. In inpatient scenarios, the mean cost increased progressively from \$18 531 in 1993 to \$73 529 in 2015.<sup>3</sup>
- 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.<sup>123</sup>

### Global Burden

- Of patients with PH, 80% live in developing countries, and the cause of their PH is primarily HD and lung disease (25 million worldwide), but schistosomiasis ( $\approx$ 13 000 in Latin America), rheumatic HD (3.75 million worldwide), HIV (150 000 worldwide), and sickle cell disease (2 million worldwide) remain prominent compared with developed countries. In these countries, younger people are more often affected (average age at onset, <40 years).<sup>101</sup>
- In high-income countries, annual incidence of CTEPH is believed to be lower in Japan (1.9 cases/100 000 people) than in the United States and Europe (3–5 cases/100 000 people).<sup>102</sup>



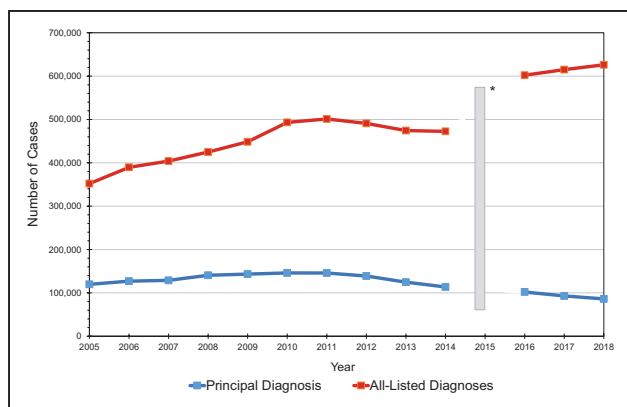


**Chart 24-1. Trends in hospitalized PE, United States, 1996 to 2018.**

PE indicates pulmonary embolism.

\*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the ninth 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.<sup>3</sup>

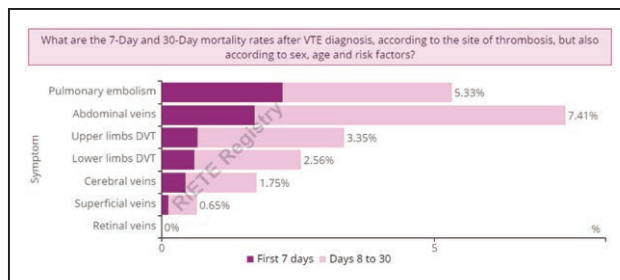


**Chart 24-2. Trends in hospitalized DVT, United States, 2005 to 2018.**

DVT indicates deep vein thrombosis.

\*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.<sup>3</sup>



**Chart 24-3. The 30-day mortality rates after diagnosed VTE according to site of thrombosis, 26 countries.**

DVT indicates deep vein thrombosis; and VTE, venous thromboembolism.

Source: Reprinted from the Computerized Registry of Patients with Venous Thromboembolism (RIETE) registry.<sup>63</sup>

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## 25. 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 25-1 through 25-3 and Charts 25-1 through 25-9**

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[Click here to return to the Abbreviations](#)

### Peripheral Artery Disease

#### Prevalence

(Charts 25-1 and 25-2)

- Estimates for the prevalence of atherosclerotic PAD in the United States among individuals  $\geq 40$  years of age range from 5.8% to 10.7% and are derived from data ascertained before 2010.<sup>1-3</sup>
- Population-based estimates indicate that  $\approx 6.5$  million (5.8%) individuals  $\geq 40$  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.<sup>1</sup> Estimates of PAD prevalence by age, sex, and race and ethnicity are shown in Charts 25-1 and 25-2.
  - PAD prevalence increases with age, approximately doubling per decade.<sup>1,4</sup>
  - PAD prevalence in females and males varies by age and race and ethnicity.<sup>1</sup>
  - PAD prevalence is greater in Black compared with NH White individuals, particularly after 50 and 60 years of age in males and females, respectively.<sup>1,4</sup>
- Approximately 8.5 million (7.2%) adults  $\geq 40$  years of age have PAD when individuals with borderline ABI values 0.90 to 0.99 are included in the aforementioned analysis.<sup>1</sup>
- The overall prevalence of PAD, defined as an ABI  $< 0.9$ , was 8.6% among adult participants in the NHANES 1999 to 2004.<sup>3</sup>
- 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

The 2022 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 2022. 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.

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 chronic limb-threatening ischemia, the most severe form of PAD, was 1.3%.<sup>2</sup>

- 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  $\geq 70$  years of age or 50 to 69 years of age with diabetes or history of smoking cigarettes.<sup>5</sup> In a similar study of 6880 individuals  $\geq 65$  years of age seen in general practitioner clinics in Germany in 2001, the prevalence of PAD was 16.8% and 19.8% in females and males, respectively.<sup>6</sup> In 2 studies of Danish males 65 to 74 years of age conducted between 2011 and 2017, PAD was present in  $\approx 11\%$  of individuals.<sup>7,8</sup>

#### Incidence

- Among individuals  $> 40$  years of age, the annual incidence of PAD and chronic limb-threatening 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.<sup>2</sup>

#### Lifetime Risk and Cumulative Incidence

- The lifetime risk (80-year horizon) of PAD, defined as an ABI  $< 0.90$ , was estimated at  $\approx 19\%$ , 22%, and 30% in White, Hispanic, and Black individuals, respectively, with the use of pooled data from 6 US community-based cohorts.<sup>3</sup>

#### Secular Trends

See Table 25-1

- Between 2000 and 2010, the prevalence of PAD, defined as an ABI  $\leq 0.9$ , increased in both high- and low- to middle-income countries by 13.1% and 28.7%, respectively.<sup>9</sup> The global prevalence of PAD was estimated at 202 million individuals in 2010.<sup>9</sup>
- From 2011 to 2019, with the same definition of PAD, the global prevalence was 5.56% with a higher prevalence in high- compared with low- to middle-income countries (7.37% versus 5.09%, respectively).<sup>10</sup>
- In 2015, it was estimated that 236.62 million people  $\geq 25$  years of age were living with PAD.<sup>9</sup>
- 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%.<sup>11</sup>
- From 2008 to 2018, principal discharge diagnosis for PAD decreased from 160 000 to 86 000 (HCUP,<sup>12</sup> unpublished NHLBI tabulation; Table 25-1).
- Between 2003 and 2011, admission rates for chronic limb-threatening ischemia remained

constant in the NIS ( $\approx 150$  admissions per 100 000 individuals).<sup>13</sup>

- Between 2006 and 2011, the annual rate of lower-extremity peripheral artery intervention increased slightly from 401.4 to 419.6 per 100 000 individuals among Medicare beneficiaries.<sup>14</sup>
- Between 2003 and 2011, endovascular treatment for chronic limb-threatening ischemia increased from 5.1% to 11.0%.<sup>13</sup>
- Between 2000 and 2008, the overall rate of lower-extremity amputation decreased significantly, from 7258 to 5790 per 100 000 Medicare beneficiaries with PAD.<sup>15</sup>
- 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.<sup>16</sup>

### Risk Factors

- Modifiable PAD risk factors largely parallel those for atherosclerosis in other vascular beds, for example, CAD, and include smoking, diabetes, hypertension, and atherogenic dyslipidemia.<sup>3,4,9,17</sup>
  - Current or former smoking is among the strongest PAD risk factors, with ORs ranging from 1.3 to 5.4 (all  $P < 0.05$ ) and relatively greater risk among current smokers.<sup>3,4,9</sup>
    - Heavy smoking, defined by pack-years, smoking duration, or smoking intensity, is a stronger risk factor for PAD compared with CAD (all  $P < 0.05$ ).<sup>18</sup>
  - Diabetes is associated with increased risk for PAD, with ORs ranging from 1.38 to 1.84.<sup>3,9</sup>
  - Hypertension, defined as BP  $\geq 140/90$  mmHg, is associated with  $\approx 50\%$  increased odds of PAD (OR, 1.47 [95% CI, 1.37–1.57]).<sup>9</sup>
    - Each 20-mm Hg increase in SBP was associated with an OR of 1.27 (95% CI, 1.22–1.32) for PAD.<sup>3</sup>
    - Among patients treated for hypertension, SBP is more strongly associated with incident PAD (HR per 1-SD increase in SBP, 1.46 [95% CI, 1.29–1.65]) than diastolic blood pressure (HR per 1-SD increase in DBP, 1.12 [95% CI, 0.97–1.30]).<sup>19</sup>
  - In both ARIC and WHS, each 1-SD increase in both TC and LDL-C was not associated with incident PAD (all  $P > 0.05$ ) but was associated with incident CAD.<sup>20,21</sup>
    - In contrast, each 1-SD decrease in HDL-C is strongly associated with incident PAD (HR, 1.39 [95% CI, 1.16–1.67] and 1.92 [95% CI, 1.49–2.50], respectively).<sup>20,21</sup>
    - Further lipid subfraction analyses suggest that markers of atherogenic dyslipidemia, including elevated concentrations of triglyceride-rich

lipoproteins such as small LDL particles (HR, 2.17 [95% CI, 1.10–4.27]) and total HDL particles (HR, 0.29 [95% CI, 0.16–0.52]), are independently associated with PAD.<sup>20–23</sup>

- Mendelian randomization analyses have causally linked some thrombotic markers, including von Willebrand factor (OR, 1.28 [95% CI, 1.07–1.52]) and clotting factor VIII (OR, 1.41 [1.23–1.62]), to PAD.<sup>24</sup>
- 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 HPFS of males.<sup>25</sup>
- MetS was associated with increased risk for incident PAD on the basis of data from the CHS (HR, 1.47 [95% CI, 1.11–1.94]) and WHS (HR, 1.48 [95% CI, 1.00–2.19]).<sup>26,27</sup>
- Other possible PAD risk factors include sedentary lifestyle, inflammation, hypertension in pregnancy, and CKD.<sup>17,26,28,29</sup>
- 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.<sup>30</sup>

### Social Determinants of Health

#### See Chart 25-3

- Lower income and lower education are associated with greater incidence and prevalence of PAD according to ARIC and NHANES (1999–2004) data, respectively.<sup>31,32</sup>
- Lower SES is associated with greater risk for amputation (HR, 1.12 [95% CI, 1.06–1.17]).<sup>33</sup>
- The rate of lower-extremity amputation varies geographically within the United States (Chart 25-3) and may be influenced by patient rurality and race.<sup>15,34</sup>
  - Data from the Vascular Quality Initiative suggest that rural non-White individuals have a 52% greater odds of amputation than urban non-White individuals (95% CI, 1.19–1.94).<sup>34</sup>

### Risk Prediction

- Models for predicting the probability of an ABI  $< 0.9$  have been developed from NHANES data.<sup>3,35</sup> Included variables were age, sex, race, pulse pressure, TC and HDL (or their ratio), and smoking status, with a C statistic of 0.76 (95% CI, 0.72–0.79).<sup>35</sup> Another model with NHANES data additionally included diabetes and history of CAD or stroke, which yielded a similar C statistic of 0.75.<sup>3,36</sup>
- A lifetime risk prediction model for PAD using the variables described above, including diabetes and history of CAD or stroke, has been developed.<sup>3</sup>

### Subclinical/Unrecognized Disease

- Intermittent claudication, the classic PAD symptom, is present in a minority (8.7% to 32%) of individuals with PAD.<sup>5,37</sup>
  - More commonly ( $\approx 50\%$ ), 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).<sup>5,37</sup>
  - Approximately 20% to 34% of individuals with ABI  $< 0.9$  are asymptomatic, that is, have no associated limb symptoms.<sup>5,37</sup>
- 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.<sup>38</sup>

### Genetics/Family History

- Atherosclerotic PAD is heritable, independently of the heritable risk factors described above. A family history of PAD was independently associated with a 1.83-fold greater odds of PAD (95% CI, 1.03–3.26) in the San Diego Population Study.<sup>39</sup>
- Monozygotic twins compared with dizygotic twins had a greater risk for PAD with an OR of 17.7 (95% CI, 11.7–26.6) and 5.7 (95% CI, 4.1–7.9), respectively, in the Swedish Twin Registry, with heritable factors accounting for 58% of phenotypic variance between twins.<sup>40</sup> The NHLBI Twin Study found that 48% of the variability in ABI with similar environmental risk factors could be attributed to additive genetic effects.<sup>41</sup>
- GWASs have identified genetic loci associated with common atherosclerotic PAD, including the CHD-associated chromosome 9p21 genetic locus associated with PAD, AAA, and intracranial aneurysm.<sup>42</sup>
  - Other common PAD-associated genetic loci include SNPs on chromosome 9 near *CDKN2B*, *DAB21P*, and *CYBA* genes.<sup>43</sup>
  - A large-scale GWAS in  $> 31\ 000$  cases with PAD 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 atherosclerotic 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*).<sup>44</sup>
  - 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]).<sup>45</sup> In another study, targeted sequencing of 41 genome regions associated with CHD performed in 1749

cases with PAD and 1855 controls found overlap of several genes between CHD and PAD.<sup>46</sup>

### 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  $\geq 50$  years of age in 2006, 25% of individuals expressed familiarity with PAD compared with 67.1% for CAD and 73.9% for stroke.<sup>47</sup>
    - Of those familiar with PAD,  $\approx 50\%$  were aware of smoking, diabetes, hypertension, and dyslipidemia as PAD risk factors.<sup>47</sup>
    - 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.<sup>47</sup>
    - Income and education levels were positively associated with all knowledge domain levels.<sup>47</sup>
  - Physicians may underappreciate PAD.
    - A US-based cross-sectional study conducted at 350 primary care clinics in 1999 examined awareness of PAD in individuals  $\geq 70$  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.<sup>5</sup>
    - 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.<sup>48</sup>
    - 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.<sup>49</sup>

#### Treatment

- Treatment of patients with lower-extremity PAD is summarized in the 2016 AHA/ACC guideline and includes addressing modifiable risk factors, including PA, smoking cessation, dyslipidemia,



BP and glycemic control, and revascularization approaches.<sup>50</sup>

- Optimal exercise programs for patients with PAD are summarized in a 2019 AHA scientific statement.<sup>51</sup>
- In a 2017 Cochrane review with meta-analysis, aerobic exercise compared with usual care was associated with the following<sup>52</sup>:
  - 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).<sup>53</sup>
- 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.<sup>54,55</sup>
- Lipid-lowering therapy with a high-intensity statin is recommended for the treatment of PAD.<sup>50,56</sup>
  - The HPS demonstrated that compared with placebo, simvastatin treatment was associated with 22% lower risk (95% CI, 15%–29%) of first major vascular event among patients with PAD and 16% lower risk (95% CI, 5%–25%) of first peripheral vascular event in all subjects.<sup>57</sup>
  - Among 155 647 patients with incident PAD in the Veterans Affairs health system, high-intensity statin use was associated with a lower risk of both amputation (HR, 0.67 [95% CI, 0.61–0.74]) and mortality (HR, 0.74 [95% CI, 0.70–0.77]).<sup>58</sup>
  - In a subanalysis of the FOURIER trial, 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 and already receiving statin therapy.<sup>59</sup>
  - In a subanalysis of the ODYSSEY Outcomes trial, compared with placebo, the PCSK9 inhibitor alirocumab similarly reduced the risk of major adverse limb events, including chronic limb threatening ischemia, limb

revascularization, or amputation (HR, 0.69 [95% CI, 0.54–0.80]).<sup>60</sup>

- The antithrombotic medications rivaroxaban and vorapaxar may reduce the risk of adverse limb outcomes (eg, revascularization or amputation) among patients with PAD.<sup>61,62</sup>
  - In a subanalysis of the COMPASS trial, among the 6391 subjects with PAD at baseline, compared with aspirin alone, the combination of rivaroxaban 2.5 mg twice daily plus aspirin 100 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];  $P=0.01$ ).<sup>61</sup>
  - In the VOYAGER trial, among 6564 subjects with PAD who recently underwent lower-extremity revascularization, compared with aspirin alone, the combination of rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily reduced the risk of a composite of major adverse cardiovascular and limb events (17.3% versus 19.9%; HR, 0.85 [95% CI, 0.76–0.96];  $P=0.009$ ).<sup>63</sup>
- Glycemic control may be associated with better limb outcomes among patients with PAD according to observational studies<sup>64,65</sup>:
  - In 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]).<sup>64</sup>
  - Among 197 Japanese patients with diabetes who underwent percutaneous transluminal angioplasty for chronic limb-threatening ischemia, an HbA1c ≥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.<sup>65</sup>
- Revascularization for patients with claudication or chronic limb-threatening ischemia may be associated with improvement in quality of life and limb preservation. 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.<sup>66</sup>

### Mortality

#### (Table 25-1 and Chart 25-4)

- In 2019, PAD was the underlying cause in 11 753 deaths. The number of any-mention deaths attributable to PAD was 57 188 (Table 25-1; unpublished NHLBI tabulation using NVSS<sup>67</sup> and CDC WONDER).<sup>68</sup>
- In 2019, the overall any-mention age-adjusted death rate for PAD was 13.9 per 100 000 (unpublished NHLBI tabulation using CDC WONDER).<sup>68</sup>
  - Any mention-death rates were 11.7 for NH White females, 14.4 for NH Black females, 5.3 for NH

Asian or Pacific Islander females, 11.3 for NH American Indian or Alaska Native females, and 8.7 for Hispanic females.

- Any mention-death rates were 17.4 for NH White males, 21.5 for NH Black males, 7.5 for NH Asian or Pacific Islander males, 14.7 for NH American Indian or Alaska Native males, and 13.8 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  $\leq 1.1$ , whereas individuals with an ABI between 1.11 and 1.40 had the lowest risk (Chart 25-4).<sup>69</sup>
  - ABI  $\leq 0.9$  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]).<sup>69</sup>
- 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)<sup>70</sup>:
  - 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 chronic limb-threatening ischemia; and
  - 2.7% versus 2.2% after surgical revascularization for chronic limb-threatening ischemia.
- In EUCLID, females with symptomatic PAD were at lower risk of both all-cause and cardiovascular mortality (HR, 0.61 [95% CI, 0.53–0.71],  $P < 0.001$ ; HR, 0.65 [95% CI, 0.54–0.78],  $P < 0.001$ , respectively).<sup>71</sup>

## Complications

### Cardiovascular Disease

- Individuals with PAD are at higher risk for other types of CVD.
  - 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).<sup>72</sup>

### Tissue (Limb) Loss

- Risk factors for amputation were evaluated in 2 730 742 Medicare beneficiaries  $\geq 65$  years of age with PAD using data from 2000 to 2008<sup>15</sup>:
  - Black race and diabetes each accounted for  $\approx 30\%$  of the multivariable-adjusted logistic model for predicting lower-extremity amputation and had an OR of 2.90 (95% CI, 2.83–2.90) and

2.40 (95% CI, 2.38–2.43), respectively. CKD (OR, 1.63 [95% CI, 1.61–1.65]), dementia (OR, 2.09 [95% CI, 2.05–2.13]), older age, HF, cerebrovascular disease, and male sex were the next strongest factors associated with increased risk of amputation. CAD (OR, 0.67 [95% CI, 0.66–0.68]), cancer, hypertension, and Asian race were associated with significantly lower risk of amputation. Smoking status was not included in the models.

- In an analysis of 393 017 patients in the Premier Healthcare Database who underwent lower-extremity arterial revascularization, 50 750 patients (12.9%) had at least 1 subsequent hospitalization for major adverse limb events.<sup>73</sup>
- 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, among 125 674 patients in the Veterans Aging Cohort Study.<sup>74</sup>
- Mortality by 1 year after major lower-extremity amputation was estimated at 48.3% among 186 338 older Medicare patients with PAD.<sup>75</sup>

### Impaired Quality of Life

- Even individuals with borderline ABI (0.90–0.99) are at risk for mobility loss, defined as the loss of ability to walk one-quarter of a mile or up and down 1 flight of stairs independently (HR, 3.07 [95% CI, 1.21–7.84]).<sup>76</sup>
- Among patients with PAD, lower PA levels are associated with faster rates of functional decline measured by 6MWD performance, 4-m walking velocity, and the Short Performance Physical Battery (all  $P < 0.05$ ).<sup>77</sup> In addition, shorter 6MWD and slower walking speed are associated with higher rates of all-cause mortality (HR, 2.36 [95% CI, 1.33–4.18]) and cardiovascular mortality (HR, 5.59 [95% CI, 1.97–15.90]).<sup>78</sup>

### Health Care Use: Hospital Discharges and Ambulatory Care Visits

- In 2018, primary diagnosis of PAD accounted for 1 875 000 physician office visits (NAMCS,<sup>79</sup> unpublished NHLBI tabulation), 86 000 hospital discharges (HCUP<sup>12</sup> unpublished NHLBI tabulation), and 60 000 ED visits (HCUP<sup>12</sup> unpublished NHLBI tabulation).

### Cost

- Among patients with PAD in the REACH registry, average health care costs over 2 years for vascular-related hospitalizations ranged from \$7000 to \$11 693 in 2004 US dollars.<sup>80</sup>
- 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 MACE (mean difference, \$44 659) or major limb event (mean difference, \$34 216) event compared with patients without these events.<sup>81</sup>

- In 72 199 Medicare beneficiaries admitted to the hospital in 2011 with chronic limb-threatening ischemia, average annual health care cost ranged from \$49 200 to \$55 700.<sup>82</sup>
- In a cohort of 22 203 patients with PAD in Minnesota, total health care costs were approximately \$18 000 (2011 US dollars) greater among tobacco users (9.0%) compared with nonusers over 1 year.<sup>83</sup>

### Global Burden

(Table 25-2 and Charts 25-5 and 25-6)

#### Prevalence

- In 2015, an estimated 237 million people worldwide had PAD according to a systematic review of 116 studies.<sup>10</sup>
- 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.<sup>84</sup>
- PAD estimates in sub-Saharan Africa range from 3.1% to 24% in adults ≥50 years of age.<sup>85</sup>
- The GBD 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020. (Data courtesy of the Global Burden of Disease Study.)
  - PAD affected 110.32 million (95% UI, 96.44–126.89 million) individuals (Table 25-2).
  - PAD age-standardized prevalence was highest in high-income North America and Western Europe (Chart 25-5).

#### Mortality

- In the GBD 2020 study the age-standardized mortality estimated for PAD was 0.93 (95% UI, 0.80–1.00) per 100 000 individuals (Table 25-2).<sup>86</sup>
  - PAD age-standardized mortality was highest in Central and Eastern Europe in 2020 (Chart 25-6).

### 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.<sup>87,88</sup>

- AAA is more common in males than females, and its prevalence increases with age.<sup>89–92</sup>
  - 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.<sup>93,94</sup>
    - 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.<sup>95</sup>
    - 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%.<sup>96,97</sup>

#### Incidence

- The incidence of thoracoabdominal aortic dissection was 6 per 100 000 per year (95% CI, 4–7) from 2002 to 2012 in Oxfordshire, UK.<sup>98</sup>
- In a Swedish study of 14 229 individuals with thoracic aortic disease, the incidence of thoracic aortic aneurysm or dissection was 16.3 per 100 000 per year in men and 9.1 per 100 000 per year in women in 2002. The median age at diagnosis was 71 years.<sup>99</sup>
- 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.<sup>100</sup>

#### 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.<sup>101</sup>

#### 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.<sup>102</sup>
- 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.<sup>103</sup>

### Risk Factors

- TAAs in younger individuals are more likely caused by familial disease or genetic syndromes, the prototype examples being bicuspid aortic valve disease and Marfan syndrome. In older individuals 60 to 74 years of age, male sex (OR, 1.9 [95% CI, 1.1–3.1]), hypertension (OR 1.8 [95% CI, 1.5–2.1]), and family history (OR, 1.6 [95% CI, 1.1–2.2]) contribute to the risk of TAA.<sup>104</sup>
- Inflammatory conditions such as giant cell arteritis, Takayasu arteritis, or infectious aortitis also may cause TAA.
  - Giant cell arteritis is associated with a 2-fold higher risk for developing a thoracoabdominal aortic aneurysm (sub-HR, 1.92 [95% CI, 1.52–2.41]) even after adjustment for competing risks according to data from the United Kingdom.<sup>105</sup>
- Risk factors for AAA were assessed in a retrospective analysis of 3.1 million patients between 2003 and 2008.<sup>106</sup> Male sex (OR, 5.71 [95% CI, 5.57–5.85]), hypertension (OR, 1.25 [95% CI, 1.21–1.28]), and family history (OR, 3.80 [95% CI, 3.66–3.95]) were strongly associated with developing AAA. Individuals of all groups  $\geq 55$  years of age were at greater risk of developing AAA compared with those  $< 55$  years of age (all  $P < 0.0001$ ).
- Diabetes may be associated with lower risk of aortic aneurysmal disease.<sup>107,108</sup> 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]).<sup>107</sup>

### Social Determinants of Health

Few data exist on social determinants of health for TAA.

- In a retrospective study of 60784 patients who underwent thoracic aortic repair procedures between 2005 and 2008, thoracic endovascular aortic repair was more common than open surgical repair among individuals who were Black (OR, 1.71 [95% CI, 1.37–2.13]), Hispanic (OR, 1.70 [95% CI, 1.22–2.37]), and Native American (OR, 2.37 [95% CI, 1.44–3.91]) compared with White individuals. Those with a mean annual income  $< \$25\,000$  were also more likely to undergo endovascular rather than open surgical repair than those with a mean annual income  $> \$35\,000$  (OR, 1.24 [95% CI, 1.03–1.62]).<sup>109</sup>
- Lower SES is associated with a greater risk of 90-day readmission after AAA repair (OR, 1.18 [95% CI, 1.10–1.23]) on the basis of multistate US administrative claims data for 92028 patients between 2007 and 2014.<sup>110</sup>

- 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 (all  $P < 0.0001$ ).<sup>111</sup>

### Subclinical/Unrecognized Disease

#### See Chart 25-7

- TAAs typically expand slowly, increasing in size at rates of 0.1 and 0.3 cm/y in the ascending and descending aorta, respectively.<sup>112,113</sup> TAAs with familial and genetic causes may display faster rates of expansion ( $P < 0.0001$ ).<sup>114</sup> Expansion rate accelerates as the size increases.<sup>115</sup>
- One-time screening for AAA in males 65 to 80 years of age had a number needed to screen of 350 to prevent a single AAA-related death over 7 to 15 years in a meta-analysis of 4 randomized trials (Chart 25-7).<sup>116</sup> In a nationwide Swedish program targeting men  $\geq 65$  years of age, the initiation of an AAA screening program found a number needed to screen of 667 to prevent a single premature death.<sup>117</sup>
- A meta-analysis of 15475 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.<sup>118</sup>
  - 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).<sup>118</sup>
- Aneurysms in 1 location are associated with aneurysms in another, for example, cerebral berry aneurysms in thoracic aortic disease or TAA in AAA.<sup>119–121</sup> Approximately 25% of patients with TAA have concomitant AAA.

### Genetics/Family History

- Aortic dissection is heritable. In a study in the Taiwan National Health Insurance database of  $> 23\,000$  patients, a family history of aortic dissection in first-degree relatives was associated with an RR of aortic dissection of 6.82 (95% CI, 5.12–9.07) with an estimated heritability of 57.0% for genetic factors.<sup>122</sup>
- There are monogenic (mendelian) thoracic aortic diseases caused by rare genetic variants including Marfan syndrome (caused primarily by variants in the *FBN1* gene), Loeys-Dietz syndrome (TGF- $\beta$  pathway-related genes, including *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, and *TGFB3*), vascular Ehlers-Danlos syndrome (*COL3A1*), arterial tortuosity syndrome (*SLC2A10*), and familial TAA syndrome (*ACTA2*, *TGFR2*, and variants in several other genes).



- Individuals with variants in the aforementioned genes are at significantly increased risk for vascular aneurysms, dissections, or ruptures, as well as other systemic manifestations. 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 variants cause Marfan syndrome), *LRP1* (LDL receptor protein–related 1), and *ULK4* (unc-51–like kinase 4).<sup>123,124</sup>
- 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]).<sup>125</sup>
- A GWAS of individuals in the Million Veterans Program identified 24 common genetic variants associated with AAA, including a locus on chromosome 9p21, as well as SNPs in *LPA*, *IL6R*, *LDLR*, and *APOE* (all  $P < 5 \times 10^{-8}$ ).<sup>126</sup>
- Genetic variants associated with intracranial aneurysms have been found in several genes, including *RBBP8*, *STRAD13/KL*, *SOX17*, and *CDKN2A/B* (all  $P < 5 \times 10^{-8}$ ).<sup>127</sup> Rare variants in *ANGPTL6* are associated with familial cases of intracranial aneurysms ( $P < 0.05$ ).<sup>128</sup>
- GWAS data demonstrate that 16 common genetic variants associated with AAA are also associated with cerebral and lower-extremity arterial aneurysms (all  $P < 0.05$ ).<sup>126</sup>
- 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 ( $P < 10^{-4}$ ),<sup>129</sup> and functional analyses have demonstrated that this locus regulates endothelin-1 expression.<sup>130</sup>
  - A variant at chromosome 1q21.2 that affects *ADAMTSL4* expression and variants in *PHACTR1*, *LRP1*, and *LINC00310* are associated with spontaneous coronary artery dissection (all  $P < 5 \times 10^{-8}$ ).<sup>131</sup>
  - 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.<sup>132</sup>
- 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 from CMS data.<sup>133</sup>
- Treatment of TAA and AAA is aimed at slowing progression and preventing complications, namely rupture and dissection.
  - Surgical approaches to TAA are mixed between open and endovascular repair.
    - Elective AAA repair is typically not recommended among asymptomatic individuals until diameter exceeds 5.5 cm or if annual expansion rate is  $\geq 0.5$  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.<sup>134,135</sup>
    - 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%;  $P < 0.001$ ).<sup>136</sup>
    - Racial disparities in perioperative 30-day mortality after TAA repair appear to be present with open (Black people, 18% versus White people, 10%;  $P < 0.001$ ) compared with endovascular (8% versus 9%;  $P=0.54$ ) approaches on the basis of Medicare data from 1999 to 2007.<sup>136</sup>
    - Timing of presentation with both TAA and AAA rupture is associated with mortality, with higher risk for weekend (OR, 2.55 [95% CI, 1.77–3.68] and 1.32 [95% CI, 1.13–1.55], respectively) compared with weekday repair on the basis of NIS data from 2009.<sup>137,138</sup>
  - Statin therapy may be associated with slower rate of AAA growth (0.82 mm/y [95% CI, 0.33–1.32]) and 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.<sup>139</sup>
  - After elective AAA repair, survival after endovascular versus open surgical repair varies on the basis of the timing since intervention.
    - Among Medicare patients, open versus endovascular AAA repair had a higher risk of all-cause mortality (HR, 1.24 [95% CI,

### Awareness, Treatment, and Control

- Aortic aneurysmal disease is typically asymptomatic until complications occur.

1.05–1.47]), AAA-related mortality (HR, 4.37 [95% CI, 2.51–7.66]), and complications at 1 year.<sup>140</sup> After 8 years of follow-up, however, survival was similar between the 2 groups ( $P=0.76$ ). The rate of eventual aneurysm rupture was higher with endovascular (5.4%) compared with open (1.4%) repair.<sup>141</sup>

- 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]).<sup>142</sup>
- 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  $\leq 3$  cases versus 3.8% in 14–62 cases;  $P<0.01$ ) and hospital (6.3% in  $\leq 5$  cases versus 3.8% in 14–62 cases;  $P<0.01$ ).<sup>143</sup>
- Of all AAA repairs, endovascular AAA repair increased from 5% to 74% between 2000 and 2010 despite stable overall number of AAAs ( $\approx 45\,000$  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.<sup>144</sup>
- Similarly, annual costs for TAA repair increased over the period of 2003 to 2016 according to data from Ontario, Canada (\$13 million versus \$18 million Canadian dollars, respectively;  $P<0.001$ ).<sup>145</sup>

### Mortality

2019: Mortality—9904. Any-mention mortality—17 626.

- 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.<sup>146</sup>
  - Mesenteric malperfusion with type A acute dissections was present in  $\approx 3.7\%$  of patients in IRAD and associated with greater mortality

than among patients without malperfusion (63.2% versus 23.8%;  $P<0.001$ ).<sup>147</sup>

- 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 ( $P=0.006$ ).<sup>148</sup>
- 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.<sup>149</sup>
  - 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.<sup>150</sup>
  - Among 4638 ruptured AAA repairs from 2004 to 2018 in the Vascular Quality Initiative, there was no difference in 5-year survival for endovascular versus open repair (HR, 0.88 [95% CI, 0.69–1.11];  $P=0.28$ ) for the years 2004 to 2012. However, from 2013 to 2018, endovascular repair was associated with longer 5-year survival compared with open repair (HR, 0.69 [95% CI, 0.60–0.79];  $P<0.001$ ).<sup>138</sup>

### Complications

(See Chart 25-8)

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  $\approx 2\%$  and  $\approx 7\%$ , respectively.<sup>151</sup>
- 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.<sup>152</sup>

- 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.<sup>153</sup>

#### AAA:

- The risk of AAA rupture is also proportionately related to diameter (Chart 25-8).<sup>154</sup> For incidentally identified AAA, the 5-year risk of rupture ranges from 1% to 7% and 25% to 40% for 4.0 to 5.0 and >5.0 cm, respectively.<sup>155,156</sup>
- 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];  $P<0.001$ ).<sup>118</sup>

#### Health Care Use: Hospital Discharges and Ambulatory Care Visits

- In 2018, hospital discharges with aortic aneurysm as principal diagnoses totaled 69 000 (HCUP,<sup>12</sup> unpublished NHLBI tabulation).

#### Global Burden

##### (See Table 25-3 and Chart 25-9)

- Global mortality attributable to aortic aneurysm by sex according to the GBD 2020 Study of 204 countries is shown in Table 25-3.
  - There were 0.15 million (95% UI, 0.13–0.16 million) deaths attributable to aortic aneurysm, an increase of 74.62% (95% UI, 63.12%–85.99%) from 1990.
  - The highest age-standardized mortality rates estimated for aortic aneurysm were in tropical Latin America, high-income Asia Pacific, and Eastern Europe (Chart 25-9).

#### 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.<sup>157</sup> 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.<sup>158,159</sup>

##### 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.<sup>160</sup>

#### 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.<sup>160</sup>

#### Risk Factors

- Traditional atherosclerotic risk factors such as advanced age, diabetes, smoking, and hypertension are associated with higher prevalence of atherosclerotic renal artery stenosis.<sup>161</sup>
- Atherosclerosis in another vascular bed is significantly associated with the presence of renal artery stenosis.<sup>159,160,162</sup>

#### 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  $\geq 70\%$  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).<sup>163</sup>

#### 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  $\geq 2$  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 MACEs or major renal events over a median follow-up of 43 months (HR, 0.94 [95% CI, 0.76–1.17]).<sup>164</sup>

#### Mortality

- An Irish study reported that among a total of 3987 patients undergoing coronary angiography, the presence of renal artery stenosis conferred a great risk of mortality (HR, 2.01 [95% CI, 1.51–2.67]).<sup>165</sup>

#### Complications

- The main long-term complications of renal artery stenosis are decline in renal function and a heightened risk of CVD.
  - In the CHS, renal artery stenosis was associated with an increased risk of CHD (HR, 1.96 [95% CI, 1.00–3.83]).<sup>166</sup>
  - In an analysis of Medicare recipients, patients with atherosclerotic renal artery stenosis were at higher risk of incident congestive heart failure, stroke, death, and need for renal replacement therapy (all  $P<0.0001$ ).<sup>160</sup>

**Table 25-1. PAD in the United States**

Population group	Mortality, 2019, all ages*	Hospital discharges, 2018, all ages
Both sexes	11 753	86 000
Males	5549 (47.2%)†	
Females	6204 (52.8%)†	
NH White males	4365	...
NH White females	4820	...
NH Black males	685	...
NH Black females	821	...
Hispanic males	361	...
Hispanic females	389	...
NH Asian or Pacific Islander males	103	...
NH Asian or Pacific Islander females	136	...
NH American Indian/Alaska Native	54	...

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.<sup>67</sup> Hospital discharges: Unpublished NHLBI tabulation using Hospital Cost and Utilization Project.<sup>12</sup>

**Table 25-2. Global Mortality and Prevalence of Lower Extremity PAD, by Sex, 2020**

	Both sexes combined		Male		Female	
	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)
Total number (millions), 2020	0.07 (0.06 to 0.08)	110.32 (96.44 to 126.89)	0.03 (0.03 to 0.03)	36.29 (31.76 to 41.84)	0.04 (0.03 to 0.04)	74.03 (64.63 to 85.06)
Percent change in total number, 1990–2020	86.55 (71.23 to 96.85)	96.07 (93.78 to 98.53)	83.34 (67.82 to 94.99)	105.78 (102.59 to 109.20)	89.37 (72.29 to 100.99)	91.63 (89.17 to 94.31)
Percent change in total number, 2010–2020	23.99 (19.53 to 28.02)	30.13 (29.19 to 31.12)	22.20 (16.26 to 27.37)	31.84 (30.56 to 33.21)	25.56 (19.44 to 30.33)	29.31 (28.31 to 30.29)
Rate per 100 000, age standardized, 2020	0.93 (0.80 to 1.00)	1332.07 (1164.95 to 1528.87)	1.02 (0.92 to 1.09)	955.80 (838.82 to 1098.03)	0.84 (0.70 to 0.92)	1650.46 (1441.13 to 1895.76)
Percent change in rate, age standardized, 1990–2020	−28.51 (−33.30 to −25.04)	−12.95 (−14.16 to −11.77)	−29.83 (−35.10 to −25.90)	−11.39 (−12.80 to −9.91)	−28.00 (−33.61 to −23.96)	−12.36 (−13.53 to −11.13)
Percent change in rate, age standardized, 2010–2020	−12.50 (−15.52 to −9.80)	−2.82 (−3.40 to −2.24)	−13.02 (−16.84 to −9.54)	−2.15 (−3.01 to −1.25)	−11.61 (−15.78 to −8.31)	−2.77 (−3.38 to −2.14)

PAD indicates peripheral artery disease; and UI, uncertainty interval.

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington.

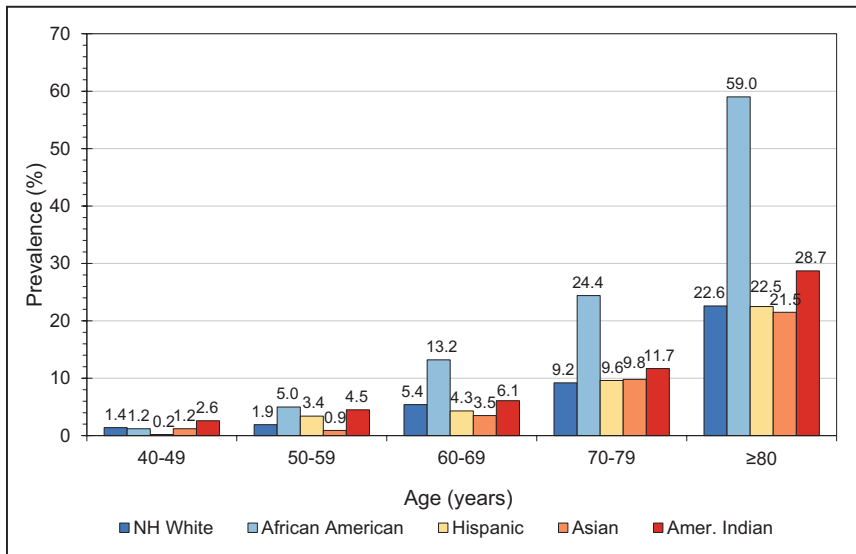


**Table 25-3. Global Mortality of Aortic Aneurysm, by Sex, 2020**

	Both sexes (95% UI)	Male (95% UI)	Female (95% UI)
Total number (millions), 2020	0.15 (0.13 to 0.16)	0.09 (0.09 to 0.10)	0.06 (0.05 to 0.06)
Percent change in total number, 1990–2020	74.62 (63.12 to 85.99)	64.18 (50.53 to 76.17)	95.70 (76.51 to 111.15)
Percent change in total number, 2010–2020	25.83 (20.91 to 30.69)	23.38 (16.37 to 29.61)	30.20 (24.07 to 35.41)
Rate per 100 000, age standardized, 2020	1.87 (1.68 to 1.99)	2.67 (2.48 to 2.83)	1.23 (1.04 to 1.33)
Percent change in rate, age standardized, 1990–2020	−24.25 (−28.58 to −19.76)	−31.16 (−36.11 to −26.63)	−16.33 (−23.48 to −10.42)
Percent change in rate, age standardized, 2010–2020	−7.39 (−10.77 to −3.89)	−10.01 (−14.63 to −5.81)	−4.81 (−8.97 to −1.05)

UI indicates uncertainty interval.

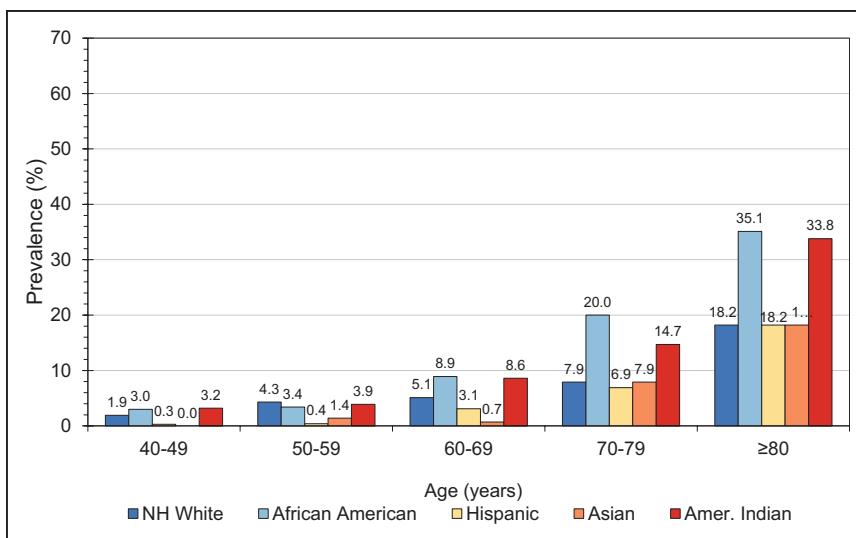
Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington.



**Chart 25-1. Estimates of prevalence of PAD in males, by age and ethnicity, United States, 2000.**

NH indicates non-Hispanic; and PAD, peripheral artery disease.

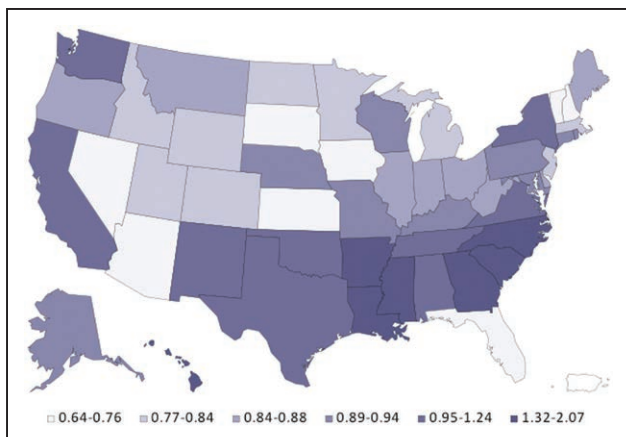
Source: Data derived from Allison et al.<sup>1</sup>



**Chart 25-2. Estimates of prevalence of PAD in females, by age and ethnicity, United States, 2000.**

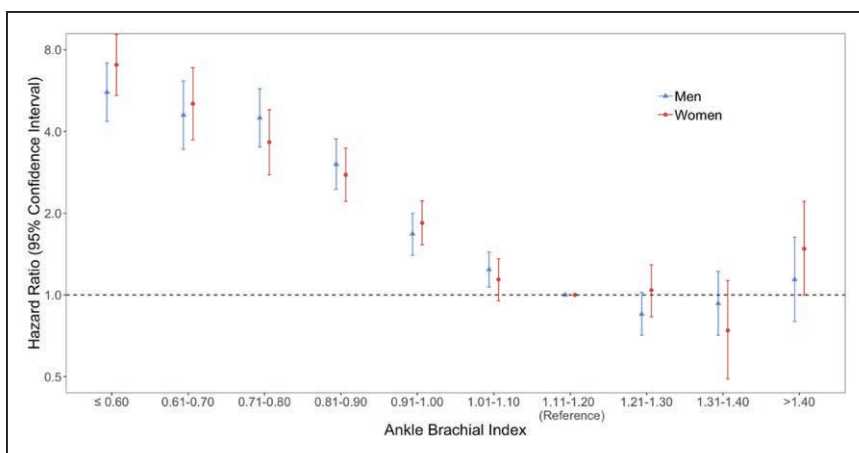
NH indicates non-Hispanic; and PAD, peripheral artery disease.

Source: Data derived from Allison et al.<sup>1</sup>



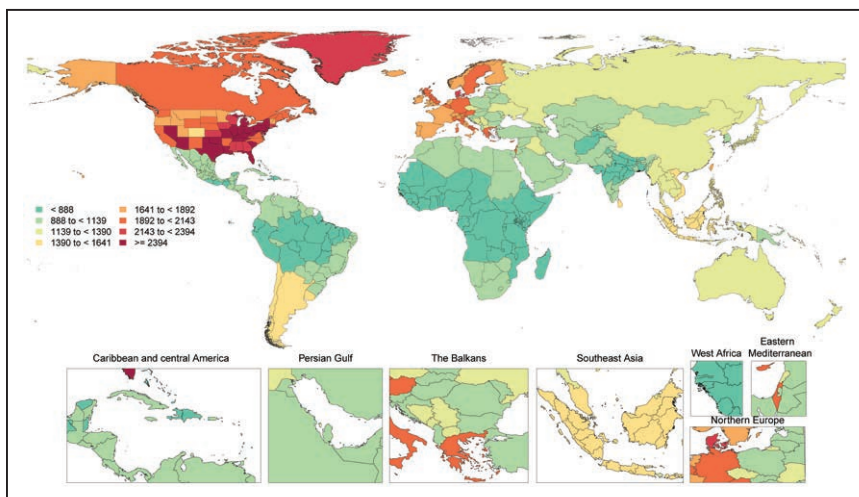
**Chart 25-3. Geographic variation in rates of lower-extremity amputation in the United States based on Centers for Medicare & Medicaid Services data from 2000 to 2008.**

Source: Reprinted from Jones et al<sup>15</sup> with permission from the American College of Cardiology Foundation. Copyright © 2012 American College of Cardiology Foundation.



**Chart 25-4. HRs of global cardiovascular mortality with 95% CI by categories, 1976 to 2000 (baseline years).**

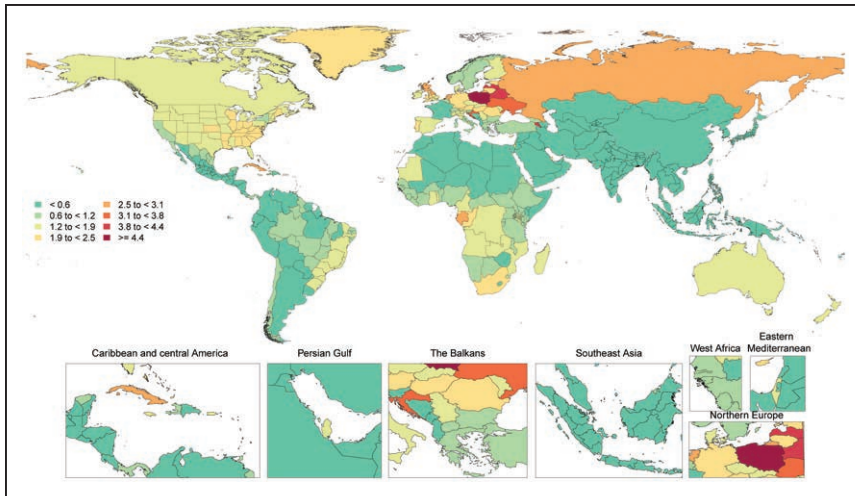
HR indicates hazard ratio. Source: Data derived from Fowkes et al.<sup>69</sup>



**Chart 25-5. Age-standardized global prevalence of lower-extremity PAD per 100,000, both sexes, 2020.**

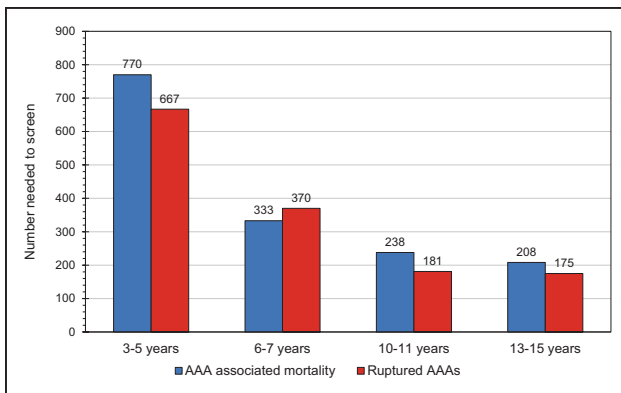
PAD indicates peripheral artery disease. Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>167</sup>

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**Chart 25-6. Age-standardized global mortality rates of lower-extremity PAD per 100 000, both sexes, 2020.**

PAD indicates peripheral artery disease. Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>167</sup>

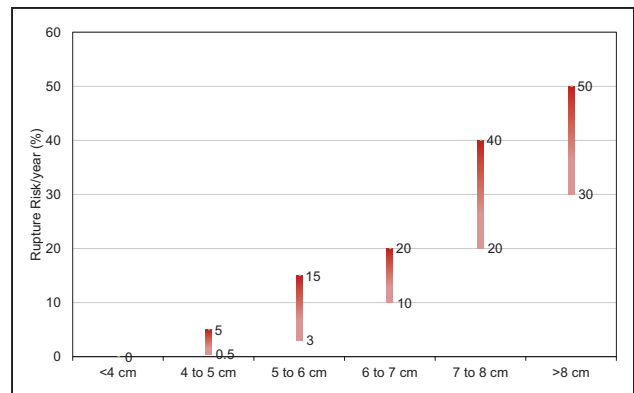


**Chart 25-7. Numbers needed to screen to avoid an AAA-associated death and a ruptured AAA, 1988 to 1999 (baseline years), with average follow-up of 4 to 15 years.**

Global data.

AAA indicates abdominal aortic aneurysm.

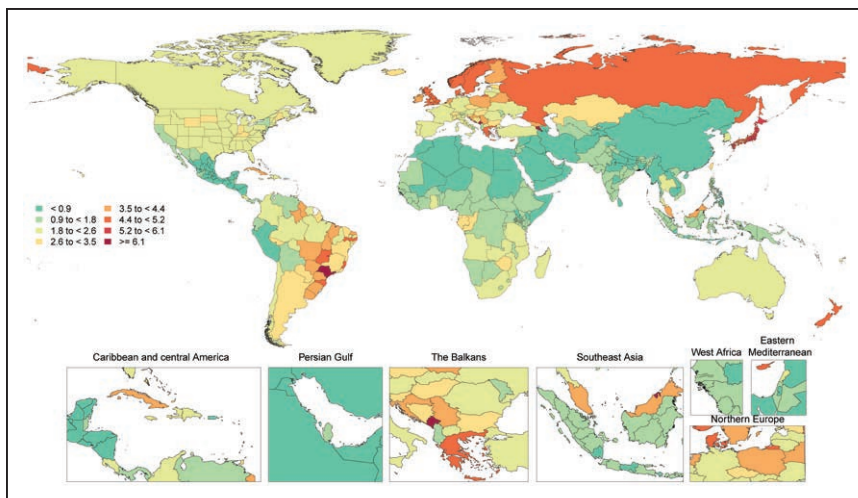
Source: Data derived from Eckstein et al.<sup>116</sup>



**Chart 25-8. Association between diameter and minimum and maximum risk of AAA rupture per year.**

AAA indicates abdominal aortic aneurysm.

Source: Data derived from Brewster et al.<sup>154</sup>



**Chart 25-9. Age-standardized global mortality rates of aortic aneurysm per 100 000, both sexes, 2020.**

Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation, University of Washington. Printed with permission. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.<sup>167</sup>

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## 26. QUALITY OF CARE

See Tables 26-1 through 26-8

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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,”<sup>1</sup> identifying 6 specific domains for improving health care: safety, effectiveness, patient- or people-centeredness, timeliness, efficiency, and equity.

Quality-of-care assessment uses performance measures, explicit standards against which care delivery can be judged.<sup>2</sup> This differs from guidelines, which provide clinical recommendations to inform usual clinical scenarios but ultimately leave decisions to reasonable clinician discretion. Measuring performance requires robust 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<sup>3</sup> and the AHA's GWTG program.<sup>4</sup> 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 post-marketing 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

The 2022 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 2022. 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.

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 AHA.<sup>2,5,6</sup>

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 26-1 through 26-3)

- The ACC's Chest Pain–MI Registry (formerly the ACTION Registry)<sup>7</sup> is currently the largest US-based hospital registry of inpatient AMI care (Tables 26-1 through 26-3).
- In 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).<sup>8</sup>
- 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.<sup>9</sup> 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 (aOR, 1.11 [95% CI, 1.02–1.21]). 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];  $P_{\text{interaction}} = 0.48$ ).
- With public outcome reporting from 2009 to 2015 across 2751 hospitals, 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;  $P < 0.001$ ];  $P_{\text{interaction}} < 0.001$ ).<sup>6</sup>

- In hospitals with higher-than-expected risk-adjusted 30-day readmission rates (ERR >1) after AMI, there was 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).<sup>10</sup> Among 51 453 patients with 1-year outcomes data, higher AMI ERR was associated with higher all-cause readmission within 1 year of discharge (aOR, 1.06 [95% CI, 1.03–1.08]); 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.
- 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 hospital RSMR for MI was 13.1% (IQR, 12.6%–13.5%), and the median risk-standardized 30-day readmission rate was 15.8% (IQR, 15.5%–16.2%).<sup>11</sup>
- In 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 (HR, 0.90 [95% CI, 0.85–0.96]).<sup>12</sup>
- In an analysis from 2005 to 2015 including 1.8 million hospitalizations for AMI, outcomes in 4 time periods were evaluated in relation to announcement and implementation of the HRRP.<sup>13</sup> 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 change significantly after HRRP implementation.
- A 20-year evaluation from January 1, 1995, to December 31, 2014, assessed AMI outcomes in older adults.<sup>14</sup> 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 (from 21% to 31%;  $P < 0.0001$ ) 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 (RR, 0.87 [95% CI, 0.80–0.94]). However, 1-year all-cause mortality was comparable for females and males (HR, 1.10 [95% CI, 0.83–1.45]).<sup>15</sup>
  - A national cross-sectional study highlighted discordance in measurement of quality between AHA/ACC metrics and federal value-based programs.<sup>16</sup> In fiscal year 2018, the analysis included hospitals participating in the HRRP (N=3175 hospitals) or the Hospital Value-Based Purchasing Program (N=2781 hospitals).
    - Hospitals that were recognized with awards for high-quality care from national quality improvement initiatives of the AHA and ACC were more likely to receive financial penalties from the HRRP compared with other hospitals (419 [85.5%] versus 2112 [78.7%];  $P < 0.001$ ). Award hospitals also were more commonly penalized compared with other hospitals in the Hospital Value-Based Purchasing Program (250 [51.7%] versus 950 [41.4%];  $P < 0.001$ ), with fewer financial rewards (234 [48.4%] versus 1347 [58.6%];  $P < 0.001$ ).
    - Thirty-day AMI mortality at award hospitals was similar to that at other hospitals (13.2% versus 13.2%;  $P = 0.76$ ).
  - An analysis spanning from April 2011 through December 2017 of patients with AMI from 625 sites using the NCDR Chest Pain–MI Registry (N=776 890 patients) and CathPCI Registry (N=853 386) explored hospital-level disease-based mortality compared with PCI procedural mortality.<sup>17</sup> There was moderate correlation between disease-based and procedural mortality (Spearman rank correlation coefficient, 0.53 [95% CI, 0.47–0.58]). Among patients with AMI who had cardiogenic shock or cardiac arrest, procedural mortality was lower than disease-based mortality (mean difference in excess mortality ratio, −0.64% [95% CI, −4.41% to 3.12%;  $P < 0.001$ ]), suggesting risk avoidance in this high-risk group.

## Heart Failure

### (See Tables 26-4 and 26-5)

- Current US HF quality data are best captured by the widespread but voluntary GWTG-HF program (Tables 26-4 and 26-5).
- In a study based on the GWTG-HF program linked to 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.<sup>18</sup>
- In an evaluation of hospital volume as a structural metric for quality of HF care, patients admitted with acute HF in the GWTG-HF registry with linked Medicare inpatient data were examined.<sup>19</sup> In 125 595 patients at 342 hospitals, hospital volume correlated with process measures but not with 30-day outcomes ( $P=0.26$ ) and only marginally with outcomes in up to 6 months of follow-up ( $P=0.025$ ). 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 differences in 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]).<sup>20</sup>
- Among a cohort of 115 245 fee-for-service Medicare beneficiaries discharged after HF hospitalizations, after HRRP implementation, 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]).<sup>21</sup>
- In a longitudinal cohort study of 48 million hospitalizations among 20 million Medicare fee-for-service patients across 3497 hospitals, patients at hospitals subject to penalties under the HRRP had greater reductions in readmission rates than those at nonpenalized hospitals (–1.25 [95% CI, –1.64 to –0.86] percentage point reduction compared with nonpenalized hospitals).<sup>22</sup> Reductions in readmission rates were greater for target versus nontarget conditions for patients at the penalized hospitals but not at nonpenalized hospitals.
- In data from 2009 to 2015 from 3796 hospitals with publicly reported mortality data for HF, 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;  $P<0.001$ ,  $P_{\text{interaction}}<0.001$ ).<sup>6</sup>
- In a secondary analysis of the TOPCAT and HF-ACTION trials focused on patient-reported outcomes, the most recent of a series of Kansas City Cardiomyopathy Questionnaire scores was most strongly associated with subsequent death and cardiovascular hospitalization, with a 10% (95% CI, 7%–12%;  $P<0.001$ ) lower risk for subsequent cardiovascular death or HF hospitalization in patients with HFpEF and 7% (95% CI, 3%–11%;  $P<0.001$ ) lower risk for HFrEF.<sup>23</sup>
- 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.<sup>24</sup>
- In the GWTG-HF registry, quality of care and clinical outcomes were comparable among hospitals with high versus low risk-adjusted 30-day HF readmission rates.<sup>25</sup>
  - There were no differences between the low (HF ERR  $\leq 1$ ) and high (HF ERR  $> 1$ ) 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 also was 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%;  $P=0.07$ ).
- According to national Medicare data from July 2015 through June 2016, the median hospital RSMR for HF was 11.6% (IQR, 10.8%–12.4%), and the median risk-standardized 30-day readmission rate was 21.4% (IQR, 20.8%–22.1%).<sup>11</sup>



- Among patients who had multiple admissions at >1 hospital within a given year, the readmission rate was consistently higher among patients admitted to hospitals in the worse-performing quartile than among those admitted to hospitals in a best-performing quartile (absolute difference in readmission rate, 2.0 percentage points [95% CI, 0.4–3.5]).<sup>26</sup>
- In a Medicare cohort comprising almost 3 million admissions for HF and 1.2 million for MI, 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, with a correlation of 0.066 (95% CI, 0.036–0.096) for HF and 0.067 (95% CI, 0.027–0.106) for MI.<sup>27</sup>
- 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.<sup>28</sup>
- 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.<sup>29</sup>
- 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 (HR, 0.65 [95% CI, 0.49–0.85]); for those with chronic pulmonary obstructive disease, an early pneumologist visit was associated with a 29% reduction in readmissions (HR, 0.71 [95% CI, 0.55–0.91]); whereas for those individuals with HF and diabetes, an early visit was associated with a 42% reduction in mortality (HR, 0.58 [95% CI, 0.34–0.99]). 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 (HR, 0.78 [95% CI, 0.63–0.96]).<sup>30</sup>
- In a study including >15 000 individuals with HFrEF, 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]).<sup>31</sup>
- 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.<sup>32</sup>
- 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 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%).<sup>33</sup>
- In a study of 262 626 patients hospitalized with HF included in GWTG-HF, inclusion in the Medicare Advantage program was compared with inclusion in the fee-for-service Medicare.<sup>34</sup> Patients included in the Medicare Advantage program were more likely to be discharged home (adjusted OR, 1.16 [95% CI, 1.13–1.19];  $P<0.001$ ) despite lower odds of discharge within 4 days (adjusted OR, 0.97 [95% CI, 0.93–1.00];  $P=0.04$ ). In addition, no difference was reported in in-hospital mortality.

## Prevention and Risk Factor Modification (See Table 26-6)

- 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 26-6).<sup>35</sup>
- Between May 2008 and October 2013 from the ACC's PINNACLE Registry, among 215 193 patients (582 048 encounters) 40 to 75 years of age with diabetes and no CVD from 204 cardiology practices, statins were prescribed for 61.6% of patients with diabetes.<sup>36</sup> Among 182 practices with  $\geq 30$  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.
- According to data from MEPS 2002 to 2013, statin use increased overall and among those with established ASCVD from 49.8% to 58.1%, but use in higher-risk groups was suboptimal.<sup>37</sup> Statin use was significantly lower in females (OR, 0.81 [95% CI, 0.79–0.85]) and racial and 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.

- 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%.<sup>38</sup>
- In a PINNACLE Registry study of 1 655 723 patients after November 2013 reflecting a change in guideline recommendations, 57% to 62% of patients were treated with appropriate statin therapy under the ACC/AHA guidelines.<sup>39</sup> Overall, there was a small association of higher income with appropriate statin therapy (point-biserial correlation, 0.026;  $P < 0.001$ ). Logistic regression showed an independent association of income with appropriate statin therapy (OR, 1.03 for wealthiest quintile versus poorest quintile [1.01–1.04]).

### Atrial Fibrillation

- The proportion of patients with AF receiving oral anticoagulants has increased over time,<sup>40</sup> 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<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  in 2014 was 48%. In the industry-funded, informed-consent, postmarketing GLORIA-AF international registry, oral anticoagulant prescription between 2011 and 2014 was 80%.<sup>41</sup>
- 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<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  hospitalized for AF at 1 of 115 sites from 2013 to 2017. Oral anticoagulation use increased over time from 79.9% to 96.6% in the end of the follow-up period for those with no contraindications, and there was high adherence, with 93.5% of eligible patients without contraindications being prescribed oral anticoagulation therapy for stroke prevention in AF.<sup>42</sup>
- In a cross-sectional analysis spanning 2013 to 2019 and including 34 174 hospitalized patients  $\geq 65$  years of age with AF from the GWTG-AF registry, overall discharge prescription of anticoagulation was 85.6%.<sup>43</sup> However, higher morbidity burden was associated with lower odds of anticoagulation prescription (aOR, 0.72 for patients with  $\geq 6$  comorbidities versus 0–2 comorbidities [95% CI, 0.60–0.86]). In those with  $\geq 6$  comorbidities, frequent falls/frailty was the most common reason for nonprescription of anticoagulation (31.0%).
- An AHA GWTG-Stroke study compared outcomes with direct oral anticoagulant therapy (dabigatran, rivaroxaban, or apixaban) versus warfarin in 11 662 patients  $\geq 65$  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 direct oral anticoagulant therapy had more favorable outcomes compared with those discharged on warfarin, including more days at home during the first year after discharge (mean  $\pm$  SD, 287.2  $\pm$  114.7 days versus 263.0  $\pm$  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];  $P < 0.001$ ).<sup>44</sup>
- 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]).<sup>45</sup> 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 those with 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 underestimate risk associated with HFpEF in prescribing anticoagulation for patients with AF.<sup>46</sup>
- A systematic review and meta-analysis demonstrated suboptimal adherence and persistence to direct oral anticoagulants in patients with AF.<sup>47</sup> Among 48 observational studies with a combined 594 784 patients with AF (59% male; mean age, 71 years), the pooled mean proportion of days covered/medication possession ratio was 77% (95% CI, 75%–80%), with 66% (95% CI, 63%–70%) showing  $\geq 80\%$  adherence and 69% (95% CI, 65%–72%) showing persistence. Poor adherence to direct oral anticoagulant therapy was associated with greater risk of stroke (HR, 1.39 [95% CI, 1.06–1.81]).

## Stroke

### (See Tables 26-3 and 26-7)

- The AHA GWTG-Stroke program (Tables 26-3 and 26-7) 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.
- In a study from the National Acute Stroke Quality Assessment including 14 666 patients from 202 hospitals, patients admitted to lower-volume centers had higher mortality.<sup>48</sup> However, this association was no longer present once adjusted for stroke severity, suggesting that severity should be accounted for in comparisons of performance across institutions.
- 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 post-stroke functional outcomes.<sup>49</sup>
- 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.<sup>50</sup>
- 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]).<sup>51</sup>
- In an analysis comparing individuals presenting with stroke at institutions participating in the GWTG-Stroke program and those at 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]).<sup>52</sup>

- 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.<sup>53</sup>

### Implantable Defibrillators and Cardiac Resynchronization Therapy

- According to data from the ACC's Implantable Cardioverter Defibrillator Registry, 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.<sup>54</sup> 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;  $P < 0.001$ ).<sup>55</sup>

### Resuscitation

#### (See Table 26-8)

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 26-8). 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.

- Among Medicare beneficiaries participating in GWTG-Resuscitation, 1-year survival after IHCA has increased modestly over the past decade with an aRR per year of 1.05 (95% CI, 1.03–1.06).<sup>56</sup> However, despite an overall improvement in survival, there remains lower survival in IHCA during off-hours (nights and weekends) compared with on-hours events ( $P=0.02$ ).<sup>57</sup>
- Of 103932 IHCA 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.<sup>58</sup>
- 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.<sup>59</sup>
- Data from the GWTG-Resuscitation including 268031 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.<sup>60</sup>
- In a French study of 8754 OHCA 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]).<sup>61</sup>
- In a study including 84089 adult patients with an IHCA from 166 hospitals participating in GWTG-Resuscitation, the risk-standardized survival rate was consistent over the 4-year period from 2012 to 2015, although 20% of the bottom-performing hospitals had substantial improvement in survival, likely resulting from quality improvement innovations.<sup>62</sup>
- In an analysis of the impact of the 2010 and 2015 resuscitation guidelines,<sup>63,64</sup> a study including 231739 patients demonstrated an annual increase in survival of 1.09% (95% CI, 0.74%–1.43%;  $P<0.001$ ) from 2006 to 2010, 0.26% (95% CI, –0.11% to 0.64%;  $P=0.17$ ) from 2011 to 2015, and –0.43% (95% CI, –0.96% to 0.11%;  $P=0.12$ )

from 2016 to 2018 with no immediate change after the publication of either guideline.<sup>65</sup>

- In a study comparing OHCA between 2019 and 2020 to evaluate the impact of the COVID-19 pandemic, a lower proportion of cases receiving bystander cardiopulmonary resuscitation in 2020 (61% to 51%;  $P=0.02$ ) and lower use of automated external defibrillators (5% to 1%;  $P=0.02$ ) were seen.<sup>66</sup> The authors also reported longer EMS response time ( $6.6\pm 2.0$  to  $7.6\pm 3.0$  minutes, respectively;  $P<0.001$ ) and lower survival to hospital discharge (14.7% to 7.9%;  $P=0.02$ ).

## Social Determinants

- NCDR data in 390692 patients among 586 hospitals from July 2008 to December 2013 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%;  $P<0.0001$ ).<sup>67</sup> 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 socioeconomically disadvantaged neighborhoods.
- A retrospective cohort study of Medicare patients found that outpatient practices serving the most socioeconomically disadvantaged patients with CAD perform worse on 30-day AMI mortality, despite delivery of guideline-recommended care similar to that of other outpatient practices.<sup>68</sup> Patients at the most socioeconomically disadvantaged—serving outpatient practices had higher 30-day mortality rates after AMI (aOR, 1.31 [95% CI, 1.02–1.68]) compared with other outpatient practices despite similar prescription of guideline-recommended interventions (antiplatelet, antihypertensive, and statin therapy, as well as cardiac rehabilitation). The association was attenuated after additional adjustment for patient-level area deprivation index.
- 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.<sup>69</sup> Relative to Medicare, Medicaid insurance was associated with a lower odds of oral anticoagulant prescription (military, 53%; private, 53%; Medicare, 52%; other, 41%; Medicaid,



41%;  $P < 0.001$ ) and of novel oral anticoagulant use (military, 24%; private, 19%; Medicare, 17%; other, 17%; Medicaid, 8%;  $P < 0.001$ ).

- French data on OHCA from 123 municipalities suggest that municipalities with lower SES are associated with a higher incidence of OHCA.<sup>70</sup> The study clustered municipalities in 7 spatial clusters. Those 4 clusters with lower SES have an RR from 1.43 to 2 compared with the others ( $P < 0.0001$ ). Data from >3000 patients from Sweden suggest that in out-of-hospital stroke care, individuals with lower SES take longer to undergo brain CT (3 hours 47 minutes versus 3 hours 17 minutes;  $P = 0.015$ ) and are less likely to receive highest priority in the ambulance (aOR, 1.43 for high versus low tertile;  $P = 0.005$ ). They are also less likely to have their stroke recognized in the prehospital setting (aOR, 1.44 for high versus low tertile;  $P = 0.014$ ).<sup>71</sup>

### Race and Ethnicity

- Most of the mortality rate difference after AMI between Black and White individuals may be mediated by patient characteristics: 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.<sup>72</sup> Among 6402 patients with AMI, 5-year mortality occurred in 28.9% of Black individuals (476 of 1648) and 18.0% of White individuals (856 of 4754; HR, 1.72 [95% CI, 1.54–1.92];  $P < 0.001$ ). After controlling for propensity associated with being a Black individual, no difference in mortality by race was observed (aHR, 1.09 [95% CI, 0.93–1.26];  $P = 0.37$ ).
- 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 individuals 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.<sup>73</sup>
- According to NIS data, HF hospitalization rates decreased 30.8% between 2002 and 2013.<sup>74</sup>

- The ratio of males to females increased from 20% greater to 39% greater ( $P_{\text{trend}} = 0.002$ ) over that time.
- Black males and Black females had hospitalization rates that were 229% ( $P_{\text{trend}} = 0.141$ ) and 240% ( $P_{\text{trend}} = 0.725$ ) those of White individuals in 2013.
- Hispanic males had rates that were 32% greater in 2002, and the difference narrowed to 4% greater ( $P_{\text{trend}} = 0.047$ ) in 2013 relative to White males. For Hispanic females, the rate was 55% greater in 2002 and narrowed to 8% greater ( $P_{\text{trend}} = 0.004$ ) in 2013 relative to White females.
- Asian/Pacific Islander males had a 27% lower hospitalization rate in 2002, which improved to 43% lower ( $P_{\text{trend}} = 0.040$ ) in 2013 relative to White males. For Asian/Pacific Islander females, the hospitalization rate was 24% lower in 2002 and improved to 43% lower ( $P_{\text{trend}} = 0.021$ ) in 2013 relative to White females.
- 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 individuals, although 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];  $P < 0.001$ ).<sup>75</sup>
- 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 White (15.8% versus 23.2%) individuals, although a reduction in the difference between races was noted ( $P_{\text{interaction}} < 0.001$ ).<sup>76</sup>

**Table 26-1. Time Trends in the CAD Quality-of-Care Measures in the Chest Pain–MI Registry, United States, 2010 to 2020**

Quality-of-care measure	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019*	2020
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	97.4
Aspirin at discharge‡	98	98.3	98.4	98.4	98.7	98.7	98.7	98.7	98.9	98.3	98.6
β-Blockers at discharge	96	96.7	97.1	97.1	97.6	97.5	97.5	97.4	97.4	96.3	97.0
Statin use at discharge	92	98.4	98.8	98.8	99.1	99.2	99.4	99.4	99.5	99.4	NA
High-intensity statin at discharge	NA	NA	NA	NA	NA	NA	NA	NA	NA	88.1	92.4
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	86.3
Adult smoking cessation advice/counseling	98	98.4	98.4	98.4	98.6	98.0	98.1	98.0	98.2	NA	NA
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	83.7

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 NA, not available.

\*Quality-of-care metrics in 2019 were updated to align with the "2017 AHA [American Heart Association]/ACC [American College of Cardiology] Clinical Performance and Quality Measures for Adults With ST-Elevation and Non-ST-Elevation Myocardial Infarction."<sup>77</sup> 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.<sup>78</sup>

†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 ACC's Chest Pain–MI Registry.<sup>7</sup>

**Table 26-2. Additional Chest Pain–MI Registry Quality-of-Care Metrics for AMI Care, United States, 2018 to 2020**

Quality metrics	2018	2019	2020
ECG within 10 min of arrival	68.6	64.0	73.0
Aspirin within 24 h of arrival	98.7	97.6	97.4
Any anticoagulant use*	96.1	NA	NA
Dosing errors			
UFH dose	43.2	NA	NA
Enoxaparin dose	9.8	NA	NA
Glycoprotein IIb/IIIa inhibitor dose	4.3	NA	NA
Discharge			
Aspirin at discharge	98.9	98.3	98.6
Prescribed statins on discharge	99.5	NA	NA
High-intensity statin at discharge	NA	88.1	92.4
Adult smoking cessation advice/counseling	98.2	NA	NA
Cardiac rehabilitation referral	83.3	82.7	83.7
In-hospital mortality† (95% CI)	4.12 (3.96–4.39)	NA	5.4 (5.24 – 5.69)

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; NA, not available; and UFH, unfractionated heparin.

\*Includes UFH, low-molecular-weight heparin, or direct thrombin inhibitor use.

†Includes all patients. Risk standardized mortality.

Source: Data from the American College of Cardiology's Chest Pain–MI Registry.<sup>7</sup>

**Table 26-3. Timely Reperfusion for AMI and Stroke, United States**

Quality-of-care measure	GWTC-Stroke (for stroke): July 1, 2018–June 30, 2019	Chest Pain–MI Registry: STEMI, 2019	Chest Pain–MI Registry: STEMI, 2020
STEMI			
PCI within 90 min*	NA	94.0	93.0
Stroke			
IV tPA in patients who arrived <2 h after symptom onset, treated ≤3 h	88.2†	NA	NA
IV tPA in patients who arrived <3.5 h after symptom onset, treated ≤4.5 h	84.2†‡	NA	NA
IV tPA door-to-needle time ≤60 min	84.2†	NA	NA

Values are percentages. GWTC data for 2019 to 2020 are not available.

AMI indicates acute myocardial infarction; GWTC, Get With The Guidelines; IV, intravenous; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and tPA, tissue plasminogen activator.

\*Excludes transfers and is measuring hospital arrival; arrival by emergency medical service is 96%.

†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.<sup>7</sup> Stroke data from unpublished data, GWTC-Stroke, July 1, 2018, to June 30, 2019.

**Table 26-4. HF Quality-of-Care Measures, United States, 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
$\beta$ -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 26-5. Quality of Care by Race and Ethnicity and Sex in the GWTG-HF Program, United States, July 1, 2018, to June 30, 2019**

Quality-of-care measure	Race and ethnicity			Sex	
	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 $\beta$ -blockers*	94.07	95.81	94.89	94.95	94.13
$\beta$ -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 $\beta$ -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 26-6. National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set on CVD, Diabetes, Tobacco, Nutrition, and Lifestyle, United States**

	Commercial (2019 data)		Medicare (2018 data; see note below)*		Medicaid (2019 data)
	HMO	PPO	HMO	PPO	HMO
<b>CVD</b>					
β-Blocker persistence after MI†	85.1	85.6	87.1	89.1	80.9
BP control‡	62.1	47.6	69.7	68.8	60.8
Statin therapy for patients with CVD	81.9	80.8	81.1	80.4	78.0
<b>Diabetes</b>					
HbA1c testing	91.7	90.0	94.4	93.9	88.2
HbA1c >9.0%	29.8	40.1	22.5	19.9	40.4
Eye examination performed	55.1	50.3	74.2	72.7	57.2
Monitoring nephropathy	90.1	88.7	95.5	94.9	89.7
BP <140/90 mm Hg	65.0	51.3	69.5	67.3	62.1
Statin therapy for patients with diabetes	64.0	62.5	74.4	71.3	64.0
<b>Tobacco, nutrition, and lifestyle</b>					
Advising smokers and tobacco users to quit	74.9	67.0	86.5	83.2	77.2
BMI percentile assessment in children and adolescents (3–17 y of age)	73.2	59.7	NA	NA	76.9
Nutrition counseling (children and adolescents [3–17 y of age])	66.9	54.2	NA	NA	68.0
Counseling for PA (children and adolescents [3–17 y of age])	62.8	50.2	NA	NA	63.8
BMI assessment for adults (18–74 y of age)	84.9	69.7	96.2	96.3	88.4
PA discussion in older adults (≥65 y of age; 2016 data)	NA		55.3	57.7	NA
PA advice in older adults (≥65 y of age; 2016 data)	NA		52.3	51.1	NA

Values are percentages.

BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HMO, health maintenance organization; MI, myocardial infarction; NA, not available or not applicable; PA, physical activity; and PPO, preferred provider organization.

\*The Medicare numbers presented are from 2018, which are the same as last year's AHA statistics update. Updated 2019 Medicare data are not available because of CMS suspension of data reporting during the coronavirus disease 2019 (COVID-19) pandemic.

†β-Blocker persistence: received persistent β-blocker treatment for 6 months 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 and 2019.<sup>35</sup>

**Table 26-7. Quality of Care by Race and Ethnicity and Sex in the GWTG-Stroke Program, United States, July 1, 2018, to June 30, 2019**

Quality-of-care measure	Race and ethnicity			Sex	
	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 patient 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 <sup>2</sup>	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 26-8. Quality of Care of Patients With IHCA Among GWTG-Resuscitation Hospitals, United States, 2020**

	Adults	Children
Event outside critical care setting	43.8	13.4
Hospital survival to discharge for IHCA outside the ICU	23.3	42.6
End-tidal CO <sub>2</sub> monitoring used during arrest (all IHCA events)	15.1	38.3
Induced hypothermia used when initial rhythm was shockable (all IHCA events)	99.9%	99.7%
For IHCA with survival, induced hypothermia initiated	9.5	10.2

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, 2020.

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## 27. MEDICAL PROCEDURES

See Tables 27-1 and 27-2 and Charts 27-1 through 27-4

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### Trends in Operations and Procedures (See Tables 27-1 and 27-2 and Charts 27-1 and 27-2)

- The mean hospital charges for cardiovascular procedures in 2014 ranged from \$43 484 for CEA to \$808 770 for heart transplantation (Table 27-1).
- The trends in the numbers of 5 common cardiovascular procedures in the United States from 1993 to 2014 are presented in Chart 27-1. Of the 5 procedures, cardiac catheterization was the most common procedure for all years presented (Chart 27-1).
- Of the 10 leading diagnostic groups in the United States, the surgical procedures with the greatest numbers were cardiovascular and obstetric procedures (Chart 27-2).
- The total number of inpatient cardiovascular operations and procedures decreased 6%, from 8 461 000 in 2004 to 7 971 000 in 2014 (Table 27-2).
- Data from the HCUP were examined by the NHLBI for trends from 1997 to 2014 for use of PCI and CABG,<sup>1</sup> as discussed in this chapter.

### Coronary Artery Bypass Grafting

- The number of inpatient discharges for CABG decreased from 683 000 in 1997 to 371 000 in 2014 (Chart 27-1).
- 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 27-2).<sup>1</sup>

### Inpatient Cardiac Catheterization and PCI

(See Tables 27-1 and 27-2 and Chart 27-1)

- 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 27-2).

- 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). The authors also noted an increase in the number of facilities performing revascularization procedures. The authors noted that during the study period, 268 (20.2%) more sites were performing nonadmission PCIs, 136 (8.2%) more sites were performing inpatient PCIs, and 19 (1.6%) more sites were performing CABG.<sup>2</sup>
- In 2014, the mean inpatient hospital charge for PCI was \$84 813 (Table 27-1).
- From 2004 to 2014, the number of inpatient cardiac catheterizations decreased from 1 486 000 to 1 016 000 annually (Chart 27-1).
- In 2014, an estimated 480 000 inpatient PCI (previously referred to as percutaneous transluminal coronary angioplasty) procedures were performed in the United States (Chart 27-1).
- In 2014, ≈68% of inpatient PCI procedures were performed on males, and ≈50% were performed on people ≥65 years of age (Table 27-2).
- Inpatient hospital deaths for PCI increased from 0.8% in 2004 to 2.1% in 2014 (Table 27-1). 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.<sup>3</sup>

### Cardiac Open Heart Surgery

- Data from the STS Adult Cardiac Surgery Database, which voluntarily collects data from ≈80% of all hospitals that perform CABG in the United States, indicate that a total of 157 704 procedures involved isolated CABG in 2018.<sup>4</sup>
- Among other major procedures in 2018, there were 25 274 isolated aortic valve replacements and 10 669 isolated mitral valve replacements; 12 424 isolated mitral valve repairs, 15 855 procedures involving both aortic valve replacement and CABG, 3509 procedures involving both mitral valve replacement and CABG, 4093 procedures involving both mitral valve repair and CABG, and 2670 procedures involving both mitral valve replacement and aortic valve replacement.<sup>4</sup> Operative mortality for various cardiac surgical procedures in 2018 was as follows: isolated CABG, 2.2%; isolated aortic valve replacement, 1.9%; aortic valve replacement plus CABG, 3.6%; mitral valve replacement, 4.5%; mitral valve

The 2022 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 2022. 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.



replacement plus CABG, 9.6%; mitral valve repair, 1.2%; and mitral valve repair plus CABG, 5.4%. Median length of stay was 8 days for isolated CABG.

### Transcatheter Aortic Valve Replacement

- The STS-ACC TVT registry collects data on TAVR procedures performed in the United States.<sup>5</sup> Between 2011 and 2019, it collected data on 276316 TAVR procedures in the United States. Some notable findings include the following:
- TAVR volumes continue to grow, with 13723 TAVR procedures in 2011 to 2013 to 72991 TAVR procedures in 2019. In 2019, 669 sites were performing TAVR. In 2019, TAVR volumes (n=72991) exceeded the volumes for all forms of SAVR (n=57626). The number of intermediate and low-risk patients receiving TAVR has grown steadily.
- In-hospital and 30-day mortality rates of TAVR have improved over time. The in-hospital and 30-day mortality rates were 5.4% and 7%, respectively, in 2013 and before, whereas they were 1.3% and 2.5%, respectively, in 2019 ( $P<0.0001$ ). In-hospital stroke rate decreased from 1.8% before 2013 to 1.6% in 2019 ( $P<0.0001$ ). Need for a pacemaker at 30 days has not changed significantly (10.9% in 2011–2013 to 10.8% in 2019). Median length of stay was 2 days in 2019 (IQR, 1–3 days), with 90.3% of the patients discharged home.
- The femoral artery remains the most frequent access site (used in 95.3% of the patients undergoing TAVR in 2019).

### Congenital Heart Surgery, 2015 to 2018

According to data from the STS Congenital Heart Surgery Database<sup>6</sup>:

- There were 123777 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 27-3 and 27-4)

According to data from the Organ Procurement and Transplantation Network<sup>7</sup>:

- In 2020, 3658 heart transplantations were performed in the United States, the most ever (Chart 27-3). The highest numbers of heart transplantations were seen in California (496), Texas (302), Florida (288), and New York (250).
- Of the recipients in 2020, 71.6% were male individuals, 59.4% were White people, 25.0% were Black people, 10.7% were Hispanic people, and 3.4% were Asian people. Heart transplantations by recipient age are shown in Chart 27-4. The largest proportion of these patients (41.8%) were between 50 and 64 years of age.
- 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 individuals undergoing cardiac transplantation were 90.7% and 79.1%, respectively. For Black people, they were 90.7% and 74.1%, respectively. For Hispanic people, they were 90.1% and 80.0%, respectively. For Asian individuals, they were 91.4% and 80.1%, respectively.
- Between 2011 and 2014, the median wait time for individuals in United Network for Organ Sharing heart status 1A was 87 days (95% CI, 80–94 days).
- As of February 21, 2021, 3515 individuals were on the transplant waiting list for a heart transplant, and 49 people were on the list for a heart/lung transplant.

### Impact of COVID-19

- A global survey of 909 inpatient and outpatient centers performing cardiovascular diagnostic procedures in 108 countries compared procedural volumes for common cardiovascular diagnostic procedures between March 2019 and March 2020/April 2020.<sup>8</sup> Cardiovascular diagnostic procedures decreased by 64% from March 2019 to April 2020. Comparing March 2019 to April 2020 shows that transthoracic echocardiography volume decreased by 59%, stress test volume decreased by 78%, invasive angiography volume decreased by 57%, CT coronary angiography volume decreased by 54%, and transesophageal echocardiography volume decreased by 76%. In multivariable analyses, low-income and lower-middle-income countries saw an additional 22% reduction in cardiovascular diagnostic procedural volumes.
- Using data from a large health care system in Northern California, investigators showed that hospitalization rates for AMI went down significantly during the early phase of the COVID-19 pandemic.<sup>9</sup>

For example, the hospitalization rates for acute MI were 4.1 per 100 000 person-weeks for the period of January 1, 2020, to March 3, 2020, whereas the hospitalization rates were 2.1 per 100 000 person-weeks from April 8 through April 14, 2020. Overall, there was a 48% decline in hospitalizations for acute MI (IRR, 0.52 [95% CI, 0.40–0.68]). This was seen with a concomitant increase in the number of COVID-19 cases, indicating that patients were deferring care for acute MI. A similar study from the United Kingdom showed a 54% and 32% reduction in hospitalization for acute MI and HF, respectively with the first wave of COVID-19.<sup>10</sup> After recovering in June 2020, the hospitalization rates showed another decline with the second wave of COVID-19. The hospitalizations for acute MI and HF went down by 41% and 34%, respectively, with the second wave of COVID-19. These results indicate that patients deferred acute cardiovascular care during various phases of the COVID-19 pandemic.

- Despite studies showing a reduction in hospitalization rates, a study using data from the NCHS that analyzed 397 042 deaths attributable to CVD in the United States between January 1, 2020, and June 2, 2020, showed that deaths attributable to IHD and hypertensive diseases increased significantly in 2020 after the onset of the pandemic compared with the same time period in 2019.<sup>11</sup> The ratio of the relative change in deaths per 100 000 in 2020 versus 2019 was 1.11 (95% CI, 1.04–1.18) for IHD and 1.17 (95% CI, 1.09–1.26) for hypertensive disease. New York City saw a much larger relative increase in deaths caused by IHD (2.39 [95% CI, 1.39–4.09]) and hypertensive diseases (2.64 [1.52–4.56]) compared with other cities or states. Together with a reduction in hospitalizations, these results indicate that patients may have deferred care at times of COVID-19, leading to adverse cardiovascular outcomes.

**Table 27-1. 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, 9th Revision, Clinical Modification*; and PCI, percutaneous coronary intervention.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.<sup>1</sup>

**Table 27-2. 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. Over time, 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.

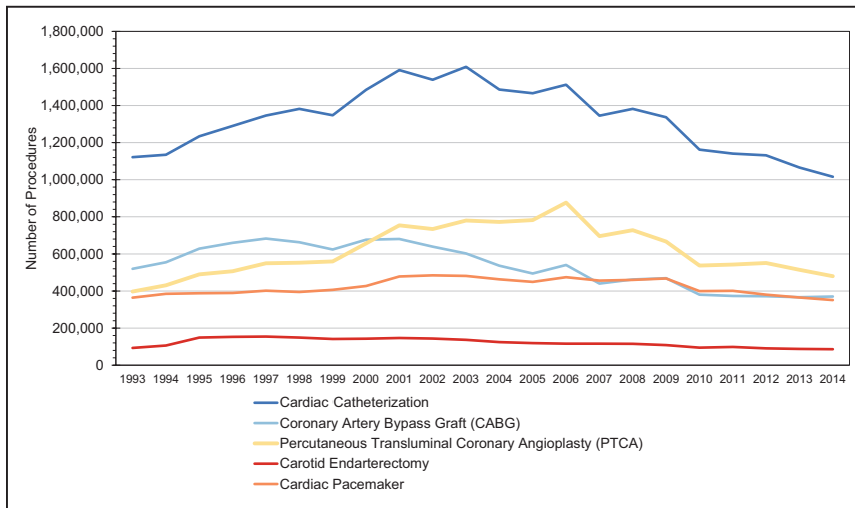
CABG indicates coronary artery bypass graft; CEA, carotid endarterectomy; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; and PCI, percutaneous coronary intervention.

\*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.

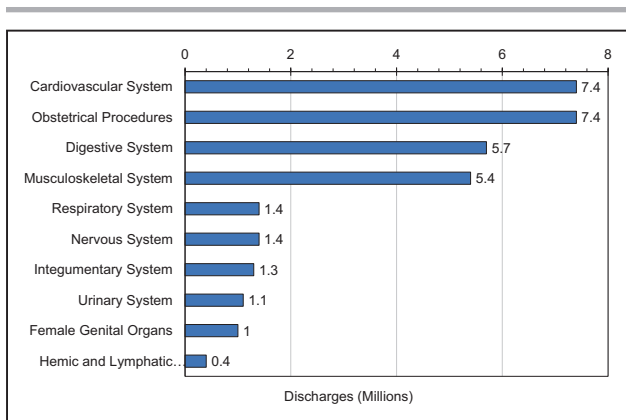
‡This estimate includes angioplasty and stent insertions for noncoronary arteries.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.<sup>1</sup>



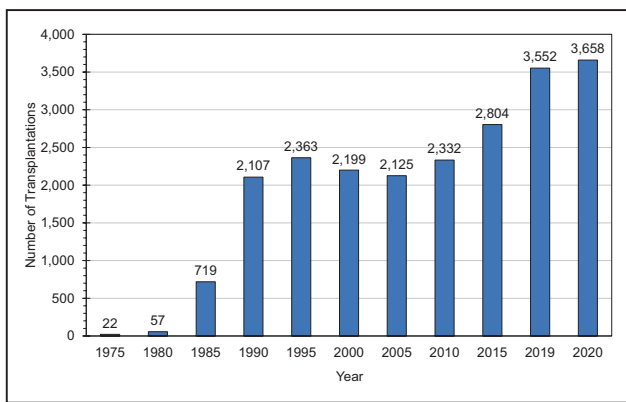
**Chart 27-1. Trends in cardiovascular procedures, United States, 1993 to 2014, inpatient procedures only.**

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.<sup>1</sup>



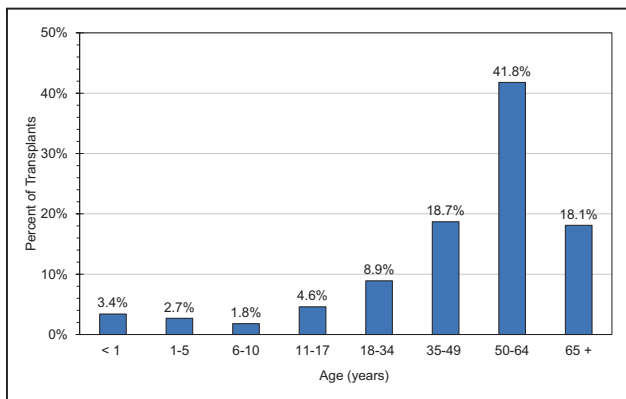
**Chart 27-2. Number of surgical procedures in the 10 leading diagnostic groups, United States, 2014.**

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.<sup>1</sup>



**Chart 27-3. Trends in heart transplantations, United States, 1975 to 2020.**

Source: Data derived from the Organ Procurement and Transplantation Network.<sup>7</sup>



**Chart 27-4. Heart transplantations, by recipient age, United States, 2020.**

Source: Data derived from the Organ Procurement and Transplantation Network.<sup>7</sup>

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## 28. ECONOMIC COST OF CARDIOVASCULAR DISEASE

See Tables 28-1 and 28-2 and Charts 28-1 through 28-3

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According to data from MEPS (2017–2018),<sup>1</sup> the annual direct and indirect cost of CVD in the United States is an estimated \$378.0 billion (Table 28-1 and Chart 28-1). This figure includes \$226.2 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 \$151.8 billion in lost future productivity (indirect costs) attributed to premature CVD mortality in 2017 to 2018.

The direct costs for CVD for 2017 to 2018 (average annual) are available on the website of the nationally representative MEPS of the Agency for Healthcare Research and Quality.<sup>1</sup> Details on the advantages or disadvantages of using MEPS data are provided in the “Heart Disease and Stroke Statistics—2011 Update.”<sup>2</sup> Indirect mortality costs are estimated for 2017 to 2018 (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 2017 to 2018. Mortality data are from the NVSS of the NCHS.<sup>3</sup> 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.<sup>4</sup> The discount rate removes the effect of inflation in income over the lifetime of earnings. The estimate is for 2014, inflated to 2018 to account for the 2014 to 2018

change in hourly worker compensation in the business sector reported by the US Bureau of Labor Statistics.<sup>5</sup> The indirect costs exclude lost productivity costs attributable to chronic, prevalent nonfatal CVD illness during 2017 to 2018 among workers, people keeping house, people in institutions, and people unable to work. Those morbidity costs were substantial in old studies, but because of the lack of contemporary data, an adequate update could not be made.

### Costliest Diseases

(See Tables 28-1 and 28-2 and Charts 28-2 and 28-3)

CVD accounted for 12% of total US health expenditures in 2017 to 2018, more than any major diagnostic group.<sup>1</sup> By way of comparison, CVD total direct costs shown in Table 28-1 are higher than the 2017 to 2018 Agency for Healthcare Research and Quality estimate for cancer, which was \$109.0 billion (49% for outpatient or office-based events, 27% for inpatient stays, and 21% for prescription drugs).<sup>1</sup>

Table 28-2 shows direct and indirect costs for CVD by sex and by 2 broad age groups. Chart 28-2 shows total direct costs for the 20 leading chronic diseases on the MEPS list. HD is the sixth costliest condition.<sup>1</sup>

The estimated direct costs of CVD in the United States increased from \$103.5 billion in 1996 to 1997 to \$226.2 billion in 2017 to 2018 (Chart 28-3).

### Economic Value of CVD Risk Factor Control

Cutler et al<sup>6</sup> 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.

The 2022 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.

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**Table 28-1. Estimated Direct and Indirect Costs (in Billions of Dollars) of CVD, United States, Average Annual, 2017 to 2018**

	HD*	Stroke	Hypertensive disease†	Other circulatory conditions‡	Total CVD
Direct costs§					
Hospital inpatient stays	54.2	19.7	6.4	19.3	99.6
Hospital ED visits	4.6	1.4	1.4	1.9	9.3
Hospital outpatient or office-based health care professional visits	25.6	3.7	14.1	11.9	55.3
Home health care	10.5	7.4	6.2	2.6	26.7
Prescribed medicines	13.9	1.2	17.4	2.8	35.3
Total expenditures	108.8	33.4	45.5	38.5	226.2
Indirect costs					
Lost productivity/mortality	119.9	19.4	5.6	6.9	151.8
Grand totals	228.7	52.8	51.1	45.4	378.0

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 2017 to 2018, discounted at 3%.

Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using Household Component of the MEPS for direct costs (average annual 2017–2018).<sup>1</sup> Indirect mortality costs are based on 2017 to 2018 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 2018 from change in worker compensation reported by the US Bureau of Labor Statistics.<sup>5</sup>

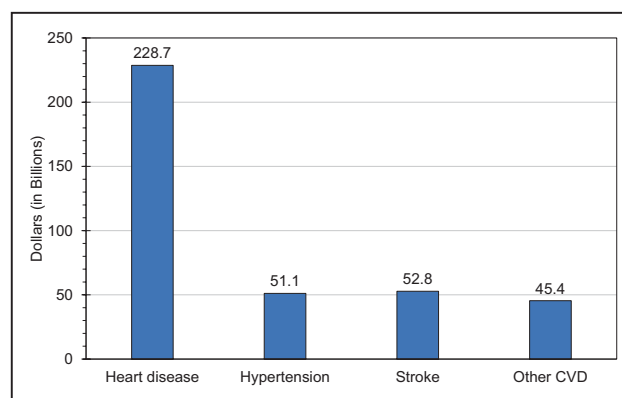
**Table 28-2. Costs of CVD in Billions of Dollars, by Age and Sex, United States, Average Annual, 2017 to 2018**

	Total	Males	Females	Age <65 y	Age ≥65 y
All direct	226.2	125.9	100.3	97.7	128.5
Indirect: mortality only	151.8	113.3	38.5	125.6	26.2
Total	378.0	239.2	138.8	223.3	154.7

Numbers may not add to total because of rounding.

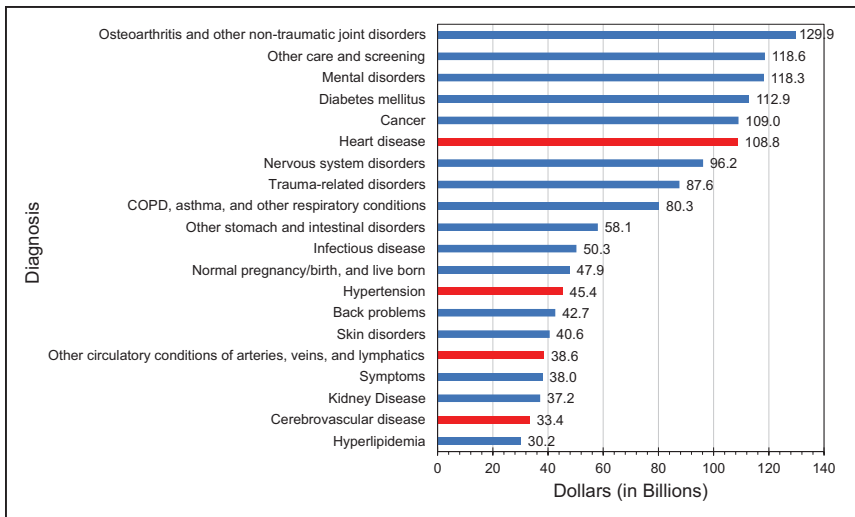
CVD indicates cardiovascular disease.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey, average annual 2017 to 2018 (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).<sup>1,3</sup>

**Chart 28-1. Direct and indirect costs of CVD (in billions of dollars), United States, average annual 2017 to 2018.**

CVD indicates cardiovascular disease.

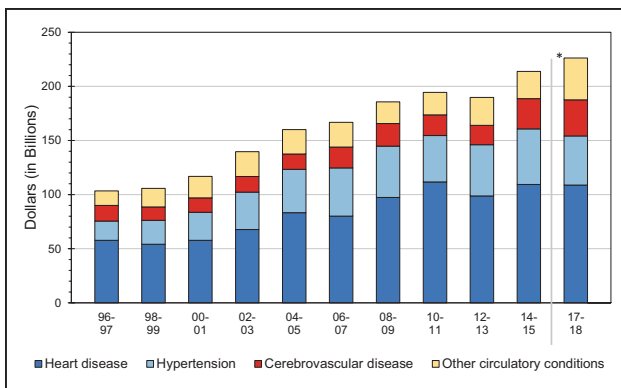
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey data and mortality data from the National Vital Statistics System.<sup>1,3</sup>



**Chart 28-2. The 20 leading diagnoses for direct health expenditures, United States, average annual 2017 to 2018 (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.<sup>1</sup>



**Chart 28-3. Estimated direct cost (in billions of dollars) of CVD, United States, average annual (1996–1997 to 2017–2018).**

\**International Classification of Diseases, Ninth Revision* coding for 1996 to 2015; *International Classification of Diseases, 10th Revision* coding for 2016 to 2018. The 2016 data are omitted from this chart. CVD indicates cardiovascular disease.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey for direct costs (average annual 1996–1997 to 2017–2018).<sup>1</sup>

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## 29. AT-A-GLANCE SUMMARY TABLES

See Tables 29-1 through 29-3

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Sources: See the following summary tables for complete details:

- Overweight, Obesity, and Severe Obesity in Youth and Adults in the United States—Table 6-1
- High TC and LDL-C and Low HDL-C in the 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 17-1
- CHD in the United States—Table 21-1; AP in the United States—Table 21-2
- HF in the United States—Table 22-2

The 2022 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 2022. 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.

**Table 29-1. 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*
<b>Overweight and obesity</b>							
Prevalence, 2015–2018							
Overweight and obesity, BMI ≥25.0 kg/m <sup>2</sup> †	170.1 M (71.3%)	85.3 M (74.8%)	73.9%	69.9%	84.8%	55.9%	...
Obesity, BMI ≥30.0 kg/m <sup>2</sup> †	96.4 M (40.6%)	45.4 M (39.9%)	40.7%	38.2%	44.0%	13.5%	...
<b>Blood cholesterol</b>							
Prevalence, 2015–2018							
TC ≥200 mg/dL‡	93.9 M (38.1%)	41.6 M (35.3%)	35.0%	31.0%	37.7%	38.6%	...
TC ≥240 mg/dL‡	28.0 M (11.5%)	12.2 M (10.5%)	10.1%	9.2%	12.4%	13.0%	...
LDL-C ≥130 mg/dL‡	68.1 M (27.8%)	32.2 M (27.4%)	26.0%	29.3%	29.4%	33.4%	...
HDL-C <40 mg/dL‡	41.9 M (17.2%)	31.6 M (26.6%)	26.3%	17.0%	32.0%	26.4%	...
<b>HBP</b>							
Prevalence, 2015–2018†	121.5 M (47.3%)	63.1 M (51.7%)	51.0%	58.3%	50.6%	51.0%	...
Mortality, 2019§	102 072	49 451 (48.4%)¶	33 788	9604	3949	1490#	679
<b>Diabetes</b>							
Prevalence, 2015–2018							
Diagnosed diabetes†	28.2 M (10.4%)	15.5 M (12.1%)	10.8%	12.8%	15.3%	14.3%	...
Undiagnosed diabetes†	9.8 M (3.8%)	5.5 M (4.5%)	4.1%	4.7%	6.0%	5.5%	...
Prediabetes†	113.6 M (45.8%)	63.1 M (52.9%)	56.5%	35.5%	49.8%	52.5%	...
Incidence, diagnosed diabetes, 2018**	1.5 M	...	...	...	...	...	...
Mortality, 2019§	87 647	49 512 (56.5%)¶	33 492	7901	5617	1763#	1077
<b>Total CVD</b>							
Prevalence, 2015–2018†							
Mortality, 2019§	874 613	453 801 (51.9%)¶	347 087	57 761	31 864	12 939#	4635
<b>Stroke</b>							
Prevalence, 2015–2018†							
New and recurrent strokes§	795.0 K	370.0 K (46.5%)¶	325.0 K††	45.0 K††	...	...	...
Mortality, 2019§	150 005	64 347 (42.9%)¶	46 589	8986	5649	2653#	741##
<b>CHD</b>							
Prevalence, CHD, 2015–2018†							
	20.1 M (7.2%)	11.0 M (8.3%)	8.7%	6.7%	6.8%	5.0%	...

(Continued)

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CLINICAL STATEMENTS AND GUIDELINES



**Table 29-1. 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*
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, 2019, CHD§	360 900	213 364 (59.1%)¶	167 340	22 643	15 166	6095	2007
Mortality, 2019, MI§	104 280	61 695 (59.2%)¶	48 465	6 487	4 475	1734#	599
<b>HF</b>							
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, 2019§	86 177	40 101 (46.6%)¶	32 335	4721	2066	755#	342

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); and NH, non-Hispanic.

\*Both sexes.

†Age ≥20 years.

‡Total data for total cholesterol are for Americans ≥20 years of age. Data for LDL-C, HDL-C, and all racial and ethnic groups are age adjusted for age ≥20 years.

§All ages.

||Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

¶|These percentages represent the portion of total incidence or mortality that is for males vs females.

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

\*\*Age ≥18 years.

††Estimates include Hispanic and non-Hispanic males. Estimates for White males include other non-Black races.

##Estimate considered unreliable or does not meet standards of reliability or precision.

§§Age ≥35 years.

||Age ≥55 years.

**Table 29-2. 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*
<b>Overweight and obesity</b>							
Prevalence, 2015–2018							
Overweight and obesity, BMI ≥25.0 kg/m <sup>2</sup> †	170.1 M (71.3%)	84.8 M (68.1%)	65.4%	78.4%	77.8%	42.9%	...
Obesity, BMI ≥30.0 kg/m <sup>2</sup> †	96.4 M (40.6%)	51.0 M (41.1%)	38.7%	55.2%	46.2%	15.9%	...
<b>Blood cholesterol</b>							
Prevalence, 2015–2018							
TC ≥200 mg/dL‡	93.9 M (38.1%)	52.3 M (40.4%)	41.8%	33.4%	37.3%	38.6%	...
TC ≥240 mg/dL‡	28.0 M (11.5%)	15.8 M (12.1%)	13.1%	10.5%	9.2%	10.3%	...
LDL-C ≥130 mg/dL‡	68.1 M (27.8%)	35.9 M (28.1%)	28.6%	24.3%	26.3%	26.9%	...
HDL-C <40 mg/dL‡	41.9 M (17.2%)	10.3 M (8.5%)	7.4%	7.9%	12.3%	6.7%	...
<b>HBP</b>							
Prevalence, 2015–2018†	121.5 M (47.3%)	58.4 M (42.8%)	40.5%	57.6%	40.8%	42.1%	...
Mortality, 2019§	102 072	52 621 (51.6%)¶	37 835	8999	3659	1688#	679
<b>Diabetes</b>							
Prevalence, 2015–2018							
Diagnosed diabetes†	28.2 M (10.4%)	12.7 M (9.0%)	7.5%	13.2%	13.1%	10.1%	...
Undiagnosed diabetes‡	9.8 M (3.8%)	4.3 M (3.2%)	2.9%	3.3%	4.6%	3.1%	...

(Continued)

**Table 29-2. 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†	113.6 M (45.8%)	50.5 M (38.9%)	37.3%	30.3%	41.2%	42.3%	...
Incidence, diagnosed diabetes, 2018**	1.5 M	...	...	...	...	...	...
Mortality, 2019§	87 647	38 135 (43.5%) ¶	23 833	7567	4549	1612#	1077
<b>Total CVD</b>							
Prevalence, 2015–2018†	126.9 M (49.2%)	60.8 M (44.4%)	42.1%	58.8%	42.7%	42.5%	...
Mortality, 2019§	874 613	420 812 (48.1%) ¶	324 795	54 544	26 820	11 862#	4635
<b>Stroke</b>							
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, 2019§	150 005	85 658 (57.1%) ¶	64 471	11 089	6310	3282#	741##
<b>CHD</b>							
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, 2019, CHD§	360 900	147 536 (40.9%) ¶	114 144	18 021	10 182	4119	2007
Mortality, 2019, MI§	104 280	42 585 (40.8%) ¶	32 752	5293	3068	1184#	599
<b>HF</b>							
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, 2019§	86 177	46 076 (53.5%) ¶	37 679	5146	2222	812#	342

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); and NH, non-Hispanic.

\*Both sexes.

†Age ≥20 years.

‡Total data for total cholesterol are for Americans ≥20 years of age. Data for LDL-C, HDL-C, and all racial and ethnic groups are age adjusted for age ≥20 years.

§All ages.

||Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

¶|These percentages represent the portion of total incidence or mortality that is for males vs females.

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

\*\*Age ≥18 years.

††Estimates include Hispanic and non-Hispanic females. Estimates for White females include other non-Black races.

##Estimate considered unreliable or does not meet standards of reliability or precision.

§§Age ≥35 years.

||Age ≥55 years.

**Table 29-3. 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, 2015–2018											
Mean TC, 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, 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, mg/dL											
12–19 y of age	87.6	87.6	87.5	88.0	86.4	84.9	94.4	85.9	83.1	82.3	95.4
CCDs (all age groups: children and adults)											
Mortality, 2019†‡§	2890	1553 (53.7%)§	1337 (46.3%)§	941	816	274	237	266	226	50	39

CCD indicates congenital cardiovascular defect; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; M, millions; and NH, non-Hispanic.

\*In children, overweight and obesity are based on body mass index (BMI)–for–age values at or above the 85th percentile of the 2000 Centers for Disease Control and Prevention (CDC) growth charts. Obesity is based on BMI-for-age values at or above the 95th percentile of the CDC growth charts.

†All ages.

‡Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

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

||NH American Indian/Alaska Native, mortality: 28.

## 30. GLOSSARY

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- *Age-adjusted rates*—Used mainly to compare the rates of  $\geq 2$  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 policymakers) 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 ( $\text{kg}/\text{m}^2$ ).
- *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–...) (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 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

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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 2022. 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.



“cardiovascular disease” (“Total cardiovascular disease” in this Glossary).

- *Diseases of the heart (ICD-10 codes 100–109, 111, 113, 120–151)*—Classification the NCHS uses in compiling the leading causes of death. Includes acute rheumatic fever/chronic rheumatic heart diseases (100–109); hypertensive heart disease (111); hypertensive heart and renal disease (113); CHD (120–125); pulmonary heart disease and diseases of pulmonary circulation (126–128); heart failure (150); and other forms of heart disease (130–149, 151). “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 100 to 178. 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 ( $\geq 150$  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 ( $\geq 130$  mmHg systolic blood pressure,  $\geq 85$  mmHg diastolic blood pressure, or drug treatment for hypertension), and elevated fasting glucose ( $\geq 100$  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  $\approx 2$  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–...) (ongoing)
  - Honolulu Heart Program (HHP; 1965–2002)
  - Cardiovascular Health Study (CHS; 1989–...) (ongoing)
  - Atherosclerosis Risk in Communities (ARIC) study (1987–...) (ongoing)
  - Strong Heart Study (SHS; 1989–...) (ongoing)
  - Multi-Ethnic Study of Atherosclerosis (MESA; 2000–...) (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 to 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.