

# Circulation

## AHA STATISTICAL UPDATE

# Heart Disease and Stroke Statistics—2023 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 Epidemiology and Prevention 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 with review of published literature through the year before writing. The 2023 Statistical Update is the product of a full year's worth of effort in 2022 by dedicated volunteer clinicians and scientists, committed government professionals, and American Heart Association staff members. The American Heart Association strives to further understand and help heal health problems inflicted by structural racism, a public health crisis that can significantly damage physical and mental health and perpetuate disparities in access to health care, education, income, housing, and several other factors vital to healthy lives. This year's edition includes additional COVID-19 (coronavirus disease 2019) publications, as well as data on the monitoring and benefits of cardiovascular health in the population, with an enhanced focus on health equity across several key domains.

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

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

Supplemental Materials are available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000001123>

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*Circulation* is available at [www.ahajournals.org/journal/circ](http://www.ahajournals.org/journal/circ)

**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

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## SUMMARY

Each year, the American Heart Association, 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 in the AHA's Life's Essential 8 (Figure),<sup>1</sup> which include 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 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 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, 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, confidence intervals for statistics reported below, and additional information.

## Cardiovascular Health (Chapter 2)

- From 2013 to March 2020, the overall CVH score combining health scores of all 8 components of the Life's Essential 8 was, on average, 73.6 for all



**Figure. AHA's My Life Check—Life's Essential 8.**

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US children between 16 and 19 years of age. The corresponding mean overall CVH score was 78.4 for NH Asian, 74.1 for NH White, and 71.3 for NH Black children. During the same period, the mean overall CVH score was 65.2 for all US adults, with a mean score of 69.6 for NH Asian, 66.0 for NH White, and 59.7 for NH Black adults.

- A report based on data from the UK Biobank found that having ideal CVH over poor CVH attenuated the all-cause and cardiometabolic disease–related mortality for males and females and was associated with life expectancy gains of 5.50 years for males and 4.20 years for females, at an index age of 45 years, among participants with cardiometabolic diseases and correspondingly 4.55 years in males and 4.89 years in females for people without cardiometabolic diseases.
- As of July 1, 2022, the cumulative number of COVID-19 (coronavirus disease 2019) deaths in the United States was 1 014 620, which equates to ≈306 deaths per 100 000 people. In metropolitan areas in the United States, the cumulative COVID-19 death rate was ≈292 deaths per 100 000 compared with ≈392 deaths per 100 000 in nonmetropolitan areas. In US counties with a high percentage (>17.3%) of the population in poverty, the cumulative COVID-19 death rate was ≈394 deaths per 100 000 compared with ≈248 deaths per 100 000 in counties with a low percentage (0.0%–12.3%) of the population that is living in poverty. As a result of the high COVID-19 mortality rates, life expectancy (at birth) in the United States decreased from 78.8 years in 2019 to 77.0 years in 2020 (−1.8 years) overall, and the

corresponding life expectancy decreased from 76.3 to 74.2 years (−2.1 years) in males and decreased from 81.4 to 79.9 years (−1.5 years) in females.

### 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 1.0% and 1.9%, respectively, in 2021.
- 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. In 2020, substantially higher tobacco use prevalence rates were observed in American Indian/Alaska Native and lesbian, gay, and bisexual adults compared with White and heterosexual/straight adults (27.1% American Indian/Alaska Native versus 13.3% White; 16.1% lesbian, gay, and bisexual versus 12.3% heterosexual/straight adults).
- Electronic cigarettes were the most commonly used tobacco product among adolescents in 2021; the prevalence of use in the past 30 days among middle and high school students in the United States was 2.8% and 11.3%, respectively, with the majority of adolescent users using flavored electronic cigarettes (85.8% of high school students and 79.2% of middle school students).

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

- According to parental report in 2019 to 2020, the nationwide prevalence of youth 6 to 17 years of age who were active ≥60 minutes every day of the week was 20.6%.
- According to self-report in 2018, the age-adjusted proportion of adults who reported meeting the aerobic PA guidelines for Americans (≥150 min/wk of moderate PA, ≥75 min/wk of vigorous PA, or an equivalent combination of the two) through leisure-time activities was 54.2%.
- 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.

### Nutrition (Chapter 5)

- The first study to use the AHA's Life's Essential 8 to quantify the CVH levels of adults and children in the United States included data from 23 409 individuals 2 through 79 years of age (13 521 adults and 9 888 children) participating in NHANES (National Health and Nutrition Examination Survey). The adults in the study population represent 201 728 000 adults, and the children in the

study represent 74 435 000 children. The composite CVH score ranges from 0 (lowest) to 100 (highest). Of the 8 metrics, diet was among the 4 with the lowest scores. The range of scores for diet across demographic groups was 23.8 to 47.7. Among children 2 to 5 years of age, a mean diet score of 61.1 was observed. The score for children 12 to 19 years of age was 28.5.

- A meta-analysis of 38 prospective cohort studies showed that the relative risk (RR) for the highest versus the lowest categories of Mediterranean diet adherence was 0.79 for total CVD mortality, 0.73 for CHD incidence, 0.83 for CHD mortality, 0.80 for stroke incidence, 0.87 for stroke mortality, and 0.73 for myocardial infarction incidence.
- Compared with a usual Western diet, a Dietary Approaches to Stop Hypertension-type dietary pattern with low sodium reduced systolic blood pressure (SBP) by 5.3, 7.5, 9.7, and 20.8 mm Hg in adults with baseline SBP <130, 130 to 139, 140 to 149, and ≥150 mm Hg, respectively.

## Overweight and Obesity (Chapter 6)

- According to data from NHANES from 2017 until March 2020, among US children and adolescents 2 to 19 years of age, the prevalence of being either overweight or obese was 36.8%, with obesity prevalence of 19.8%. The highest prevalence of obesity was seen among Hispanic male and NH Black female youth.
- According to data from NHANES from 2017 until March 2020, the age-adjusted prevalence of overweight or obesity among adults ≥20 years of age in the United States was 71.2%, and the prevalence of obesity was 41.4%. The highest prevalence of obesity was among NH Black females.
- A large umbrella review in 2021 found that every 5-kg/m<sup>2</sup> increase in body mass index was associated with a 15% increased risk for CHD, 23% increased risk for atrial fibrillation (AF), 41% increased risk for HF, and 49% increased risk for hypertension.

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

- Among adolescents in 2017 to 2020, low-density lipoprotein cholesterol (LDL-C) levels ≥130 mg/dL occurred in 5.0% of male adolescents and 4.6% of female adolescents, LDL-C levels <40 mg/dL occurred in 19.3% of male adolescents and 8.6% of female adolescents, and triglycerides ≥130 mg/dL occurred in 7.2% of male adolescents and 6.2% of female adolescents.
- In 2017 to 2020, among adults, total cholesterol ≥200 mg/dL occurred in 32.8% of males and

36.2% of females, LDL-C ≥130 mg/dL occurred in 25.6% of males and 25.4% of females, and high-density lipoprotein cholesterol <40 mg/dL occurred in 24.9% of males and 9.3% of females.

## High Blood Pressure (Chapter 8)

- 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 46.7% in NHANES in 2017 to 2020 (50.4% for males and 43.0% for females). This equates to an estimated 122.4 million adults ≥20 years of age who have high blood pressure (62.8 million males and 59.6 million females). A higher percentage of males than females had hypertension up to 64 years of age, but for those ≥65 years of age, the percentage of females with hypertension was higher than for males.
- In an individual patient meta-analysis of 33 trials including 260 447 participants with 15 012 cancer events, no associations were identified between any antihypertensive drug class and risk of any cancer (hazard ratio [HR], 0.99 for angiotensin-converting enzyme inhibitors; HR, 0.96 for angiotensin receptor blockers; HR, 0.98 for β-blockers; HR, 1.01 for thiazides), except for calcium channel blockers (HR, 1.06). In a network meta-analysis comparing each drug class with placebo, no drug class was associated with an excess cancer risk (HR, 1.00 for angiotensin-converting enzyme inhibitors; HR, 0.99 for angiotensin receptor blockers; HR, 0.99 for β-blockers; HR, 1.04 for calcium channel blockers; HR, 1.00 for thiazides).
- In an open-label, cluster-randomized trial involving 20 995 individuals from 600 villages in rural China, the use of a salt substitute (75% sodium chloride and 25% potassium chloride by mass) compared with the use of regular salt (100% sodium chloride) resulted in a lower incidence of stroke (RR, 0.86), all-cause mortality (RR, 0.88), and major adverse cardiovascular event (RR, 0.87). There was no increase in rates of hyperkalemia with use of the salt substitute (RR, 1.04).

## Diabetes (Chapter 9)

- Overall, on the basis of 2017 to 2020 data, 29.3 million adults (10.6%) in the United States had diagnosed diabetes.
- Data from the CALIBER UK cohort show the most common initial CVD complications for those with diabetes to be peripheral artery disease (16.2%) and HF (14.1%), followed by stable angina (11.9%), nonfatal myocardial infarction (11.5%), and stroke (10.3%).

- Data from the US Diabetes Collaborative Registry of 74 393 adults with diabetes demonstrate a prevalence of 74% with hemoglobin A1c <7%, 40% with blood pressure <130/80 mmHg, and 49% with LDL-C <100 mg/dL (<70 mg/dL if with atherosclerotic cardiovascular disease), but only 15% at target for all 3 factors.

## Metabolic Syndrome (Chapter 10)

- From 1999 to 2018, the prevalence of metabolic syndrome among US youths remained stable at 4.36%. Among adults, the prevalence of metabolic syndrome increased from 36.2% to 47.3%.
- According to the data from NHANES 1999 to 2018, the prevalence of metabolic syndrome among youths 12 to 19 years of age was 4.34% for NH White, 3.66% for NH Black, 7.70% for Mexican American, 4.84% for other Hispanic, and 1.84 for other race youths.
- In 2017 to 2018, Mexican American adults generally had the highest prevalence of metabolic syndrome at 52.2%, whereas NH White adults had 46.6%, NH Black adults had 47.6%, other Hispanic adults had 45.9%, and Asian/other adults had 46.7%.

## Adverse Pregnancy Outcomes (Chapter 11)

- Rates of overall hypertensive disorders of pregnancy are increasing. Analysis of delivery hospitalizations from the National Readmission Database reported a rate of hypertensive disorders of pregnancy of 912.4 per 10 000 delivery hospitalizations in 2014 compared with 528.9 in 1993 in the United States.
- Specific aspirin dosage and preeclampsia prevention were studied in 23 randomized trials (32 370 females). Females assigned at random to 150 mg experienced a 62% reduction in risk of preterm preeclampsia (RR, 0.38). Aspirin doses <150 mg produced no significant reductions. The number needed to treat with 150 mg of aspirin was 39. There was a maximum 30% reduction in risk of all gestational age preeclampsia at all aspirin doses.
- 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 (adjusted odds ratio [OR], 2.11, adjusted for age, income, parity, race and ethnicity, and study site); 22.6% of this association was statistically mediated by obesity.

## Kidney Disease (Chapter 12)

- The overall prevalence of chronic kidney disease (estimated glomerular filtration rate  $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$  or albumin-to-creatinine ratio  $\geq 30 \text{ mg/g}$ ) in 2015 to 2018 was 14.9%.
- In 2019, the age-, race-, and sex-adjusted prevalence of end-stage renal disease in the United States was 2302 per 1 million people, an increase of 1.4% over 2018.
- Total hospitalization expenditures in Medicare fee-for-service beneficiaries with end-stage renal disease was \$12.2 billion in 2019, and outpatient spending was \$13.1 billion in 2019.

## Sleep (Chapter 13)

- The proportion of adults reporting insufficient sleep ( $<7$  hours) in 2020 was 32.8%.
  - Older adults,  $>65$  years of age, report the lowest prevalence of insufficient sleep.
  - NH Black adults had the highest percentage of respondents reporting sleeping  $<7$  h/night (43.5%), whereas NH Asian adults (30.5%) and NH White adults (30.7%) had the lowest percentage of respondents reporting sleeping  $<7$  hours.
- Females report never or some of the days feeling well rested on awakening in the past days more frequently than males (46.9% versus 40.4%).
- Data from the MIDUS study (Midlife in the United States) examined the association of a composite sleep health measure (sleep regularity, satisfaction, alertness, timing, efficiency, and duration) with risk of HD (yes/no to a question on diagnosis of HD). Each unit increase in the self-reported sleep health composite was associated with a 54% higher risk of HD, whereas the objectively measured actigraphy sleep health composite was associated with 141% higher risk.



## Total Cardiovascular Disease (Chapter 14)

- On the basis of NHANES 2017 to March 2020 data, the prevalence of CVD (comprising CHD, HF, stroke, and hypertension) in adults  $\geq 20$  years of age was 48.6% overall (127.9 million in 2020) and increases with age in both males and females.
- On the basis of 2020 mortality data, HD and stroke currently claim more lives each year than cancer and chronic lower respiratory disease combined. In 2020, 207.1 of 100 000 people died of HD and stroke.
- In 2020, 19.05 million deaths were estimated for CVD globally, which amounted to an increase of

18.71% from 2010. The age-standardized death rate per 100 000 population was 239.80, which represents a decrease of 12.19% from 2010. Overall, the crude prevalence of CVD was 607.64 million cases in 2020, an increase of 29.01% compared with 2010. However, the age-standardized prevalence rate was 7354.05 per 100 000, an increase of 0.73% from 2010.

## Stroke (Cerebrovascular Diseases) (Chapter 15)

- An analysis of data from the GBD 2019 study found that from 1990 to 2019, the absolute number of incident strokes increased by 70.0, whereas the age-standardized incidence rate for total stroke decreased by 17.0%. The age-standardized incidence rate for ischemic stroke decreased by 10% and intracerebral hemorrhage decreased by 29% during the same period.
- A meta-analysis of 11 clinical trials from 1970 to 2021 with 20 163 patients with stroke found that intensive LDL-C-lowering statin-based therapies reduced the risk of recurrent ischemic stroke (RR, 0.88) compared with less intensive LDL-C-lowering statin-based therapies. This relationship was even stronger in populations with atherosclerosis (RR, 0.79).
- In a meta-analysis of 66 trials of SBP-lowering interventions including 324 812 participants and 11 437 strokes over an average follow-up of 3.3 years, SBP lowering was associated with 21% lower odds of stroke compared with control. In meta-analyses of stroke types, SBP lowering was associated with 14% lower odds of ischemic stroke (6 trials), 28% lower odds of hemorrhagic stroke (6 trials), and 28% lower odds of fatal or disabling stroke (18 trials).

## Brain Health (Chapter 16)

- The GBD study estimated secular trends from 1990 to 2017 in dementia prevalence, incidence, disability-adjusted life-years (DALYs), and mortality globally and for high-income countries. Globally, prevalent cases increased by 119%, annual incident cases increased by 113%, DALYs increased by 115%, and annual deaths increased by 146%. However, global age-standardized prevalence decreased by 4%, age-standardized annual incidence decreased by 5%, age-standardized DALYs decreased by 6%, and age-standardized annual mortality decreased by 4%. For high-income countries, percent increases in absolute burden measures were smaller than globally: Prevalent cases increased by 93%, annual incident cases

increased by 87%, DALYs increased by 90%, and annual deaths increased by 126%. The age-standardized prevalence in high-income countries decreased by 5%, age-standardized annual incidence rate decreased by 6%, age-standardized DALYs decreased by 7%, and age-standardized annual mortality rate decreased by 4%.

- Among 229 976 participants in the UK Biobank, with 2143 cases of incident dementia over a median follow-up of 9 years, each 1-point increment in Life's Simple 7 score was associated with an 11% lower hazard of dementia (HR, 0.89). Each 1-point increment in the biological component score (based on blood pressure, cholesterol, and glucose) was associated with a 7% lower hazard of dementia (HR, 0.93). However, a 1-point increment in the lifestyle component score (based on smoking, body mass index, diet, and physical activity) was not associated with dementia (HR, 0.99).
- In the HRS (Health and Retirement Study), cognitive impairment-free life expectancy at 55 years of age was estimated as 23.0 years for participants with no hypertension, HD, diabetes, or stroke; 21.2 years for those with any 1 of those conditions; 18.1 years for those with any 2 conditions; and 14.0 years for those with any 3 or all 4 conditions. The association of CVD burden with lower cognitive impairment-free life expectancy was also observed at 65, 75, and 85 years of age, with lower absolute life expectancies.

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

- 2020 mortality related to congenital cardiovascular defects was 2817 deaths in the United States, an 11.9% decrease from the number of deaths in 2010.
- Socioeconomic status (SES) is a major contributor to identified differences in infant mortality among infants with critical congenital cardiovascular defects, with greater mortality among socioeconomically deprived patients (OR, 1.7).

Since May 2020, the Centers for Disease Control and Prevention has been tracking reports of multisystem inflammatory syndrome in children. As of March 1, 2022, 7459 cases and 63 attributable deaths (0.84%) have been reported. Median age of cases was 9 years; 58% of cases have occurred in children who are Hispanic or Latino (1846 cases) or Black (2206 cases); 98% tested positive for SARS-2 (severe acute respiratory syndrome coronavirus 2; reverse transcriptase–polymerase chain reaction, serology, or antigen test); and 60% of reported patients were male.

## Disorders of Heart Rhythm (Chapter 18)

- An analysis of the Korea National Health Insurance Service (N=66 692) classified individuals by exercise status before and after AF diagnosis. Those who maintained exercise were significantly less likely to have ischemic stroke (HR, 0.86), HF (HR, 0.92), or mortality (HR, 0.61) than those who continued to abstain from exercise after AF diagnosis.
- The study of social determinants and AF remains limited. In a limited-sized cohort (N=339) followed up for a median of 2.6 years (range, 0–3.4 years), individuals in the lowest income category ( $\leq \$19\,999/y$ ) had a 2.0-fold greater hospitalization risk (OR, 2.11) compared with those in the highest income category ( $\geq \$100\,000/y$ ).
- A multicenter trial randomized individuals with at least 1 stroke risk factor and without AF in a 1:3 ratio to receive long-term rhythm monitoring with an implanted loop recorder (n=1501) or usual care (n=4503). Over a median follow-up of 64.5 months, those randomized to monitoring were 3-fold more likely to be diagnosed with AF (HR, 3.17).

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

- Recent data describing cardiac arrest or sudden cardiac death after an acute myocardial infarction suggest that contemporary short-term (3-month) risk is 0.29% or 116 per 100 000 person-years.
- Laypeople in the United States initiated cardiopulmonary resuscitation in 40.2% of out-of-hospital cardiac arrests in 2021.
- In the United States, individuals from underrepresented racial and ethnic groups are at substantially higher risk of sudden cardiac arrest and experience worse survival and neurological outcomes after sudden cardiac arrest compared with White individuals. In the ARIC study (Atherosclerosis Risk in Communities), the sex-adjusted HR for sudden cardiac death comparing Black with White participants was 2.12, and the fully adjusted HR was 1.38. In San Francisco, Black females had a 2.55 higher incidence of sudden arrhythmic death than White females.

## Subclinical Atherosclerosis (Chapter 20)

- In a study-level meta-analysis involving 10 867 participants (6699 HIV positive, 4168 HIV negative; mean age, 52 years; 86% male; 32% Black), the prevalence of noncalcified plaque was 49% in HIV-positive individuals versus 20% in HIV-negative individuals (OR, 1.23).

- In individuals without diabetes or CVD, higher hemoglobin A1c was associated with the extent of subclinical atherosclerosis assessed by intima-media thickness; atherosclerotic plaque of the carotids, abdominal aorta, and iliofemoral arteries; and coronary artery calcification (OR, 1.05, 1.27, 1.27, 1.36, 1.80, 1.87, and 2.47 for hemoglobin A1c 4.9%–5.0%, 5.1%–5.2%, 5.3%–5.4%, 5.5%–5.6%, 5.7%–5.8%, 5.9%–6.0%, and 6.1%–6.4%, respectively; reference hemoglobin A1c  $\leq 4.8\%$ ).
- In the Rotterdam Study of older adults, the presence of intraplaque hemorrhage (but not calcification or lipid-rich core) by high-resolution magnetic resonance imaging demonstrated an association with incident stroke and CHD (HR, 2.42 and 1.95, respectively).

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

- According to data from the 2005 to 2014 ARIC study, the estimated annual incidence of myocardial infarction 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.
- An NIS (National Inpatient Sample) analysis of sex differences spanning 2004–2015 identified 7 026 432 hospitalizations for acute myocardial infarction. Compared with males, females were less likely to undergo coronary angiography (adjusted OR, 0.92) and percutaneous coronary intervention (adjusted OR, 0.82). Females had a higher risk of mortality (adjusted OR, 1.03) compared with males.
- In 2020, CHD age-adjusted death rates per 100 000 were 128.5 for NH White males, 153.6 for NH Black males, and 102.2 for Hispanic males. For NH White females, the rate was 63.8; for NH Black females, it was 85.9; and for Hispanic females, it was 54.2.

## Cardiomyopathy and Heart Failure (Chapter 22)

- On the basis of data from NHANES 2017 to 2020,  $\approx 6.7$  million Americans  $\geq 20$  years of age had HF, which is increased from  $\approx 6.0$  million according to NHANES 2015 to 2018.
- The lifetime risk of HF at 50 years of age increased among participants of the FHS (Framingham Heart Study) when comparing two 25-year epochs (1965–1989 versus 1990–2014) from 18.9% to 22.6% in females and 19.1% to 25.3% in males.
- 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;

however, estimated 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).

### 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 was 12.4%, and the prevalence of severe aortic stenosis was 3.4%.
- In 1000 patients with severe aortic stenosis at low surgical risk randomized in the PARTNER 3 trial (Placement of Aortic Transcatheter Valve 3) to either balloon-expandable transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement, the primary composite end point (death, stroke, or rehospitalization) rate was significantly lower in the TAVR versus surgical aortic valve replacement group (8.5% versus 15.1%; absolute difference, -6.6 percentage points for noninferiority; HR, 0.54). At 2 years, the primary end point was significantly reduced after TAVR compared with surgical aortic valve replacement (11.5% versus 17.4%; HR, 0.63), although TAVR valve thrombosis at 2 years was increased (2.6%; 13 events) compared with surgery (0.7%; 3 events).
- Among 96 256 transfemoral TAVR procedures, adjusted 30-day mortality was higher at institutions with low procedural volume (3.19%) than at institutions with high procedural volume (2.66%; OR, 1.21).

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

- In 2019, there were an estimated ≈393 000 cases of pulmonary embolism, ≈643 000 cases of deep vein thrombosis, and ≈1 036 000 total venous thromboembolism cases in the United States.
- In patients with COVID-19, there is a double risk of death after venous thromboembolism. In those admitted to the intensive care unit, this risk is 2.63 times higher, with a 3-fold increase in patients on mechanical ventilation.
- In 2018, there were 578 000 outpatient visits for pulmonary hypertension as the principal diagnosis. In addition, there were 14 000 hospital discharges with pulmonary hypertension as the principal diagnosis.

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

- Data from MarketScan and Medicare databases showed that only 33.9% of patients with peripheral artery disease were prescribed statins compared with 51.7% of patients with coronary artery disease, and only 24.5% of patients with peripheral artery disease in the MarketScan database achieved a target LDL-C <70 mg/dL.
- Among Medicare beneficiaries, zip codes in the top quartile of amputation rates had a larger mean proportion of Black residents than zip codes in the bottom quartile (17.5% versus 4.4%).
- In older individuals 60 to 74 years of age, male sex (OR, 1.9), hypertension (OR, 1.8), and family history (OR, 1.6) are the strongest contributors to risk of thoracic aortic aneurysm.

### Quality of Care (Chapter 26)

- Despite substantial disruptions to cardiovascular care delivery during the COVID-19 pandemic, among patients in the GWTG Registry (Get With The Guidelines) who were hospitalized for HF in 2021, 91.7% received angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or angiotensin receptor-neprilysin inhibitors at discharge; 93.4% received evidence-based specific β-blockers; 99.2% had a measurement of left ventricular function; and 85.5% had a scheduled post-discharge appointment.
- In 18 262 adults with hypertension, the age-adjusted estimated proportion with controlled blood pressure (blood pressure <140/90 mmHg) improved from 31.8% in 1999 to 2000 to 48.5% in 2007 to 2008, was similar in 2013 to 2014 (53.8%), and then declined to 43.7% in 2017 to 2018.
- In 390 692 patients receiving care at 586 hospitals from July 2008 to December 2013, patients residing in lower-SES neighborhoods had longer median arrival-to-angiography time (lowest quintile of SES, 8.0 hours; highest quintile of SES, 3.4 hours) and a higher rate of fibrinolysis (versus primary angioplasty) for ST-segment-elevation myocardial infarction (lowest quintile of SES, 23.1%; highest quintile of SES, 5.9%) compared with higher-SES neighborhoods. Patients from lower-SES neighborhoods had greater independent risk of in-hospital mortality and major bleeding and a lower quality of discharge care.

### Medical Procedures (Chapter 27)

- According to Healthcare Cost and Utilization Project data from the Agency for Healthcare Research and

Quality for the year 2018, 481 780 percutaneous coronary interventions were performed on an inpatient basis in the United States.

- Data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database, which voluntarily collects data from ≈80% of all hospitals that perform coronary artery bypass grafts in the United States, indicate that a total of 161 816 procedures involved isolated coronary artery bypass graft in 2019.
- In 2021, 3817 heart transplantations were performed in the United States, the most ever. The highest numbers of heart transplantations were performed in California (529), Texas (359), New York (307), and Florida (263).

## Economic Cost of Cardiovascular Disease (Chapter 28)

- The average annual direct and indirect cost of CVD in the United States was an estimated \$407.3 billion in 2018 to 2019.
- The estimated direct costs of CVD in the United States increased from \$103.5 billion in 1996 to 1997 to \$251.4 billion in 2018 to 2019.
- By event type, hospital inpatient stays accounted for the highest direct cost (\$111.4 billion) in 2018 to 2019 in the United States.

## Conclusions

The AHA, through its Epidemiology and Prevention 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 2023 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

The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; the US Department of Health and Human Services; or the US Department of Veterans Affairs.

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

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The American Heart Association requests that this document be cited as follows: Tsao CW, Aday AW, Almarzoog ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Beaton AZ, Boehme AK, Buxton AE, Commodore-Mensah Y, Elkind MSV, Evenson KR, Eze-Nliam C, Fugar S, Generoso G, Heard DG, Hiremath S, Ho JE, Kalani R, Kazi DS, Ko D, Levine DA, Liu J, Ma J, Magnani JW, Michos ED, Mussolini ME, Navaneethan SD, Parikh NI, Poudel R, Rezk-Hanna M, Roth GA, Shah NS, St-Onge M-P, Thacker EL, Virani SS, Voeks JH, Wang N-Y, Wong ND, Wong SS, Yaffe K, Martin SS; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. *Heart disease and stroke statistics—2023 update: a report from the American Heart Association.* *Circulation.* 2023;147:e93–e621. doi: 10.1161/CIR.0000000000001123

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## Acknowledgments

The writing group thanks its colleagues Lucy Hsu and Michael Wolz at the National Heart, Lung, and Blood Institute; the team at the Institute for Health Metrics and Evaluation at the University of Washington; Bryan McNally and Rabab Al-Araji at the CARES (Cardiac Arrest Registry to Enhance Survival) program; Hongyan Ning and Donald Lloyd-Jones at Northwestern University; and Christina Koutras and Fran Thorpe at the American College of Cardiology for their valuable contributions and review.

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(Continued)

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\*Modest.

†Significant.

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the American Heart Association. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/CIR.0000000000001078

**ABBREVIATIONS TABLE**[Click here to return to the Table of Contents](#)

3C	Three City Study
4D Study	Deutsche Diabetes Dialyse Studie
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
ACE	angiotensin-converting enzyme
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
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
AMI	acute myocardial infarction
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
ARNI	angiotensin receptor-neprilysin inhibitor
aRR	adjusted relative risk
ARVC	arrhythmogenic right ventricular cardiomyopathy
ASB	artificially sweetened beverage
ASCVD	atherosclerotic cardiovascular disease
ASD	atrial septal defect
ASPECTS	Alberta Stroke Program Early CT Score
ASPIRE	Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre Registry

ASPREE	Aspirin in Reducing Events in the Elderly
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
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
CALIBER UK	Cardiovascular Research Using Linked Bespoke Studies and Electronic Health Records
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  American Heart Association.
CARDIoGRAMplusC4D	Coronary Artery Disease Genome Wide Replication and Meta-Analysis (CARDIoGRAM) Plus the Coronary Artery Disease (C4D) Genetics
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
CERAD-TS	Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery, total score
CHA2DS2-VASc	clinical prediction rule for estimating the risk of stroke based on congestive heart failure, hypertension, diabetes, and sex (1 point each); age ≥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
CHADS2	clinical prediction rule for estimating the risk of stroke based on congestive heart failure, hypertension, age ≥75 years, diabetes (1 point each), and prior stroke/transient ischemic attack/thromboembolism (2 points)
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
CHARM	Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity
CHD	coronary heart disease

CHS	Cardiovascular Health Study
CI	confidence interval
CICAT	Codi Ictus Catalunya Registry
CKD	chronic kidney disease
CKiD	Chronic Kidney Disease in Children
COAPT	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation
COAST	Comparative Outcomes Services Utilization Trends
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
CPVT	catecholaminergic polymorphic ventricular tachycardia
CREOLE	Comparison of Three Combination Therapies in Lowering Blood Pressure in Black Africans
CRIC	Chronic Renal Insufficiency Cohort
CROMIS-2	Clinical Relevance of Microbleeds in Stroke
CRP	C-reactive protein
CRS	Cardiovascular Risk Survey
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
DANISH	Danish Study to Assess the Efficacy of ICDs in Patients With Non-Ischaemic Systolic Heart Failure on Mortality
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
DOAC	direct oral anticoagulant
DPP	Diabetes Prevention Program
DREAM-LDL	Diabetes (fasting blood glucose level), Rating (National Institutes of Health Stroke Scale), level of education, age, baseline Montreal Cognitive Assessment Scale score, and LDL-C level
DR's EXTRA	Dose Responses to Exercise Training
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
ELSA	English Longitudinal Study of Ageing
EMPHASIS-HF	Eplre 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
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
EXAMINE	Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care
FDA	US Food and Drug Administration
FH	familial hypercholesterolemia
FHS	Framingham Heart Study
FIDELIO DKD	Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease
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
GBD Study	Global Burden of Diseases, Injuries, and Risk Factors Study
GCKNS	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
GLP1-RA	glucagon-like peptide 1 receptor agonist
GRS	genetic risk score
GWAS	genome-wide association study
GWTG	Get With The Guidelines

HANDLS	Healthy 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
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
HFrEF	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
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-PLUS	International Collaboration on Endocarditis—PLUS
ICH	intracerebral hemorrhage
ICU	intensive care unit
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
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
ISCHEMIA	International Study of Comparative Health Effectiveness With Medical and Invasive Approaches
IVIG	intravenous immunoglobulin
Iwate-KENCO	Iwate-Kenpoku Cohort
JHS	Jackson Heart Study
KD	Kawasaki disease
LAAO	Left Atrial Appendage Occlusion
LASI	Longitudinal Aging Study in India
LBW	low birth weight
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LEAD	Louisiana Experiment Assessing Diabetes
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
LIBRA	Lifestyle for Brain Health
LOAD	late-onset Alzheimer disease
Look AHEAD	Look: Action for Health in Diabetes
LQTS	long QT syndrome
LTPA	leisure-time physical activity
LV	left ventricular
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MACE	major adverse cardiovascular event
MAP	Memory and Aging Project
MAPT	Multidomain Alzheimer Preventive Trial
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
MHAS	Mexican Health and Aging study
MHO	metabolically healthy obesity
MI	myocardial infarction
MIDA	Mitral Regurgitation International Database
MIDAS	Myocardial Infarction Data Acquisition System
MIDUS	Midlife in the United States
MIMS	Monitor Independent Movement Summary
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
MMSE	Mini-Mental State Examination
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
NNT5	number needed to treat for 5 years
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
NYTS	National Youth Tobacco Survey
ODYSSEY Outcomes	Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab
OHCA	out-of-hospital cardiac arrest
ONTARGET	Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial and to Telmisartan Randomized Assessment
OPACH	Objectively Measured Physical Activity and Cardiovascular Health
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
PAGE	Placental Abruptio Genetic Epidemiology
PAH	pulmonary arterial hypertension
PALM	Patient and Provider Assessment of Lipid Management Registry
PAPE	Peruvian Abruptio Placentae Epidemiology
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
PATH-BP	Regular Acetaminophen Use and Blood Pressure in People With Hypertension
PCE	Pooled Cohort Equations
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PE	pulmonary embolism
PESA	Progression of Early Subclinical Atherosclerosis
PHC	Pulmonary Hypertension Connection
PHIRST	Pulmonary Arterial Hypertension and Response to Tadalafil Study
PINNACLE	Practice Innovation and Clinical Excellence
PM2.5	fine particulate matter <2.5-μm 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
PreDIVA	Prevention of Dementia by Intensive Vascular Care
PREMA	Prediction of Metabolic Syndrome in Adolescence
PREMIER	Lifestyle Interventions for Blood Pressure Control
PREVEND	Prevention of Renal and Vascular End-Stage Disease
PRODIGY	Progress in Diabetes Genetics in Youth
PROFESS	Prevention Regimen for Effectively Avoiding Second Stroke
PRS	polygenic risk score
PTB	preterm birth
PTS	postthrombotic syndrome
PUFA	polyunsaturated fatty acid
PURE	Prospective Urban Rural Epidemiology study
PWV	pulse-wave velocity
QALY	quality-adjusted life-year
QTc	corrected QT interval
RCT	randomized controlled trial
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
REPLACE	Riociguat Replacing PDE5i Therapy Evaluated Against Continued PDE5i Therapy
REVEAL	Registry to Evaluate Early and Long-term PAH Disease Management
RIETE	Registro Informatizado de Enfermedad Tromboembólica
ROC	Resuscitation Outcomes Consortium
ROS	Religious Orders Study

RR	relative risk
RSMR	risk-standardized mortality rate
RV	right ventricular
RYR2	ryanodine receptor 2
SAGES	Sujets AGÉS—Aged Subjects
SADHS	South African Demographic Health and Surveillance Study
SAFEHEART	Spanish Familial Hypercholesterolemia Cohort Study
SAGE	Study on Global Ageing and Adult Health
SAH	subarachnoid hemorrhage
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
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
SGLT-2	sodium-glucose cotransporter 2
SHIP	Study of Health in Pomerania
SHIP AHOY	Study of Hypertension in Pediatrics, Adult Hypertension Onset in Youth
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
SPRINT	Systolic Blood Pressure Intervention Trial
SSB	sugar-sweetened beverage
START	South Asian Birth Cohort
STEMI	ST-segment–elevation myocardial infarction
STEP 1	Research Study Investigating How Well Semaglutide Works in People Suffering From Overweight or Obesity
STEP 3	Research Study To Look at How Well Semaglutide Is at Lowering Weight When Taken Together With an Intensive Lifestyle Program
STROKE-AF	Rate of Atrial Fibrillation Through 12 Months in Patients With Recent Ischemic Stroke of Presumed Known Origin
STS	Society of Thoracic Surgeons
SUN	Seguimiento Universidad de Navarra
SURMOUNT-1	Efficacy and Safety of Tirzepatide Once Weekly Versus Placebo in Participants Who Are Either Obese or Overweight With Weight-Related Comorbidities

SURTAVI	Surgical Replacement and Transcatheter Aortic Valve Implantation
SVT	supraventricular tachycardia
SWAN	Study of Women's Health Across the Nation
SwissTAVI	Swiss Transcatheter Aortic Valve Implantation
SYNTAX	Synergy Between PCI With Taxus and Cardiac Surgery
TAA	thoracic aortic aneurysm
TAVI	transcatheter aortic valve implantation
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
TIA	transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction
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 
UI	uncertainty interval
USRDS	US Renal Data System
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
WIC	Special Supplemental Nutrition Program for Women, Infants, and Children
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

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,

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As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

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 2023 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 2017 to 2020. These are applied to census population estimates for 2020. 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 2023 Statistical Update, there is an emphasis on health equity across the various chapters, and global estimates are provided when available.

### Risk Factor Prevalence



The NHANES 2017 to 2020 data are used in this Statistical Update to present estimates of the percentage of people with high LDL-C and diabetes. NHANES 2017 to 2020 are used to present estimates of the percentage of people with overweight, obesity, and high TC and HDL-C. BRFSS 2020 and NHIS 2020 data are used for the prevalence of sleep issues. The NHIS 2020 data, BRFSS 2020, and NYTS 2021 are used for the prevalence of cigarette smoking. The prevalence of physical inactivity is obtained from YRBS 2019 and NHIS 2018.

### 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 2020 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 2023 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>1,2</sup>

## Population Estimates

In this publication, we have used national population estimates from the US Census Bureau<sup>3</sup> for 2020 in the computation of morbidity data. CDC/NCHS population estimates for 2020 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 HCUP 2019 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 NAMCS 2018 of the CDC/NCHS. ED visit estimates are from the HCUP 2019 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 9th 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.

## 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>6</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 2023 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 2020. For disease and risk factor prevalence, most rates in this report are calculated from NHANES 2017 to 2020. Because NHANES is conducted only in the noninstitutionalized population, we extrapolated the rates to the total US resident population on July 1, 2020, 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 2019. The numbers of visits to primary health care professionals' offices are for 2018. Except as noted, economic cost estimates are for 2018 to 2019.

## 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 (Total Cardiovascular Diseases) 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 Study 2020, the most recent iteration of the study, was produced by the collective efforts of >7500 researchers in >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 Study 2020, estimates were produced for 1990 to 2020 for 204 countries and territories, strati-

fied by age and sex, with subnational estimates made available for an increasing number of countries. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in results across GBD Study cycles for both the most recent and earlier years.

For more information about the GBD Study and to access GBD resources, data visualizations, and most recent publications, please visit the study website.<sup>7</sup>

The Statistical Update Supplementary Material includes additional global and regional CVD statistics.

## 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**

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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.

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 based on the metrics of Life’s Simple 7. Because of the SARS-CoV-2 pandemic, NHANES data collection was suspended in March 2020. As a result, data collected from 2019 to March 2020 were combined with the full data collection from 2017 to 2018 to form the most up-to-date nationally representative sample for evaluating CVH.

To update the construct of CVH metrics on the basis of extensive evidence and insights accumulated over the decade after introduction of Life’s Simple 7, the AHA released a presidential advisory in 2022 to introduce an enhanced approach of assessing CVH: the Life’s Essential 8.<sup>3</sup> The components of Life’s Essential 8 include updates for the original 7 CVH components to provide metrics in a more refined and continuous scale for better contrasting interindividual differences in CVH at a given point in time and tracking intraindividual changes in CVH over time. Furthermore, sleep health was added into the

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As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

CVH metrics to better reflect its important role in human biology and sustainment of life, as well as its impact on cardiometabolic health. Table 2-1 summarizes the definitions and scoring algorithms for each of the CVH components under this new approach in both adults and youth.

With this new approach to assess CVH, this chapter now provides statistical updates under both CVH metrics as the health research and clinical practice fields migrate toward the use of Life’s Essential 8. Changes in the leading causes and risk factors for YLDs and YLLs between 1990 and 2019, first added to the 2021 Statistical Update, highlight the influence of the components of CVH on premature death and disability in populations.

### Relevance of Ideal CVH

- Multiple independent investigations (summaries of which are provided in this chapter) have confirmed the importance of having ideal levels of these components, along with the overall concept of CVH. Findings include strong inverse, stepwise associations in the United States of the number of CVH components at ideal levels with all-cause mortality, CVD mortality, IHD mortality, CVD, and HF; with subclinical measures of atherosclerosis such as carotid IMT, arterial stiffness, and CAC prevalence and progression; with physical functional impairment and frailty; with cognitive decline and depression; and with longevity.<sup>4–9</sup> Similar relationships have also been seen in non-US populations.<sup>4,10–24</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>5</sup>
- A study of Black people in the United States found that the risk of incident HF was 61% lower among those with ≥4 ideal CVH components than among those with 0 to 2 ideal components.<sup>6</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>25</sup>
- In a cohort of 91 204 participants from mainland China with 1985 incident major CVD events observed over a mean follow-up of 3.7 years, having greater numbers of ideal CVH components (categories ranged from ≤1, 2, 3, to ≥4) was associated with a significant reduction in CVD risk in a stepwise fashion in participants with stage 1 hypertension and similarly in participants with stage 2

- hypertension. Moreover, participants with stage 1 hypertension having ≥4 ideal CVH components did not have significantly greater CVD risk compared with all participants without hypertension (HR, 1.04 [95% CI, 0.83–1.31]).<sup>23</sup>
- A meta-analysis of 9 prospective cohort studies involving 12878 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>26</sup>
  - Results using NHANES III mortality data through 2011 estimated the PAFs of CVD mortality for components of CVH under revised definitions as follows<sup>27</sup>:
    - 47.5% (95% CI, 38.2%–57.3%) for HBP (using thresholds from the 2017 AHA/ACC guideline);
    - 10.7% (95% CI, 4.0%–17.0%) for smoking;
    - 10.1% (95% CI, 2.6%–18.6%) for TC;
    - 5.91% (95% CI, 0.03%–14.1%) for insufficient PA; and
    - 11.6% (95% CI, 6.1%–16.8%) for abnormal glucose levels.
    - A previous analysis using NHANES III mortality data through 2006 reported an estimated PAF of 13.2% (95% CI, 3.5%–29.2%) for poor diet.<sup>28</sup>
  - Many studies have been published in which investigators have assigned individuals a CVH score ranging from 0 to 14 on the basis of the sum of points assigned to each component of CVH (poor=0, intermediate=1, ideal=2 points). With this approach, data from the REGARDS cohort were used to demonstrate an inverse stepwise association between a higher CVH score component and 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>29</sup> A similar association between CVH score and incidence of stroke was also observed in a large Chinese cohort.<sup>30</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>31</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>32</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>33</sup> Another report from the ARIC study estimated CVD risk and all-cause mortality associated with patterns of overall CVH level (classified as poor, intermediate, and ideal to correspond to 0–2, 3–4, and 5–7 CVH metrics at ideal levels) over time. The authors observed that participants attaining ideal CVH at the first follow-up visit had the lowest levels of CVD risks and mortality regardless of subsequent change in CVH level, and improvement from poor CVH over time was consistently associated with lower CVD risk and mortality subsequently.<sup>34</sup> Reduced CVD risk associated with improvement of CVH over time was also observed in the elderly and very elderly populations without CVD.<sup>35</sup>
- Ideal CVH in parents was associated with greater CVD-free survival in offspring, and maternal CVH was found to be a more robust predictor of an offspring's CVD-free survival than paternal CVH.<sup>36</sup> Furthermore, better maternal CVH at 28 weeks' gestation during pregnancy was significantly associated with better offspring CVH in early adolescence.<sup>37</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 ≥1 of these CVH factors. For example, at an index age of 45 years, males with optimal risk factor profiles lived on average 14 years longer free of all CVD events and 12 years longer overall than people with ≥2 risk factors.<sup>38</sup> A large community-based prospective study in China showed that greater CVH was associated with lower lifetime risk of CVD and that improvement in CVH could lower the lifetime risk of CVD and prolong the years of life free from CVD.<sup>39</sup> Another report based on a large data set from the UK Biobank found that having ideal CVH over poor CVH attenuated the all-cause and cardiometabolic

disease-related mortality for males and females and was associated with life expectancy gains of 5.50 (95% CI, 3.94–7.05) years for males and 4.20 (95% CI, 2.77–5.62) years for females, at an index age of 45 years, among participants with cardiometabolic diseases, and correspondingly 4.55 (95% CI, 3.62–5.48) years in males and 4.89 (95% CI, 3.99–5.79) years in females for people without cardiometabolic diseases.<sup>40</sup>

- Better CVH as defined by the AHA is associated with a lower incidence of HF,<sup>46–8,22</sup> less subclinical vascular disease,<sup>9,15,17,41,42</sup> better global cognitive performance and cognitive function,<sup>16,43</sup> lower hazard of subsequent dementia,<sup>44–46</sup> fewer depressive symptoms,<sup>47–49</sup> longer leukocyte telomere length,<sup>50</sup> less ESRD,<sup>51</sup> less pneumonia,<sup>52</sup> less chronic obstructive pulmonary disease,<sup>53</sup> lower prevalence of aortic sclerosis and stenosis,<sup>54</sup> lower risk of calcific aortic valve stenosis,<sup>55</sup> better prognosis after MI,<sup>56</sup> lower risk of AF,<sup>57,58</sup> and lower odds of having elevated resting heart rate.<sup>59</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>60</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>61</sup> Better CVH in midlife was associated with a lower prevalence of frailty in a large community-based cohort study.<sup>62</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>63</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>64</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>65</sup> Furthermore, higher quality of life scores were associated with better CVH metrics,<sup>66</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>67</sup> A recent report from the ARIC study found that people of Black race (versus White race: OR, 0.68 [95% CI, 0.57–0.80]), with low income (OR, 0.71 [95% CI, 0.57–0.87]), or with low education (OR, 0.65 [95% CI, 0.53–0.79]) were at higher odds of having worsening CVH over time,<sup>68</sup> whereas analysis of NHANES data from 2013 to 2016 found that the association between educational attainment and likelihood of ideal CVH differed by race and ethnicity, underscoring the need for elucidating specific barriers preventing achievement of CVH across different racial and ethnic subgroups in the population.<sup>69</sup>

- Other recent reports on CVH disparity include a study focused on people with serious mental illness, which found that individuals of underrepresented races and ethnicities had significantly lower CVH scores based on 5 of the Life's Simple 7 components,<sup>70</sup> and data from BRFSS identifying racial and ethnic and geographic disparities in CVH among females of childbearing age in the United States: NH Black females were found to have lower adjusted odds (OR, 0.54 [95% CI, 0.46–0.63]) of attaining ideal CVH compared with NH White females, whereas 5 spatial clusters in the Southwest, South, Midwest, and Mid-Atlantic region<sup>71</sup> were identified as having significantly lower prevalence of ideal CVH.<sup>71</sup> A systematic review and meta-analysis summarized the finding on demographic differences and socio-economic disparities in ideal CVH in the literature through June 2020, with females having a significantly higher prevalence of ideal smoking (81% versus 60% in males), BP (41% versus 30% in males), and overall CVH (6% versus 3% in males) and people with higher education and individuals who were economically more affluent being more likely to have ideal CVH.<sup>72</sup>
- Neighborhood factors and contextual relationships have been linked to health disparities in CVH, but more research is needed to better understand these complex relationships.<sup>73</sup> Recent reports on the association between better neighborhood perceptions and higher CVH score in Black communities<sup>74</sup> and the relationship between greater perceived social status and higher CVH score in Hispanic/Latino population in the United States<sup>75</sup> are some examples of effort toward identifying complex relationships between demographic and socioeconomic factors and attaining ideal CVH. A recently published narrative review<sup>76</sup> described knowledge gaps and outlined potential steps toward equity in CVH, which is the objective of the interim<sup>77</sup> and longer-term<sup>78</sup> Impact Goals set forth by the AHA.
- Having more ideal CVH components in middle age has been associated with lower non-CVD and

CVD health care costs in later life.<sup>79</sup> An investigation of 4906 participants in the Cooper Center Longitudinal Study reported that participants with ≥5 ideal CVH components exhibited 24.9% (95% CI, 11.7%–36.0%) lower median annual non-CVD costs and 74.5% (95% CI, 57.5%–84.7%) lower median CVD costs than those with ≤2 ideal CVH components.<sup>79</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>80</sup>

- The 2022 AHA presidential advisory on Life's Essential 8 also provided summaries of knowledge gained on CVH since 2010 and evidence supporting psychological health and well-being, as well as social determinants, as foundational factors for CVH.<sup>3</sup> Additional information on the relevance of sleep to cardiometabolic health can be found in Chapter 13 (Sleep) of this Statistical Update.

## CVH in the United States: Prevalence (NHANES 2013–March 2020)

(See Table 2-2)

- The national estimates of the 8 CVH components for children (2–19 years of age) and adults (≥20 years of age) are displayed in Table 2-2.<sup>81</sup> Multiple cycles of NHANES data were combined to provide more precise estimates on all CVH components. Dietary, PA, and BMI scores were calculated for all children who were 2 to 19 years of age; blood lipid and BP scores were calculated for children who were 6 to 19 and 8 to 19 years of age, respectively; and blood glucose and nicotine exposure scores were calculated for those who were 12 to 19 years of age in the sample. The sleep health score was available only for youth 16 to 19 years of age, so the mean score of this component and the overall CVH score were derived for this age range only. Dietary estimates were available only through data up to the 2017 to 2018 NHANES cycle at the time of this report.
  - For most components of CVH, mean scores were higher in US children (within corresponding age ranges of the components) than in US adults (≥20 years of age), except for the diet score and the sleep health score, for which mean scores in children were lower than in adults. Mean diet scores were the lowest among the 8 CVH components for both US children and adults.
  - Among US children, BP, blood glucose, and nicotine exposure were the CVH components scoring highest compared with the rest of the CVH components, with all mean scores in the 80s and the 90s (of 100 points as the ideal score) across

race and ethnicity groups. In contrast, mean PA, lipids, and sleep health scores within the corresponding age ranges were all in the 70s across race and ethnicity categories.

- Among US adults (Table 2-2), the lowest mean scores for CVH were observed in diet, PA, and BMI components, with mean scores ranging from the 30s to the 50s across all race and ethnicity categories. Sleep health scores were the highest among the CVH components in US adults, with mean scores in the 80s across all race and ethnicity groups except in the NH Black adult population, for whom the mean score was 75.6 (95% CI, 74.5–76.7). Mean scores for blood lipids, blood glucose, and BP among US adults were all in the 60s to the 70s range across race and ethnicity categories.
- From 2013 to March 2020, the overall CVH score combining health scores of all 8 components was, on average, 73.6 (95% CI, 72.4–74.7) for all US children between 16 and 19 years of age. The corresponding mean overall CVH score was 78.4 (95% CI, 75.7–81.1) for NH Asian, 74.1 (95% CI, 72.0–76.2) for NH White, 72.7 (95% CI, 70.6–76.3) for Mexican American, and 71.3 (95% CI, 68.8–73.8) for NH Black children.
- During the same period, the mean overall CVH score was 65.2 (95% CI, 64.2–66.1) for all US adults, with mean score of 69.6 (95% CI, 68.1–71.1) for NH Asian, 66.0 (95% CI, 64.8–67.2) for NH White, 63.5 (95% CI, 62.2–64.8) for Mexican American, and 59.7 (95% CI, 58.4–60.9) for NH Black adults.
- An article appeared online ahead of print on the same day as the presidential advisory on Life's Essential 8 providing CVH score estimates by additional sociodemographic categories under this new CVH metrics using NHANES data from 2013 to 2018.<sup>82</sup>

## 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 the 18th to 5th leading YLL risk factor with a 242.3% increase in the age-standardized YLL rate.
  - In 2019, CVH components accounted for 13 (among which 7 were related to poor diet) of the

- 20 leading YLL risk factors, with 6 of the 7 diet-related risk factors rising in the risk factor rankings since 1990.
- 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 the 46th to 4th leading YLL cause with a 799.2% increase in the age-standardized YLL rate. Type 2 diabetes also rose from the 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 the ninth to third leading YLD cause with a 55.8% increase in the age-standardized YLD rates.
    - Opioid use disorders rose from the 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 the 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 the first to second leading cause, and age-standardized YLL rates declined 62.7%.
  - ICH and ischemic stroke rose from the 9th to 4th and from the 13th to 8th leading cause of global YLL, respectively, between 1990 and 2019.
  - Type 2 diabetes also rose from the 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 77.1% 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 the 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 the 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 July 1, 2022, the cumulative number of COVID-19 deaths in the United States was 1 014 620, which equates to ≈306 deaths per 100 000 people.<sup>83</sup> In metropolitan areas in the United States, the cumulative COVID-19 death rate was ≈292 deaths per 100 000 compared with ≈392 deaths per 100 000 in nonmetropolitan areas.<sup>83</sup>
- In US counties with a high percentage (>37%) of the population that is NH Black individuals, the COVID-19 death rate was ≈354 deaths per 100 000 compared with ≈297 deaths per 100 000 in counties with a low percentage (<2.5%) of the population that is NH Black individuals.<sup>83</sup>
- In US counties with a high percentage (>45.5%) of the population that is Hispanic individuals, the cumulative COVID-19 death rate was ≈348 deaths per 100 000 compared with ≈307 deaths per 100 000 in counties with a low percentage (≤18.3%) of the population that is Hispanic individuals.<sup>83</sup>
- In US counties with a high percentage (>17.3%) of the population in poverty, the cumulative COVID-19 death rate was ≈394 deaths per 100 000 compared with ≈248 deaths per 100 000 in counties with a low percentage (≤12.3%) of the population that is living in poverty.<sup>83</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.
- US life expectancy estimates released in December 2021<sup>84,85</sup> indicate that life expectancy (at birth) decreased from 78.8 years in 2019 to 77.0 years in 2020 (−1.8 years) overall; corresponding life expectancy decreased from 76.3 to 74.2 years (−2.1 years) in males and from 81.4 to 79.9 years (−1.5 years) in females. Provisional estimates released in December 2021 indicated that life expectancy decreased from 74.7 to 71.8 years (−2.9 years) for NH Black individuals, from 81.8 to 78.8 years (−3.0 years) for Hispanic individuals, and from 78.8 to 77.6 years (−1.2 years) for NH White individuals.<sup>84</sup>

## 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>25</sup> AD,<sup>86</sup> stroke,<sup>87,88</sup> CKD,<sup>89</sup> diabetes,<sup>90,91</sup> and breast cancer<sup>92,93</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, AD, 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>94</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.** Life's Essential 8: New and Updated Metrics for Measurement and Quantitative Assessment of Cardiovascular Health

Domain	CVH metric	Method of measurement	Quantification of CVH metric: adults (≥20 y of age)	Quantification of CVH metric: children (up to 19 y of age)
Health behaviors	Diet	Measurement: Self-reported daily intake of a DASH-style eating pattern Example tools for measurement: DASH diet score <sup>95,96</sup> (populations); MEPA <sup>97</sup> (individuals)	Quantiles of DASH-style diet adherence or HEI-2015 (population) Scoring (population): <u>Points</u> <u>Quantile</u> 100   ≥95th percentile (top/ideal diet) 80   75th–94th percentile 50   50th–74th percentile 25   25th–49th percentile 0   1st–24th percentile (bottom/least ideal quartile) Scoring (individual): <u>Points</u> <u>MEPA score (points)</u> 100   15–16 80   12–14 50   8–11 25   4–7 0   0–3	Quantiles of DASH-style diet adherence or HEI-2015 (population) or MEPA (individuals)*; 2–19 y of age (see <i>Supplemental Material</i> for younger ages) Scoring (population): <u>Points</u> <u>Quantile</u> 100   ≥95th percentile (top/ideal diet) 80   75th–94th percentile 50   50th–74th percentile 25   25th–49th percentile 0   1st–24th percentile (bottom/least ideal quartile) Scoring (individual): <u>Points</u> <u>MEPA score (points)</u> 100   9–10 80   7–8 50   5–6 25   3–4 0   0–2
	PA	Measurement: Self-reported minutes of moderate or vigorous PA per week Example tools for measurement: NHANES PAQ-K questionnaire <sup>98</sup>	Metric: Minutes of moderate- (or greater) intensity activity per week Scoring: <u>Points</u> <u>Minutes</u> 100   ≥150 90   120–149 80   90–119 60   60–89 40   30–59 20   1–29 0   0	Metric: Minutes of moderate- (or greater) intensity activity per week; 6–19 y of age (see notes and <i>Supplemental Material</i> for younger ages) Scoring: <u>Points</u> <u>Minutes</u> 100   ≥420 90   360–419 80   300–359 60   240–299 40   120–239 20   1–119 0   0
	Nicotine exposure	Measurement: Self-reported use of cigarettes or inhaled NDS Example tools for measurement: NHANES SMQ <sup>99</sup>	Metric: Combustible tobacco use or inhaled NDS use; or secondhand smoke exposure Scoring: <u>Points</u> <u>Status</u> 100   Never-smoker 75   Former smoker, quit ≥5 y 50   Former smoker, quit 1–<5 y 25   Former smoker, quit <1 y, or currently using inhaled NDS 0   Current smoker Subtract 20 points (unless score is 0) for living with active indoor smoker in home	Metric: Combustible tobacco use or inhaled NDS use at any age (per clinician discretion); or secondhand smoke exposure Scoring: <u>Points</u> <u>Status</u> 100   Never tried 50   Tried any nicotine product but >30 ago 25   Currently using inhaled NDS 0   Current combustible use (any within 30 d) Subtract 20 points (unless score is 0) for living with active indoor smoker in home
	Sleep health	Measurement: Self-reported average hours of sleep per night Example tools for measurement: "On average, how many hours of sleep do you get per night?" Consider objective sleep/actigraphy data from wearable technology if available	Metric: Average hours of sleep per night Scoring: <u>Points</u> <u>Level</u> 100   7–<9 90   9–<10 70   6–<7 40   5–<6 or ≥10 20   4–<5 0   <4	Metric: Average hours of sleep per night (or per 24 h for ≤5 y of age; see notes for age-appropriate ranges) Scoring: <u>Points</u> <u>Level</u> 100   Age-appropriate optimal range 90   <1 h above optimal range 70   <1 h below optimal range 40   1–<2 h below or ≥1 h above optimal 20   2–<3 h below optimal range 0   ≥3 h below optimal range
Health factors	BMI	Measurement: Body weight (kilograms) divided by height squared (meters squared) Example tools for measurement: Objective measurement of height and weight	Metric: BMI ( $\text{kg}/\text{m}^2$ ) Scoring: <u>Points</u> <u>Level</u> 100   <25 70   25.0–29.9 30   30.0–34.9 15   35.0–39.9 0   ≥40.0	Metric: BMI percentiles for age and sex, starting in infancy; see <i>Supplemental Material</i> for suggestions for <2 y of age Scoring: <u>Points</u> <u>Level</u> 100   5th–<85th percentile 70   85th–<95th percentile 30   95th percentile–<120% of the 95th percentile 15   120% of the 95th percentile–<140% of the 95th percentile 0   ≥140% of the 95th percentile

(Continued)

**Table 2-1.** Continued

Domain	CVH metric	Method of measurement	Quantification of CVH metric: adults (≥20 y of age)	Quantification of CVH metric: children (up to 19 y of age)																																
	Blood lipids	Measurement: Plasma TC and HDL-C with calculation of non-HDL-C Example tools for measurement: Fasting or nonfasting blood sample	Metric: Non-HDL-C (mg/dL) Scoring: <table border="1"> <thead> <tr> <th>Points</th> <th>Level</th> </tr> </thead> <tbody> <tr> <td>100</td> <td>&lt;130</td> </tr> <tr> <td>60</td> <td>130–159</td> </tr> <tr> <td>40</td> <td>160–189</td> </tr> <tr> <td>20</td> <td>190–219</td> </tr> <tr> <td>0</td> <td>≥220</td> </tr> </tbody> </table> If drug-treated level, subtract 20 points	Points	Level	100	<130	60	130–159	40	160–189	20	190–219	0	≥220	Metric: Non-HDL-C (mg/dL), starting no later than 9–11 y of age and earlier per clinician discretion Scoring: <table border="1"> <thead> <tr> <th>Points</th> <th>Level</th> </tr> </thead> <tbody> <tr> <td>100</td> <td>&lt;100</td> </tr> <tr> <td>60</td> <td>100–119</td> </tr> <tr> <td>40</td> <td>120–144</td> </tr> <tr> <td>20</td> <td>145–189</td> </tr> <tr> <td>0</td> <td>≥190</td> </tr> </tbody> </table> If drug-treated level, subtract 20 points	Points	Level	100	<100	60	100–119	40	120–144	20	145–189	0	≥190								
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	Blood glucose	Measurement: FBG or casual HbA1c Example tools for measurement: Fasting (FBG, HbA1c) or nonfasting (HbA1c) blood sample	Metric: FBG (mg/dL) or HbA1c (%) Scoring: <table border="1"> <thead> <tr> <th>Points</th> <th>Level</th> </tr> </thead> <tbody> <tr> <td>100</td> <td>No history of diabetes and FBG &lt;100 (or HbA1c &lt;5.7)</td> </tr> <tr> <td>60</td> <td>No diabetes and FBG 100–125 (or HbA1c 5.7–6.4; prediabetes)</td> </tr> <tr> <td>40</td> <td>Diabetes with HbA1c &lt;7.0</td> </tr> <tr> <td>30</td> <td>Diabetes with HbA1c 7.0–7.9</td> </tr> <tr> <td>20</td> <td>Diabetes with HbA1c 8.0–8.9</td> </tr> <tr> <td>10</td> <td>Diabetes with HbA1c 9.0–9.9</td> </tr> <tr> <td>0</td> <td>Diabetes with HbA1c ≥10.0</td> </tr> </tbody> </table>	Points	Level	100	No history of diabetes and FBG <100 (or HbA1c <5.7)	60	No diabetes and FBG 100–125 (or HbA1c 5.7–6.4; prediabetes)	40	Diabetes with HbA1c <7.0	30	Diabetes with HbA1c 7.0–7.9	20	Diabetes with HbA1c 8.0–8.9	10	Diabetes with HbA1c 9.0–9.9	0	Diabetes with HbA1c ≥10.0	Metric: FBG (mg/dL) or HbA1c (%), symptom-based screening at any age or risk-based screening starting at ≥10 y of age or onset of puberty per clinician discretion Scoring: <table border="1"> <thead> <tr> <th>Points</th> <th>Level</th> </tr> </thead> <tbody> <tr> <td>100</td> <td>No history of diabetes and FBG &lt;100 (or HbA1c &lt;5.7)</td> </tr> <tr> <td>60</td> <td>No diabetes and FBG 100–125 (or HbA1c 5.7–6.4; prediabetes)</td> </tr> <tr> <td>40</td> <td>Diabetes with HbA1c &lt;7.0</td> </tr> <tr> <td>30</td> <td>Diabetes with HbA1c 7.0–7.9</td> </tr> <tr> <td>20</td> <td>Diabetes with HbA1c 8.0–8.9</td> </tr> <tr> <td>10</td> <td>Diabetes with HbA1c 9.0–9.9</td> </tr> <tr> <td>0</td> <td>Diabetes with HbA1c ≥10.0</td> </tr> </tbody> </table>	Points	Level	100	No history of diabetes and FBG <100 (or HbA1c <5.7)	60	No diabetes and FBG 100–125 (or HbA1c 5.7–6.4; prediabetes)	40	Diabetes with HbA1c <7.0	30	Diabetes with HbA1c 7.0–7.9	20	Diabetes with HbA1c 8.0–8.9	10	Diabetes with HbA1c 9.0–9.9	0	Diabetes with HbA1c ≥10.0
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BMI indicates body mass index; BP, blood pressure; CVH, cardiovascular health; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HEI, Healthy Eating Index; MEPA, Mediterranean Eating Pattern for Americans; NDS, nicotine-delivery system; NHANES, National Health and Nutrition Examination Surveys; PA, physical activity; PAQ-K, Physical Activity Questionnaire K; SBP, systolic blood pressure; SMQ, smoking assessment; and TC, total cholesterol.

\*Cannot meet these metrics until solid foods are being consumed.

Notes on implementation:

Diet: See [Supplemental Material Appendix 1](#). For adults and children, a score of 100 points for the CVH diet metric should be assigned for the top (95th percentile) or a score of 15 to 16 on the MEPA (for individuals) or for those in the ≥95th percentile on the DASH score or HEI-2015 (for populations). The 75th to 94th percentile should be assigned 80 points, given that improvement likely can be made even among those in this top quartile. For individuals, the MEPA points are stratified for the 100-point scoring system approximately by quantiles. In children, a modified MEPA is suggested that is based on age-appropriate foods. The writing group recognizes that the quantiles may need to be adjusted or recalibrated at intervals with population shifts in eating patterns. In children, the scoring applies only once solid foods are being consumed. For now, the reference population for quantiles of HEI or DASH score should be the NHANES sample from 2015 to 2018. The writing group acknowledges that this may need to change or be updated over time. Clinicians should use judgment in assigning points for culturally contextual healthy diets. For additional notes on scoring in children, see [Supplemental Material Appendix 2](#).

PA: Thresholds are based in part on US Physical Activity Guidelines. For adults, each minute of moderate activity should count as 1 minute and each minute of vigorous activity should count as 2 minutes toward the total for the week. For children, each minute of moderate or vigorous activity should count as 1 minute. The score for PA is not linear, given that there is a greater increase in health benefit for each minute of marginal exercise at the lower end of the range and the association tends to approach an asymptote at the higher end of the range.

If scoring is desired for children ≤5 years of age, see [Supplemental Material](#). For additional notes on scoring in children, see [Supplemental Material Appendix 2](#).

Nicotine exposure: The writing group recommends subtracting 20 points for children and adults exposed to indoor secondhand smoke at home, given its potential for long-term effects on cardiopulmonary health.<sup>100</sup> For additional notes on scoring in children, see [Supplemental Material Appendix 2](#).

Sleep health: Thresholds are based in part on sleep guidelines. Clinicians may consider subtracting 20 points from the sleep score for adults or children with untreated or undertreated sleep apnea if information is available. Note that overall scoring reflects the inverse-U-shaped association of sleep duration with health outcomes, such that excessive sleep duration is also considered to be suboptimal for CVH.

(Continued)

**Table 2-1. Continued**

For children, age-appropriate optimal sleep durations are as follows<sup>101</sup>:

- 4 to 12 months of age, 12 to 16 hours per 24 hours (includes naps);
- 1 to 2 years of age, 11 to 14 hours per 24 hours;
- 3 to 5 years of age, 10 to 13 hours per 24 hours;
- 6 to 12 years of age, 9 to 12 hours; and
- 13 to 18 years of age, 8 to 10 hours.

For additional notes on scoring in children, see [Supplemental Material Appendix 2](#).

BMI: Thresholds are based in part on National Heart, Lung, and Blood Institute (NHLBI) guidelines. The writing group acknowledges that BMI is an imperfect metric for determining healthy body weight and body composition. Nonetheless, it is widely available and routinely calculated in clinical and research settings. BMI ranges may differ for individuals from diverse ancestries. For example, the World Health Organization has recommended different BMI ranges for individuals of Asian or Pacific ancestry. For individuals in these groups, point scores should be aligned as appropriate:

Points	Level, kg/m <sup>2</sup>
100	18.5–22.9
75	23.0–24.9
50	25.0–29.9
25	30.0–34.9
0	≥35.0

Clinicians may want to assign 100 points for overweight individuals (BMI, 25.0–29.9 kg/m<sup>2</sup>) who are lean with higher muscle mass. For underweight individuals (<18.5 kg/m<sup>2</sup> in adults or below the fifth percentile in children), the writing group defers to clinician judgment in assigning points on the basis of individual assessment as to whether the underweight BMI is healthy or unhealthy. Conditions that should be considered unhealthy include chronic catabolic illnesses (eg, cancer), eating disorders, and growth failure (for children). For additional notes on scoring in children, see [Supplemental Material Appendix 2](#).

Blood lipids: Thresholds are based in part on 2018 Cholesterol Clinical Practice Guideline.<sup>102</sup> The levels of non-HDL-C for adults were selected on the basis of current guideline recommendations and in concert with the observation that non-HDL-C levels are generally ≈30 mg/dL higher than low-density lipoprotein cholesterol levels in normative ranges in the population. For children, thresholds for non-HDL-C were chosen on the basis of NHLBI pediatric guidelines, pediatric low-density lipoprotein cholesterol thresholds for diagnosis of familial hypercholesterolemia phenotypes (+30 mg/dL), and current distributions of non-HDL-C to smooth transitions to adult point scales. The writing group recommends subtracting 20 points from the blood lipid score if the level of non-HDL-C represents a treated value, given the residual risk present in those who require treatment. There may be a modest shift in point scores for this metric as individuals age from pediatric to adult metrics. For additional notes on scoring in children, see [Supplemental Material Appendix 2](#).

Blood glucose: Thresholds are based in part on American Diabetes Association guidelines.<sup>103</sup> If an individual patient with prediabetes (ie, not yet diagnosed formally with diabetes) is being treated with metformin to prevent the onset of diabetes and has normoglycemic levels, the writing group recommends clinician judgment for assigning point values (ie, consider subtracting 20 points). The maximal point value for patients with well-controlled diabetes was set at 40, given the residual risk present in those with diabetes. For additional notes on scoring in children, see [Supplemental Material Appendix 2](#).

BP: Thresholds are based in part on the 2017 Hypertension Clinical Practice Guidelines and the guidelines for children.<sup>104</sup> The writing group recommends subtracting 20 points from the BP score if the level of BP represents a treated value, given the residual risk present in those who require treatment. For additional notes on scoring in children, see [Supplemental Material Appendix 2](#).

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**Table 2-2.** Mean (95% CI) Score for Each Component of CVH Metrics by Race and Ethnicity Strata Among US Children 2 to 19 Years of Age and US Adults ≥20 Years of Age: NHANES 2013 to March 2020

Individual component of CVH metrics	NHANES years	Overall	NH Black	NH White	NH Asian	MA
Health behaviors		2–19 y of age				
Diet* score (2–19 y)	2013–2018	41.2 (39.0–43.5)	31.7 (28.8–34.6)	41.1 (37.6–44.5)	49.8 (43.0–56.5)	44.3 (40.8–47.8)
PA score (2–19 y)	2013–March 2020	75.2 (74.2–76.3)	74.7 (73.0–76.3)	77.5 (76.0–78.9)	72.5 (69.9–74.9)	71.0 (68.4–73.7)
Nicotine exposure core (12–19 y)	2013–March 2020	85.4 (84.1–86.7)	86.8 (84.6–88.9)	83.3 (81.0–85.5)	92.8 (90.5–95.1)	88.0 (85.7–90.3)
Sleep health score (16–19 y)	2013–March 2020	77.8 (76.0–79.6)	72.5 (70.0–75.0)	79.8 (77.1–82.5)	77.9 (74.7–81.2)	77.7 (75.1–80.4)
Health factors						
BMI score (2–19 y)	2013–March 2020	81.4 (80.0–82.8)	78.9 (75.7–82.0)	84.3 (82.5–86.0)	89.3 (87.0–91.7)	74.9 (72.6–77.2)
Blood lipids score (6–19 y)	2013–March 2020	73.7 (72.6–74.8)	77.3 (75.3–79.2)	73.6 (71.8–75.4)	69.9 (66.9–73.0)	73.5 (71.6–75.4)
Blood glucose score (12–19 y)	2013–March 2020	92.5 (91.7–93.2)	89.3 (88.0–90.7)	93.3 (92.0–94.5)	93.0 (90.8–95.2)	91.7 (90.2–93.2)
BP score (8–19 y)	2013–March 2020	95.5 (95.0–96.0)	94.2 (93.3–95.0)	95.8 (95.1–96.3)	96.1 (95.1–97.0)	95.5 (94.6–96.3)
Overall score (16–19 y)	2013–March 2020	73.6 (72.4–74.7)	71.3 (68.8–73.8)	74.1 (72.0–76.2)	78.4 (75.7–81.1)	72.7 (70.6–76.3)
Health behaviors		≥20 y of age†				
Diet* score	2013–2018	44.38 (42.6–46.1)	31.4 (28.5–34.3)	46.6 (44.4–48.8)	53.1 (49.7–56.5)	42.9 (40.9–44.9)
PA score	2013–March 2020	49.23 (47.4–51.0)	45.1 (42.7–47.6)	51.0 (48.9–53.1)	51.8 (48.3–55.3) <small>American Heart Association</small>	42.4 (39.9–44.9)
Nicotine exposure score	2013–March 2020	69.3 (68.0–70.5)	64.0 (62.1–65.9)	68.1 (66.3–69.9)	85.4 (83.5–82.3)	75.7 (73.8–77.6)
Sleep health score	2013–March 2020	84.2 (83.6–84.8)	75.6 (74.5–76.7)	86.1 (85.4–86.9)	86.3 (84.9–87.7)	83.1 (81.9–84.3)
Health factors						
BMI score	2013–March 2020	57.2 (56.2–58.2)	52.0 (50.5–53.5)	58.9 (57.6–60.2)	58.5 (57.0–60.1)	50.9 (49.2–52.5)
Blood lipids score	2013–March 2020	67.7 (66.8–68.6)	73.7 (72.4–74.9)	67.0 (65.9–68.1)	66.9 (65.4–68.5)	66.2 (64.4–68.0)
Blood glucose score	2013–March 2020	76.4 (75.7–77.2)	72.2 (71.3–73.2)	77.8 (76.9–78.6)	74.7 (72.9–76.5)	73.2 (71.2–75.2)
BP score	2013–March 2020	68.2 (67.3–69.0)	60.6 (59.2–62.0)	68.2 (67.1–69.4)	70.7 (68.9–72.5)	73.4 (71.8–75.0)
Overall score	2013–March 2020	65.2 (64.2–66.1)	59.7 (58.4–60.9)	66.0 (64.8–67.2)	69.6 (68.1–71.1)	63.5 (62.2–64.8)

Values are mean (95% CI). In March 2020, the COVID-19 (coronavirus disease 2019) pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>105</sup>

BMI indicates body mass index; BP, blood pressure; CVH, cardiovascular health; MA, Mexican American; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and PA, physical activity.

\*Scaled to 2000 kcal/d and in the context of appropriate energy balance and a Dietary Approaches to Stop Hypertension-type eating pattern.

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

Source: Unpublished American Heart Association tabulation using NHANES.<sup>81</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	8 466.11 (7 465.95 to 9 424.27)	7 815.63 (6 814.38 to 8 821.87)	-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	4 994.23 (3 131.76 to 6 877.86)	7 778.57 (5 416.09 to 9 912.24)	55.75% (41.31% to 80.47%)	-9.18% (-17.75% to 5.86%)	232.16 (138.00 to 334.08)	393.86 (257.61 to 528.44)	69.65% (52.54% to 98.96%)	-5.82% (-15.3% to 10%)
High FPG	5	4	4 664.81 (3 563.73 to 6 006.04)	7 121.62 (5 548.50 to 9 006.14)	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 1 135.28)	4 265.41 (4 080.78 to 4 494.41)	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	2 708.90 (2 327.61 to 3 129.89)	3 936.71 (3 457.94 to 4 524.58)	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	6 291.91 (5 210.65 to 7 354.85)	3 863.72 (3 077.21 to 4 730.88)	-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	2 138.32 (1 781.84 to 2 527.38)	3 159.52 (2 795.42 to 3 536.01)	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% of population)	-15% (-20.89% to -6.95%)
Diet low in whole grains	9	9	1 897.21 (868.61 to 2 445.35)	1 778.79 (855.23 to 2 258.78)	-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	1 320.06 (1 079.50 to 1 579.76)	1 734.12 (1 488.09 to 1 989.52)	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	1 471.67 (348.59 to 2 464.41)	1 299.03 (337.88 to 2 145.69)	-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	1 258.35 (677.77 to 1 830.45)	1 268.70 (754.94 to 1 787.30)	0.82% (-7.68% to 16.14%)	-40.06% (-45.03% to -30.7%)	59.84 (31.13 to 88.85)	65.65 (37.01 to 94.39)	9.71% (-0.52% to 29.65%)	-38.55% (-44.31% to -27.11%)
Diet high in trans fatty acids	14	13	1 311.91 (77.03 to 1 776.96)	1 097.24 (55.44 to 1 490.02)	-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 1 366.73)	969.35 (405.97 to 1 459.61)	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	2 001.60 (842.72 to 3 490.50)	931.95 (526.95 to 1 361.42)	-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 1 999.45)	914.24 (61.08 to 2 622.57)	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%)
LBW	10	17	1 512.98 (1 436.65 to 1 601.27)	853.24 (778.57 to 935.91)	-43.61% (-49.31% to -37.44%)	-38.47% (-44.69% to -31.75%)	17.04 (16.18 to 18.03)	9.61 (8.77 to 10.54)	-43.62% (-49.32% to -37.46%)	-38.49% (-44.71% to -31.77%)
Short gestation	11	18	1 492.43 (1 415.76 to 1 577.76)	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	1 072.52 (858.49 to 1 288.00)	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 1 141.76)	745.10 (463.85 to 1 006.64)	-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%)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

BMI indicates body mass index; FPG, fasting plasma glucose; GBD, Global Burden of Disease; LBW, low birth weight; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UI, uncertainty interval; and YLL, year of life lost to premature mortality.

Source: Data derived from GBD Study 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>106</sup>

**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)	8 651.61 (8 081.02 to 9 124.13)	-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	3 559.62 (3 479.49 to 3 617.41)	4 124.65 (3 950.45 to 4 261.93)	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	1 592.74 (1 505.38 to 1 778.28)	3 100.42 (2 620.31 to 3 305.63)	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 (218.29 to 241.61)	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	1 291.48 (1 249.20 to 1 320.46)	1 640.65 (1 574.85 to 1 689.21)	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)	1 365.65 (1 299.49 to 1 422.98)	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%)
AD and other dementias	15	7	743.80 (180.25 to 2011.60)	139.08 (333.70 to 3431.38)	80.03% (65.82% to 99.45%)	-3.65% (-10.86% to 5.5%)	73.08 (18.40 to 194.71)	143.92 (37.07 to 354.96)	96.94% (80.52% to 119.01%)	-1.92% (-9.65% to 7.87%)
Motor vehicle road injuries	3	8	1 836.51 (1 812.57 to 1 864.76)	1 231.24 (1 152.15 to 1 272.09)	-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	1 199.58 (1 165.78 to 1 222.05)	1 212.43 (1 157.03 to 1 261.82)	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	1 223.88 (1 159.84 to 1 261.53)	1 210.65 (1 124.89 to 1 262.59)	-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	1 324.40 (1 218.20 to 1 381.45)	1 185.52 (1 045.83 to 1 295.90)	-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)	1 134.93 (1 078.47 to 1 178.70)	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)	1 099.70 (1 033.09 to 1 188.13)	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 1 004.91)	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 1 027.23)	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 1 014.78)	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 1 037.53)	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%)

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AD indicates Alzheimer disease; GBD, Global Burden of Disease; HD, heart disease; ICH, intracerebral hemorrhage; IHD, ischemic heart disease; UI, uncertainty interval; and YLL, year of life lost to premature mortality.

Source: Data derived from GBD Study 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>107</sup>

**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%)
LBW	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%)

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BMI indicates body mass index; FPG, fasting plasma glucose; GBD, Global Burden of Disease; LDL-C, low-density lipoprotein cholesterol; LBW, low birth weight; SBP, systolic blood pressure; UI, uncertainty interval; and YLD, year of life lived with disability or injury.

Source: Data derived from GBD Study 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>106</sup>

**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%)
AD 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%)

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AD indicates Alzheimer disease; GBD, Global Burden of Disease; UI, uncertainty interval; and YLD, year of life lived with disability or injury.

Source: Data derived from GBD Study 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>107</sup>

**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%)
LBW	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 55.68% American Association)	-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)	79 187.22 (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 -64.32%)	-73.05% (-78.35% to -66.7%)
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 (41 786.87 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 4194.71)	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%)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

BMI indicates body mass index; FPG, fasting plasma glucose; GBD, Global Burden of Disease; LBW, low birth weight; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UI, uncertainty interval; and YLL, year of life lost because of premature mortality.

Source: Data derived from GBD Study 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>106</sup>

**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 PTB	4	5	112 709.17 (103 574.46 to 122 915.10)	58 942.91 (49 829.35 to 70 084.83)	-47.7% (-56.13% to -37.42%)	-47.02% (-55.56% to -36.61%)	1269.04 (1166.14 to 1383.98)	663.52 (560.96 to 788.95)	-47.71% (-56.14% to -37.44%)	-47.04% (-55.57% to -36.63%)
Chronic obstructive pulmonary disease	11	6	48 769.20 (40 770.89 to 52 860.94)	54 594.90 (48 711.47 to 59 513.37)	11.95% (-0.47% to 35.12%)	-46.81% (-52.61% to -36.11%)	2520.22 (2118.06 to 2719.39)	3280.64 (2902.85 to 3572.37)	30.17% (15.74% to 55.05%)	-41.74% (-48.03% to -31.07%)
Neonatal encephalopathy caused by birth asphyxia and trauma	6	7	71 832.72 (64 553.03 to 80 228.20)	50 368.25 (42 242.80 to 59 745.92)	-29.88% (-41.7% to -15.68%)	-28.91% (-40.9% to -14.52%)	808.68 (726.80 to 903.20)	566.98 (475.54 to 672.55)	-29.89% (-41.71% to -15.69%)	-28.92% (-40.91% to -14.54%)
Ischemic stroke	13	8	34 004.54 (31 954.95 to 37 258.43)	50 349.74 (46 232.45 to 54 066.67)	48.07% (32.31% to 61.3%)	-33.35% (-40% to -27.56%)	2049.67 (1900.02 to 2234.21)	3293.40 (2973.54 to 3536.08)	60.68% (45.83% to 74.65% American Association)	-33.64% (-39.16% to -28.15%)
Tracheal, bronchus, and lung cancer	19	9	26 859.81 (25 598.42 to 28 199.92)	45 313.75 (41 866.20 to 48 831.01)	68.7% (52.68% to 85.03%)	-16.34% (-24.19% to -8.38%)	1065.14 (1019.22 to 1117.18)	2042.64 (1879.24 to 2193.27)	91.77% (74.52% to 108.97%)	-7.77% (-15.93% to 0.23%)
Malaria	8	10	63 480.60 (34 802.94 to 103 091.05)	43 824.70 (21 055.36 to 77 962.79)	-30.96% (-58.84% to 6.4%)	-39.03% (-63.65% to -6.42%)	840.55 (463.32 to 1356.07)	643.38 (301.60 to 1153.66)	-23.46% (-54.89% to 18.46%)	-37.93% (-63.46% to -4.52%)
Drug-susceptible tuberculosis	5	11	74 658.58 (68 441.13 to 81 346.25)	38 431.33 (33 206.79 to 43 219.46)	-48.52% (-55.92% to -40.77%)	-67.54% (-72.12% to -62.69%)	1760.71 (610.86 to 1908.32)	1061.29 (924.21 to 1186.12)	-39.72% (-48.03% to -30.36%)	-66.82% (-71.34% to -61.52%)
Other neonatal disorders	12	12	47 950.24 (40 831.64 to 57 251.83)	33 099.91 (27 646.20 to 40 129.55)	-30.97% (-48% to -11.34%)	-30.12% (-47.35% to -10.26%)	539.95 (459.81 to 644.56)	372.68 (311.26 to 451.84)	-30.98% (-48% to -11.37%)	-30.13% (-47.36% to -10.29%)
HIV/AIDS resulting in other diseases	32	13	12 728.09 (9716.63 to 17 727.71)	32 470.01 (26 796.66 to 40 802.58)	155.11% (119.22% to 204.68%)	77.01% (51.97% to 111.74%)	216.91 (162.89 to 308.68)	646.76 (551.85 to 780.47)	198.17% (147.74% to 269.45%)	94.13% (61.07% to 141.2%)
Type 2 diabetes	28	14	13 851.47 (13 104.90 to 14 647.61)	31 149.12 (29 302.02 to 33 148.25)	124.88% (110.14% to 141.3%)	9.11% (2.06% to 16.65%)	606.41 (573.07 to 637.51)	1472.93 (1371.94 to 1565.86)	142.9% (128.32% to 158.37%)	10.77% (4.42% to 17.44%)
Self-harm by other specified means	15	15	32 879.52 (29 065.89 to 35 287.35)	30 986.82 (27 870.17 to 34 246.63)	-5.76% (-14.84% to 4.31%)	-38.8% (-44.56% to -32.43%)	687.85 (607.61 to 736.36)	706.33 (633.90 to 777.33)	2.69% (-6.38% to 13.66%)	-38.83% (-43.96% to -32.27%)
Colon and rectum cancer	34	16	12 013.14 (11 481.93 to 12 503.78)	23 218.75 (21 662.64 to 24 591.16)	93.28% (79.51% to 106.26%)	-5.29% (-11.8% to 0.81%)	518.13 (493.68 to 537.88)	1085.80 (1002.80 to 1149.68)	109.56% (96.2% to 121.74%)	-4.37% (-10.03% to 0.93%)
Motor vehicle road injuries	21	17	22 260.33 (19 219.44 to 25 401.32)	21 982.25 (19 334.80 to 24 633.49)	-1.25% (-14.6% to 15.23%)	-30.61% (-39.82% to -19.51%)	399.99 (349.88 to 452.26)	448.73 (396.67 to 500.41)	12.19% (-2.49% to 28.58%)	-27.7% (-37.11% to -17.51%)
Stomach cancer	24	18	20 241.69 (19 030.22 to 21 513.16)	21 872.43 (19 972.71 to 23 712.52)	8.06% (-2.52% to 19.94%)	-45.85% (-51.1% to -39.99%)	788.32 (742.79 to 834.00)	957.19 (870.95 to 1034.65)	21.42% (10.17% to 33.59%)	-41.98% (-47.18% to -36.33%)
Neonatal sepsis and other neonatal infections	20	19	23 105.79 (18 521.37 to 26 599.32)	20 118.04 (16 896.71 to 24 474.48)	-12.93% (-29.92% to 11.86%)	-11.91% (-29.12% to 13.14%)	260.15 (208.54 to 299.46)	226.52 (190.25 to 275.55)	-12.93% (-29.93% to 11.86%)	-11.91% (-29.12% to 13.15%)
Hypertensive HD	31	20	13 303.40 (10 669.61 to 14 984.15)	19 991.58 (14 951.10 to 22 179.67)	50.27% (31.09% to 74.64%)	-28.13% (-38.1% to -17.04%)	654.91 (530.57 to 732.73)	1156.73 (859.83 to 1278.56)	76.63% (49.7% to 103.4%)	-21.49% (-35.18% to -10.13%)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; HD, heart disease; ICH, intracerebral hemorrhage; IHD, ischemic heart disease; PTB, preterm birth; UI, uncertainty interval; and YLL, year of life lost to premature mortality.

Source: Data derived from GBD Study 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>107</sup>

**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 (6901.43 to 20 969.73)	40 881.60 (24 508.83 to 60 876.50)	216.73% (178.46% to 276.78%)	60.16% (41.28% to 90.24%)
Smoking	2	3	20 484.09 (15 154.19 to 26 177.63)	31 556.71 (23 686.35 to 40 009.32)	54.05% (49.57% to 59.1%)	-22.88% (-24.83% to -20.74%)
Iron deficiency	1	4	25 379.25 (16 986.41 to 36 524.20)	28 798.47 (19 425.22 to 41 491.77)	13.47% (10.15% to 16.89%)	-16.67% (-19.02% to -14.23%)
High SBP	7	5	10 128.23 (7295.78 to 13 093.83)	21 164.35 (15 195.78 to 27 235.49)	108.96% (102.17% to 116.39%)	0.98% (-2.31% to 4.4%)
Alcohol use	5	6	11 836.52 (8147.05 to 16 305.10)	17 182.28 (12 000.25 to 23 497.81)	45.16% (39.58% to 51.25%)	-13.47% (-15.96% to -10.79%)
Occupational ergonomic factors	6	7	11 784.36 (8098.99 to 15 893.42)	15 310.68 (10 544.90 to 20 762.41)	29.92% (24.65% to 34.57%)	-24.61% (-26.93% to -22.45%)
Ambient particulate matter pollution	17	8	3985.80 (2637.74 to 5634.02)	13 320.10 (9643.12 to 17 166.65)	234.19% (172.63% to 322.4%)	64.91% (34.85% to 107.76%)
Drug use	9	9	7479.41 (5163.69 to 10 042.08)	12 664.94 (8804.75 to 16 725.98)	69.33% (60.93% to 78.15%)	14.49% (9.59% to 19.37%)
Kidney dysfunction	14	10	5003.27 (3651.06 to 6508.03)	11 282.48 (8232.55 to 14 676.40)	125.5% (118.26% to 132.74%)	20.24% <small>†16.89% to 23.23% American Heart Association</small>
Short gestation	12	11	5054.73 (3854.95 to 6433.30)	9673.88 (7598.43 to 12 021.19)	91.38% (75.26% to 106.94%)	43.44% (31.94% to 54.79%)
LBW	13	12	5054.73 (3854.95 to 6433.30)	9673.88 (7598.43 to 12 021.19)	91.38% (75.26% to 106.94%)	43.44% (31.94% to 54.79%)
Low bone mineral density	16	13	4082.06 (2923.34 to 5511.96)	8620.52 (6115.78 to 11 640.10)	111.18% (108.01% to 114.56%)	-1.7% (-2.77% to -0.66%)
Household air pollution from solid fuels	8	14	8277.99 (5837.95 to 11 127.29)	7908.60 (5254.80 to 11 299.35)	-4.46% (-20.63% to 15.04%)	-52.14% (-60.18% to -42.55%)
Unsafe water source	11	15	6054.63 (3781.50 to 8815.37)	7455.38 (4530.39 to 10 914.15)	23.14% (16.02% to 29.05%)	-11.82% (-16.58% to -8.1%)
Occupational noise	18	16	3933.44 (2688.10 to 5599.97)	7001.45 (4760.56 to 10 059.34)	78% (71.39% to 83.61%)	-1.71% (-4.07% to 0.35%)
Occupational injuries	10	17	6779.60 (4833.81 to 9123.27)	6842.83 (4831.64 to 9300.85)	0.93% (-10.59% to 13.14%)	-39.26% (-46.08% to -31.85%)
High LDL-C	22	18	3035.02 (1990.11 to 4342.73)	5713.21 (3677.82 to 8268.24)	88.24% (82.75% to 94.36%)	-7.77% (-9.68% to -6.05%)
Secondhand smoke	24	19	2652.31 (1685.26 to 3741.03)	5512.81 (3246.56 to 8105.45)	107.85% (84.4% to 123.61%)	6.66% (-4.51% to 14.89%)
Unsafe sex	32	20	1609.09 (1135.71 to 2172.24)	4646.23 (3296.41 to 6215.68)	188.75% (161.84% to 225.83%)	80.75% (63.79% to 103.78%)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

BMI indicates body mass index; FPG, fasting plasma glucose; GBD, Global Burden of Disease; LBW, low birth weight; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UI, uncertainty interval; and YLD, year of life lived with disability or injury.

Source: Data derived from GBD Study 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>106</sup>

**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 YLD, in thousands (95% UI)		Percent change, 1990–2019 (95% UI)	
	1990	2019	1990	2019	Total No. of YLDs	Age-standardized YLD rate
Low back pain	1	1	43 361.65 (30 529.53 to 57 934.97)	63 685.12 (44 999.20 to 85 192.92)	46.87% (43.31% to 50.52%)	-16.34% (-17.12% to -15.55%)
Migraine	2	2	26 863.35 (3969.24 to 61 445.23)	42 077.67 (6418.38 to 95 645.21)	56.64% (52.61% to 62.08%)	1.54% (-4.43% to 3.27%)
Age-related and other hearing loss	5	3	22 008.10 (14 914.22 to 31 340.37)	40 235.30 (27 393.19 to 57 131.94)	82.82% (75.22% to 88.94%)	-1.82% (-3.65% to -0.14%)
Other musculoskeletal disorders	7	4	16 608.89 (11 264.34 to 23 176.10)	38 459.70 (26 253.49 to 53 553.79)	131.56% (124.6% to 139.54%)	32.24% (28.82% to 36.45%)
Major depressive disorder	4	5	23 461.28 (16 026.05 to 32 502.66)	37 202.74 (25 650.21 to 51 217.04)	58.57% (53.61% to 62.96%)	-2.83% (-4.06% to -1.63%)
Type 2 diabetes	10	6	11 626.63 (7964.90 to 15 799.45)	35 150.63 (23 966.55 to 47 810.13)	202.33% (197.13% to 207.63%)	50.23% (48.08% to 52.22%)
Anxiety disorders	6	7	18 661.02 (12 901.15 to 25 547.29)	28 676.05 (19 858.08 to 39 315.12)	53.67% (48.76% to 59.06%)	-0.12% (-0.95% to 0.74%)
Dietary iron deficiency	3	8	25 069.79 (16 835.78 to 36 058.21)	28 534.68 (19 127.59 to 41 139.28)	13.82% (10.49% to 17.17%)	-16.39% (-18.72% to -14%)
Neck pain	9	9	12 393.48 (8128.87 to 17 740.32)	22 081.32 (14 508.24 to 31 726.93)	78.17% (69.45% to 87.06%)	-0.34% (-2.47% to 1.85%)
Falls	8	10	12 639.31 (8965.44 to 17 334.90)	21 383.29 (15 161.79 to 29 501.22)	69.18% (65.42% to 73.71%)	-7% (-8.56% to -5.35%)
Chronic obstructive pulmonary disease	13	11	10 472.74 (8682.19 to 11 830.68)	19 837.47 (16 596.49 to 22 441.73)	89.42% (85.38% to 93.59%)	-4.85% (-6.64% to -2.98%)
Endocrine, metabolic, blood, and immune disorders	11	12	11 022.44 (7513.64 to 15 340.32)	18 000.31 (12 249.60 to 24 962.91)	63.31% (59.14% to 67.48%)	-4.64% (-6.09% to -3.38%)
Other gynecological diseases	12	13	10 812.95 (7041.93 to 15 340.80)	16 382.52 (10 628.96 to 23 352.28)	51.51% (48.55% to 54.4%)	-9.37% (-11.11% to -7.59%)
Schizophrenia	14	14	9131.34 (6692.14 to 11 637.63)	15 107.25 (11 003.87 to 19 206.79)	65.44% (62.36% to 68.86%)	-0.56% (-1.57% to 0.38%)
Ischemic stroke	18	15	64 994.45 (4626.50 to 8367.19)	13 128.53 (9349.92 to 16 930.38)	101.99% (97.41% to 106.95%)	0.07% (-1.76% to 1.95%)
Osteoarthritis knee	25	16	5184.78 (2569.34 to 10 565.52)	11 534.02 (5719.12 to 23 489.98)	122.46% (120.76% to 124.08%)	7.8% (7.1% to 8.44%)
Diarrheal diseases	16	17	8035.21 (5544.86 to 11 122.17)	11 030.29 (7631.54 to 15 146.75)	37.27% (33.79% to 41.16%)	-2.63% (-4.19% to -1.02%)
Alcohol use disorders	17	18	7875.53 (5287.35 to 11 122.36)	10 732.01 (7253.40 to 15 212.46)	36.27% (31.35% to 41.08%)	-15.49% (-16.83% to -14.07%)
Asthma	15	19	8832.45 (5776.18 to 13 071.58)	10 196.26 (6654.65 to 15 061.36)	15.44% (12.66% to 18.69%)	-23.4% (-26.63% to -20.2%)
Neonatal PTB	26	20	5054.73 (3854.95 to 6433.30)	9673.88 (7598.43 to 12 021.19)	91.38% (75.26% to 106.94%)	43.44% (31.94% to 54.79%)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; PTB, preterm birth; UI, uncertainty interval; and YLD, year of life lived with disability or injury.

Source: Data derived from GBD Study 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>107</sup>

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# Circulation

### 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 combustible tobacco use or inhaled nicotine delivery system use (e-cigarettes or vaping) and secondhand smoke exposure to have adverse effects on CVH in Life's Essential 8.<sup>2</sup> Unless otherwise stated, throughout the rest of this chapter, we report tobacco use and smoking estimates from the NYTS<sup>3</sup> for adolescents and from the NHIS<sup>4</sup> for adults ( $\geq 18$  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>3</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 and nicotine 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 here 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 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

### Prevalence

#### Youth

(See Chart 3-1)

- Prevalence of cigarette use in the past 30 days for middle and high school students by sex and race and ethnicity in 2021 is shown in Chart 3-1.
- In 2021<sup>7</sup>:
  - 34.0% (95% CI, 31.6%–36.5%) of high school students (corresponding to 5.2 million users) and 11.3% (95% CI, 9.8%–13.0%) of middle school students (corresponding to 1.3 million users) reported ever use of any tobacco product; 13.4% (95% CI, 11.8%–15.2%) of high school students (corresponding to 2.1 million users) and 4.0% (95% CI, 3.3%–4.8%) of middle school students (corresponding to 470 000 users) reported current (past 30-day) tobacco product use. Of all high school students, 1.9% (95% CI, 1.5%–2.4%; corresponding to 280 000 users), and of all middle school students, 1.0% (95% CI, 0.8%–1.4%; corresponding to 120 000 users), smoked cigarettes in the past 30 days.
  - 2.1% (95% CI, 1.7%–2.6%) of high school students (310 000 users) and 0.6% (95% CI, 0.4%–0.8%) of middle school students (60 000 users) used cigars in the past 30 days.
  - 1.2% (95% CI, 0.8%–1.6%) of high school students (170 000 users) and 0.6% (95% CI, 0.4%–0.9%) of middle school students (60 000) used smokeless tobacco in the past 30 days.
  - 1.2% (95% CI, 0.9%–1.6%) of high school students (180 000 users) and 0.4% (95% CI, 0.2%–0.6%) of middle school students (40 000 users) used hookah in the past 30 days.
- Of youth who smoked cigarettes in the past 30 days in 2021, 18.9% (95% CI, 13.6%–25.7%) of middle and high school students (corresponding to 70 000 users) reported smoking cigarettes on 20 to 30 days of the past 30 days.<sup>8</sup>
- In 2021, 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 1.8% (95% CI, 1.4%–2.2%) in NH White youth compared with 1.0% (95% CI, 0.6%–1.6%) in NH Black youth and 1.5% (95% CI, 1.1%–2.0%) in Hispanic youth. For cigars, the respective percentages were 1.4% (95% CI, 1.1%–1.8%), 3.1% (95% CI, 2.4%–4.1%), and 0.9% (95% CI, 0.7%–1.2%). For hookah use, the prevalence among NH Black youth was 2.2% (95% CI, 1.4%–3.4%) compared with 0.5% (95% CI, 0.4%–0.7%) in NH White youth and 1.0% (95% CI, 0.6%–1.5%) in Hispanic youth.<sup>9</sup>
- The percentage of high school (11.3% or 1 720 000 users) and middle school (2.8% or 320 000 users) students who used e-cigarettes in the past 30 days

exceeded the proportion using cigarettes in the past 30 days in 2021 (Chart 3-1).

## Adults

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

- According to the NHIS 2020 data, among adults  $\geq 18$  years of age<sup>10</sup>:
  - 12.5% (95% CI, 11.9%–13.0%) of adults reported cigarette use every day or some days.
  - 14.1% (95% CI, 13.3%–14.9%) of males and 11.0% (95% CI, 10.3%–11.6%) of females reported cigarette use every day or some days.
  - 7.4% of those 18 to 24 years of age, 14.1% of those 25 to 44 years of age, 14.9% of those 45 to 64 years of age, and 9.0% of those  $\geq 65$  years of age reported cigarette use every day or some days.
  - 27.1% of NH American Indian or Alaska Native adults, 14.4% of NH Black adults, 8.0% of NH Asian adults, 8.0% of Hispanic adults, and 13.3% 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 20.2% of people with  $<\$35\,000$  income compared with 14.1% of those with an income of \$35 000 to \$74 999, 10.5% of those with an income of \$75 000 to \$99 999, and 6.2% of those with an income  $\geq \$100\,000$ .
  - In adults  $\geq 25$  years of age, the percentage reporting current cigarette use was 21.5% for those with  $<12$  years of education, 32.0% in those with a General Educational Development high school equivalency, 17.6% among those with a high school diploma, 14.4% among those with some college, 12.7% among those with an associate's degree, and 5.6% among those with an undergraduate degree compared with 3.5% among those with a graduate degree.
  - 16.1% of lesbian/gay/bisexual individuals were current smokers compared with 12.3% of heterosexual/straight individuals.
  - By region, the prevalence of current cigarette smokers was highest in the Midwest (15.2%) and South (14.1%) and lowest in the Northeast (10.4%) and West (9.0%).
- According to data from BRFSS 2020, the state with the highest age-adjusted percentage of current cigarette smokers was West Virginia (23.6%). The state with the lowest age-adjusted percentage of current cigarette smokers was Utah (8.2%; Chart 3-2).<sup>11</sup>
- In 2020, smoking prevalence was higher among adults  $\geq 18$  years of age who reported having a disability or activity limitation (19.8%) than among those reporting no disability or limitation (11.8%).<sup>10</sup>

- Among individuals who reported cigarette use every day or some days, 21.4% reported having regular feelings of anxiety compared with 11.3% who reported no regular feelings of anxiety; 26.9% reported having regular feeling of depression compared with 11.8% who reported having no regular feelings of depression.<sup>10</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>12</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>11</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>13</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>13</sup>
- Overall, for individuals 12 to 17 years of age, use of tobacco products in the past month declined from 21.1% to 18.7% between 2019 and 2020, and tobacco product use in the past year declined from 26.2% to 23.3% during the same time period (2020 NSDUH; Tables 6.19B and 6.18B, respectively).<sup>13</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>14</sup>

## Lifetime Risk

### Youth

- Per NSDUH data for individuals 12 to 17 years of age, overall, the lifetime use of tobacco products has changed 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>13</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>13</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>13</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 during the same years was 60.3% and 59.5%, respectively (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>13</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>13</sup>

## Secular Trends

### Youth

#### (See Chart 3-4)

- 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>13,15</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>13,16</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 CHD death rate.<sup>17</sup>
- On the basis of weighted NHIS 2019 data, 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>18</sup>
- According to data from the BRFSS, the overall prevalence of e-cigarette use nonsignificantly increased from 4.3% to 4.8% ( $P=0.18$ )<sup>19</sup> between 2016 and 2018 in US adults. Increases in e-cigarette use over this period were significant for middle-aged adults 45 to 54 years of age (from 3.9% in 2016 to 5.2% in 2018;  $P=0.004$ ), females (from 3.3% in 2016 to 4.3% in 2018;  $P<0.001$ ), and former smokers (from 5.2% in 2016 to 7.9% in 2018;  $P=0.02$ ).<sup>19</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>20</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>21</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>20</sup>
- Among the US Black population, cigarette use is associated with elevated measures of subclinical PAD in a dose-dependent manner whereby those who self-reported smoking  $\geq 20$  cigarettes per day and higher pack-years had higher odds of subclinical

- PAD compared with those who self-reported smoking 1 to 19 cigarettes per day. Current smokers had an increased adjusted odds of ABI<1 (OR, 2.2 [95% CI, 1.5–3.3]) compared with never-smokers.<sup>22</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>23</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>24</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>25</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>24,26</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>27</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 an increased risk of HF.<sup>28</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>29</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>30</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>31</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>32</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>33</sup>
  - The long-term CVD risks associated with e-cigarette use are not known because of a lack of longitudinal data.<sup>34,35</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>36</sup> In addition, daily and some-day use of e-cigarettes may be associated with MI and CHD.<sup>37,38</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>38</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>39</sup>
- In a 2-sample mendelian randomization study that examined the causal effect of 12 lifestyle risk factors on the risk of stroke, genetically predicted lifetime smoking was associated with ischemic (OR, 1.23 [95% CI, 1.10–1.39]) and large artery (OR, 1.72 [95% CI, 1.26–2.36]) stroke.<sup>40</sup> In another mendelian randomization study, genetic liability to smoking was associated with 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];  $P_{\text{interaction}}=0.04$ ).<sup>41</sup>

## Family History and Genetics

- Genetic variation contributes to smoking initiation, smoking regularity, nicotine dependence, and smoking cessation, among other smoking traits. Twin studies have estimated heritability as large as 70% for the transition from regular smoking to nicotine dependence<sup>42</sup> and  $\approx$ 50% for other smoking measures.<sup>43,44</sup> A much smaller fraction (8.6%) of variation in nicotine dependence is explained by genetic variation in commonly occurring SNPs,<sup>45</sup> although genetic variation explains higher proportions of phenotypic variance for smoking initiation (18%) and smoking cessation (12%).<sup>46</sup>
- GWASs have identified loci associated with smoking initiation, heaviness of smoking, smoking regularity, and smoking cessation. In analyses of up to 1.2 million participants, common and rare variants in 298 independent loci were identified.<sup>47</sup> Highlights of this study include identification of novel associations between  $\geq$ 1 smoking phenotypes with central nervous system-expressed nicotinic receptor genes. Loci underlying reward-related learning and memory systems, particularly the neurotransmitter glutamate, also were identified for smoking initiation phenotypes.
- Genetic loci underlying nicotine dependence also have been identified; a GWAS of >58 000

smokers of European and African ancestry identified 5 genome-wide significant loci, including 2 loci unique to nicotine dependence at *NAGI2/GNAI1* and *TENM2*.<sup>45</sup>

- GRSSs for age at smoking initiation, number of cigarettes per day, smoking cessation, and smoking initiation explain ≈1% to 4% of phenotypic variation.<sup>47</sup>
- The genetic architecture of smoking shares similarities with alcohol dependence<sup>48</sup> and CAD.<sup>49</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>50</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 used repeated cross-sectional, statewide surveys of adolescents in Minnesota in 2016 and 2019 across a range of tobacco products (including any tobacco, cigarettes, cigars, e-cigarettes, hookah, chewing tobacco, flavored tobacco, and multiple products).<sup>51</sup> Eighth and ninth grade students exposed to Tobacco 21 laws had significantly lower odds of tobacco use than unexposed students in using the following: any tobacco (aOR, 0.80 [95% CI, 0.74–0.87]), cigarettes (aOR, 0.81 [95% CI, 0.67–0.99]), e-cigarettes (aOR, 0.78 [95% CI, 0.71–0.85]), flavored tobacco (aOR, 0.79 [95% CI, 0.70–0.89]), and dual/polytobacco (aOR, 0.77 [95% CI, 0.65–0.92]).
  - In Massachusetts, investigators examined the associations between county-level Tobacco 21 laws and 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>52</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>53</sup>
- In addition, in several towns in which Tobacco 21 laws were enacted before federal legislation, reductions of up to 47% in smoking prevalence among high school students have been reported.<sup>54</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>54</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 City, KS, and Kansas City, MO) passed legislation setting the minimum age for the purchase of tobacco to 21 years.<sup>55</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>56</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>57</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>58</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>59</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>60</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>58</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>58</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>61,62</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>63</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>61</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 (HR, 0.61 [95% CI, 0.49–0.76]). However, former smokers' CVD risks remained significantly higher than risks for never-smokers beyond 5 years, and possibly for 25 years, after smoking cessation.<sup>64</sup>
  - Among 726 smokers included in the Wisconsin Smokers Health Study, smoking cessation was associated with less progression of carotid plaque (mean change, 0.093 mm [SD, 0.0094]) but not IMT.<sup>65</sup>
  - Cessation medications (including sustained-release bupropion, varenicline, nicotine gum, lozenge, nasal spray, and patch) are effective for helping smokers quit.<sup>66,67</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>68</sup>
- The EAGLES trial<sup>69</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>69</sup>
- Extended use of a nicotine patch (24 compared with 8 weeks) has been demonstrated to be safe and efficacious for abstinence (OR, 1.70 [95% CI, 1.03–2.81];  $P=0.04$ ) in randomized clinical trials.<sup>70</sup>
- An RCT demonstrated the effectiveness of individual- and group-oriented financial incentives for tobacco abstinence (abstinence rate range, 9.4%–16.0% with different incentive group versus 6.0% for usual care;  $P<0.05$  for all comparisons) through at least 12 months of follow-up.<sup>71</sup>
- In addition to medications, smoke-free policies, increases in tobacco prices, cessation advice from health care professionals, quit lines, and other counseling have contributed to smoking cessation.<sup>58,72</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>73</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>74</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>75</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>76</sup>
- In a double-blind, 2×2 factorial randomized clinical trial, patients were randomized to 1 of 4 medication groups: varenicline monotherapy for 12 weeks, varenicline plus nicotine patch for 12 weeks, varenicline monotherapy for 24 weeks, or varenicline plus nicotine patch for 24 weeks.<sup>77</sup> Results demonstrated that there were no significant differences in 7-day point prevalence abstinence at 52 weeks among those treated with combined varenicline plus nicotine patch therapy versus varenicline monotherapy or among those treated for 24 weeks versus 12 weeks.
- An RCT comparing combined treatment with varenicline and nicotine patch against placebo and nicotine patch for smoking cessation among smokers who drink heavily showed that combination treatment led to higher smoking cessation rates (44% versus 27.9%;  $P=0.04$ ) and lower likelihood of relapse (HR, 0.62 [95% CI, 0.40–0.96];  $P=0.03$ ).<sup>78</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, ≈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>79</sup> Overall mortality among US smokers is 3 times higher than that for never-smokers.<sup>61</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>17,80</sup>
- Recent analyses from multiple cycles of the Tobacco Use Supplements to the Current Population Survey (1992–1993, 1995–1996, 1998–1999, 2000, 2001–2002, 2003, 2006–2007, or 2010–2011) show that current daily (HR, 2.32 [95% CI, 2.25–2.38]) and lifelong nondaily (HR, 1.82 [95% CI, 1.65–2.01]) cigarette smokers had higher all-cause mortality risks compared with never-smokers.<sup>81</sup>
- Harmonized tobacco use data from adult participants in the 1991, 1992, 1998, 2000, 2005, and 2010 NHIS show that daily smokeless tobacco use (HR, 1.41 [95% CI, 1.20–1.66]) and daily cigar

smoking (HR, 1.52 [95% CI, 1.12–2.08]) were associated with a higher mortality risk compared with no tobacco use.<sup>82</sup>

- Increased CVD mortality risks exist among daily (HR, 1.47 [95% CI, 1.40–1.54]) and nondaily (HR, 1.24 [95% CI, 1.11–1.39]) cigarette smokers compared with never tobacco smokers<sup>83</sup> and 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>84</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>85</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>86</sup>
- If current smoking trends continue, 5.6 million US children will die of smoking prematurely during adulthood.<sup>20</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 in the United States only around 2007, there are currently >450 e-cigarette brands and vaping products on the market, with sales in the United States showing dramatic increases from 2015 (\$304 million) through 2018 (\$2 billion).<sup>87–89</sup> Juul came on the market in 2015 and has rapidly became one of the most popular vaping products sold in the United States.<sup>90</sup> The popularity of 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>91</sup> Besides e-cigarettes and Juul, electronic hookahs (ie, electronic water pipes) are a new category of vaping devices patented by Philip Morris in 2019.<sup>92,93</sup> Unlike e-cigarettes and Juul, electronic hookahs are used through traditional water pipes, allowing the flavored aerosol to pass through the water-filled bowl before being inhaled.<sup>94</sup> The popularity of electronic hookahs is driven in part by unsubstantiated claims that the presence of water “filters out toxins,” rendering electronic hookahs as healthier tobacco alternatives.<sup>95,96</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>97</sup>
- Current e-cigarette user prevalence for 2017 in the United States is shown in Chart 3-3.
- The 2021 NYTS was fully conducted amid the unprecedented COVID-19 pandemic. Because participants were allowed to participate in classrooms, at home, or at some other place, because of potential underreporting of tobacco and nicotine product use behaviors by location, estimates from the 2021 NYTS are not to be compared with previous years in which surveys were conducted primarily on school campuses. According to the 2021 NYTS data<sup>7</sup>:
  - E-cigarettes were the most commonly used tobacco products in youth: Ever use of e-cigarettes was reported by 7.3% (860 000) of middle school and 28.9% (4.4 million) of high school students. In the past 30 days, 2.8% (320 000) of middle school and 11.3% (1.7 million) of high school students reported current e-cigarette use (Chart 3-1).
  - Daily use was 27.6% among current high school e-cigarette users and 8.3% among current middle school e-cigarette users.<sup>98</sup> Among high school students, rates of current use were slightly higher among females (11.9%) than males (10.7%) and most pronounced among NH White students (14.5%).<sup>7</sup> In middle school students, current use rates among females were 3.2% compared with 2.3% among males, with higher rates among Hispanic (3.9%) compared with NH White (2.6%) students.
  - Among current e-cigarette users, 85.8% of high school users and 79.2% of middle school users used flavored e-cigarettes, with fruit being the most common flavor type used.
  - Among both middle and high school current e-cigarette users, the most commonly used e-cigarette device type was disposables, followed by prefilled or refillable pods or cartridges and tanks or mod systems.
- 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>99</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>3,8</sup>
- In 2021, 70.3% of US middle and high school students were exposed to e-cigarette marketing (advertisements or promotions).<sup>7</sup> Among adolescents and young adults, a systematic review suggested an association between exposure to e-cigarette advertisement and lower harm perceptions of e-cigarettes, intention to use e-cigarettes, and e-cigarettes trial.<sup>100</sup>
- In 2020, the prevalence of current e-cigarette use in adults, defined as use every day or on some days, was 3.7% according to data from the NHIS. The prevalence of current e-cigarette use was highest among males (4.6%), individuals 18 to 24 years of age (9.4%), and those reporting severe generalized anxiety disorder (10.1%).<sup>10</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 underrepresented individuals.<sup>101,102</sup> Data from 2017 and 2018 data sets show that the prevalence of current e-cigarette use among sexual and gender underrepresented adults was 13.0% (95% CI, 12.0%–14.2%) versus 4.8% (95% CI, 4.6%–4.9%) among heterosexuals.<sup>101</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>102</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 electronic hookah use.<sup>103</sup> Among adults >18 years of age, 4.6% reported ever electronic 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>104</sup> including volatile organic compounds.<sup>105,106</sup> However, nicotine levels have been found to be consistent across long-term cigarette and long-term e-cigarette users.<sup>36,107</sup>
- E-cigarette use has a significant cross-sectional association with a less favorable perception of physical and mental health and with depression.<sup>108,109</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>110,111</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>112</sup>
- Effective August 8, 2016, the FDA's Deeming Rule prohibited sale of e-cigarettes to individuals <18 years of age.<sup>113</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>114</sup> This policy, however, applies only to cartridge- or pod-based e-cigarette products, defined as "any small, enclosed unit (sealed or unsealed) designed to fit within or operate as part of an electronic nicotine delivery system."<sup>115</sup> Products that would be exempted from this prohibition include self-contained, customizable, or disposable products.
- According to data from the BRFSS 2016 and 2017, e-cigarette use among adults is associated with state-level regulations and policies on 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>116</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>20</sup>
  - Exposure to secondhand smoke increases the RR of stroke by 20% to 30% and is associated

with increased mortality (adjusted mortality rate ratio, 2.11) after a stroke.<sup>117</sup>

- A meta-analysis of 23 prospective and 17 case-control studies of cardiovascular risks associated with secondhand smoke exposure demonstrated an 18%, 23%, 23%, and 29% increased RR for total mortality, total CVD, CHD, and stroke, respectively, in those exposed to secondhand smoke.<sup>118</sup>
- A meta-analysis of 24 studies demonstrated that secondhand smoke can increase risks for PTB by 20%.<sup>119</sup>
- A study using the Framingham Offspring cohort found that there was an 18% increase in AF among offspring for every 1-cigarette pack/d 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>120</sup>
- As of January 27, 2022, 17 states (California, Colorado, Connecticut, Delaware, Hawaii, Massachusetts, Minnesota, New Jersey, New Mexico, New York, North Dakota, Ohio, 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>55,121</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>122</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>123,124</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>17</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/y, 60% of which was paid by public programs (eg, Medicare and Medicaid).<sup>125</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/d.<sup>126</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>127</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>128</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>129</sup>
- From 2012 through 2016, e-cigarette sales significantly increased while national e-cigarette prices significantly decreased,<sup>129</sup> with total e-cigarette unit sales exponentially increasing nearly 300% from 2016 through 2019.<sup>130</sup> Together, these trends highlight the rapidly changing landscape of the US e-cigarette marketplace.<sup>129</sup>
- Despite the morbidity and mortality resulting from tobacco use, Dieleman et al<sup>131</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 Study 2020 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 globally 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>132</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>133</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>134</sup>
- Worldwide, ≈80% of tobacco users live in low- and middle-income countries.<sup>135</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>136</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 titled 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>102,137</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>138</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% (range, 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>139</sup>

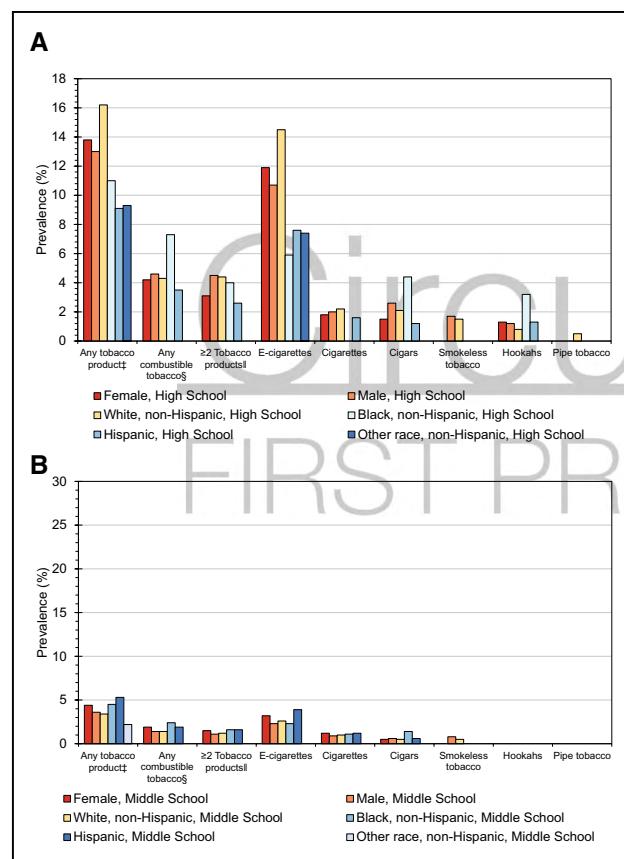
**Table 3-1.** Deaths Caused by Tobacco Worldwide by Sex, 2020

	<b>Both sexes (95% UI)</b>	<b>Males (95% UI)</b>	<b>Females (95% UI)</b>
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)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; PAF, population attributable fraction; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>132</sup>



### Chart 3-1. Prevalence (percent) of tobacco use in the United States in the past 30 days by product,<sup>\*</sup> school level, sex, and race and ethnicity† (NYTS, 2021).

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 (Continued)



**Chart 3-1 Continued.** "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: "During the past 30 days, on how many days did you use chewing tobacco, snuff, or dip, snus, or dissolvable products?" Responses from these questions were combined to derive overall smokeless tobacco use. 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 water pipe?" Past 30-day use of pipe tobacco (not hookahs) was determined by asking "In the past 30 days, on how many days did you smoke pipes filled with tobacco?" Because of missing data on the past 30-day use questions, denominators for each tobacco product might be different.

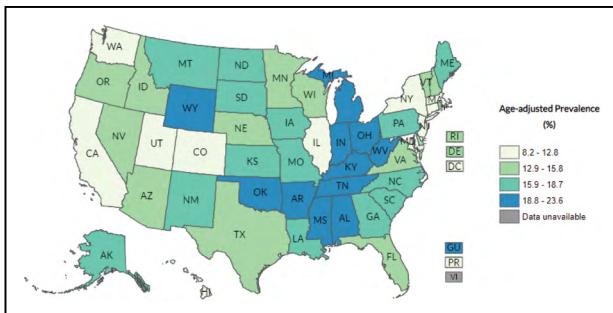
†Black people, White people, and people of other race are non-Hispanic; Hispanic people could be of any race.

‡In 2021, any tobacco product use was defined as use of any tobacco product (e-cigarettes, cigarettes, cigars [cigars, cigarillos, or little cigars], smokeless tobacco [chewing tobacco, snuff, or dip, snus, or dissolvable tobacco products], hookahs, pipe tobacco, nicotine pouches, 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 (cigars, cigarillos, or little cigars), hookahs, pipe tobacco, or bidis on ≥1 day during the past 30 days.

||In 2021, multiple tobacco product use was defined as use of ≥2 tobacco products (e-cigarettes, cigarettes, cigars [cigars, cigarillos, or little cigars], smokeless tobacco [chewing tobacco, snuff, or dip, snus, or dissolvable tobacco products], hookahs, pipe tobacco, nicotine pouches, bidis, or heated tobacco products) on ≥1 day during the past 30 days.

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

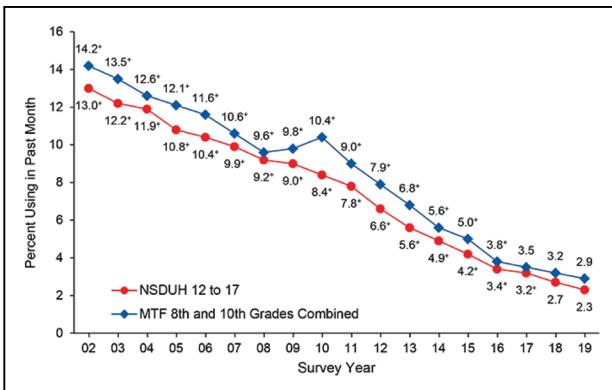


**Chart 3-2. Age-adjusted prevalence (percent) of current cigarette smoking for US adults by state (BRFSS, 2020).**

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.

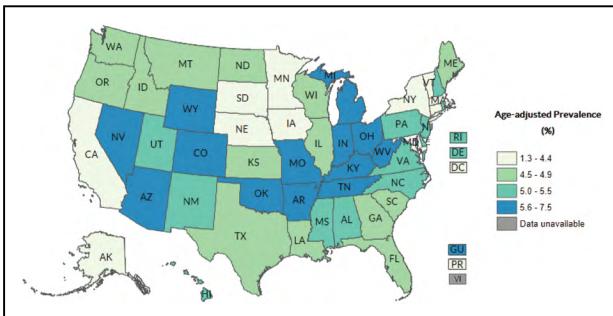
Source: BRFSS prevalence and trends data.<sup>11</sup>



**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>13,15</sup>

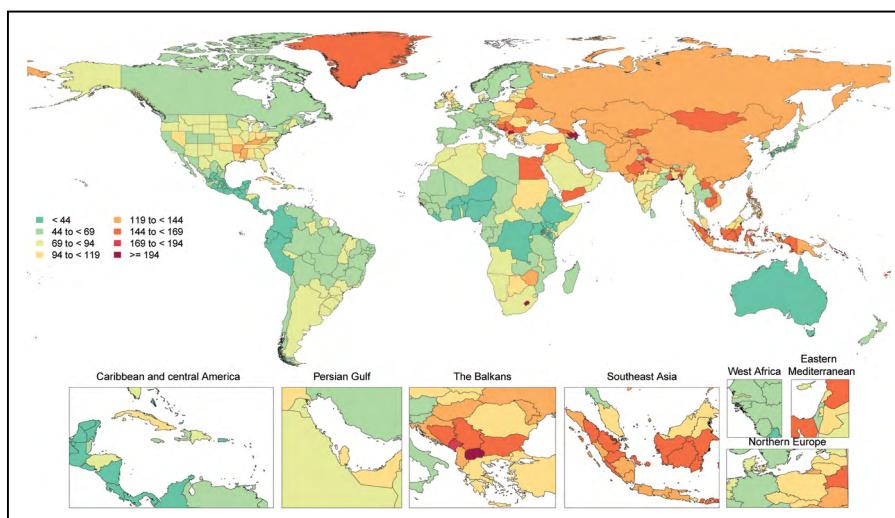


**Chart 3-3. Prevalence (age-adjusted) of current electronic cigarette use, United States (BRFSS, 2017).**

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>11</sup>



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

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>132</sup>

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## 4. PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR

(See Charts 4-1 through 4-10)

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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> The guidelines recommend that adults accumulate at least 150 min/wk of moderate-intensity or 75 min/wk of vigorous-intensity aerobic activity (or an equivalent combination) and perform muscle-strengthening activities at least 2 d/wk.<sup>3</sup> The 2019 CVD Primary Prevention Clinical Practice Guidelines<sup>4</sup> support the aerobic recommendations. For many people, examples of moderate-intensity activities include walking briskly or raking the yard, and examples of vigorous-intensity activities include jogging, carrying loads upstairs, strengthening activities, or shoveling snow. Achieving the PA guideline recommendations is 1 of the AHA's 8 components of ideal CVH for both children and adults.<sup>5</sup>

Globally, the 2020 WHO guidelines supported moderate to vigorous PA across all age groups and abilities.<sup>6</sup> Small increases in moderate-intensity PA or replacing sedentary behavior with light-intensity PA can provide health benefits.<sup>3,6</sup> The WHO guidelines for PA also include recommendations for those living with a disability<sup>7</sup> that are recently supported by other work.<sup>8,9</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>10</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,

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

using a computer), or reading. The 2018 Physical Activity Guidelines for Americans recommends adults should "move more and sit less throughout the day."<sup>3</sup> Globally, the WHO guidelines recommend reducing sedentary behaviors across all age groups and abilities.<sup>6</sup>

### Measuring PA and Sedentary Behavior

Several dimensions (eg, frequency, duration, and intensity) and modes/types (eg, occupational, domestic, transportation, and leisure time) characterize PA.

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, accelerometers). Studies that compare the findings between methods indicate discordance between self-reported and measured PA, with respondents often overestimating their PA compared with device-based measures.<sup>11</sup> Sedentary behavior also has several dimensions (eg, frequency, duration) and modes/types (eg, driving/riding in a vehicle, using a screen, reading) that can be assessed with both self-reported and device-based methods.

### Prevalence and Trends



#### Youth

#### Physical Activity

(See Charts 4-1 and 4-2)

- According to parental report, from 2019 to 2020, the nationwide prevalence of youth who were active for  $\geq 60$  minutes every day of the week was 20.6%.<sup>12</sup> The prevalence was higher for youth 6 to 11 years of age (26.2%) compared with youth 12 to 17 years of age (15.2%; Chart 4-1) and higher for males (23.1%) compared with females (18.0%).
- On the basis of self-report, the 2019 to 2020 nationwide prevalence of youth 6 to 17 years of age who were active  $\geq 60$  minutes every day of the week was 20.6% and by their race and ethnicity was 14.2% for NH Asian, 15.7% for Hispanic, 19.5% for NH Black, 22.5% for NH other, and 23.8% for NH White.<sup>12</sup> The prevalence was higher among English-speaking households (21.7%) compared with households with a primary language other than English (14.0%). 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%.<sup>13</sup> The prevalence was higher in males (30.9%) than females (15.4%) and higher among NH White youth (25.6%) compared with NH Black (21.1%) and Hispanic (20.9%) youth.
- Among high school students nationwide, the prevalence of being physically active for  $\geq 60$  minutes for at least 5 d/wk decreased from 49.5% in 2011 to 44.1% in 2019.<sup>13,14</sup> Similarly, the prevalence of being physically active for  $\geq 60$  minutes on all 7 days

in a week decreased from 28.7% in 2011 to 23.2% in 2019.

- With regard to self-reported muscle-strengthening activities, in 2019, 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 the 12th grade (45.9%) compared with the 9th grade (52.4%).<sup>13,15</sup> More high school males (59.0%) than females (39.7%) reported participating in muscle-strengthening activities on  $\geq 3$  d/wk. The prevalence of participating in muscle-strengthening activities on  $\geq 3$  d/wk decreased from 55.6% in 2011 to 49.5% in 2019.
- The proportion of youth who met guidelines for both aerobic ( $\geq 60$  minutes on all 7 d/wk) and muscle-strengthening ( $\geq 3$  d/wk) PA decreased from 21.9% in 2011 to 16.5% in 2019 (Chart 4-2).<sup>13</sup> This decline also occurred for males, females, NH White youth, and NH Black youth.
- Using 1 week of wrist-worn accelerometry data from 6030 participants 3 to 19 years of age in the NHANES National Youth Fitness Survey 2012 and NHANES 2011 to 2014 showed that the median daily MIMS units (eg, indicator of total volume of PA) peaked at 6 years of age for both males and females.<sup>16</sup> In contrast, the lowest median daily MIMS units occurred at 17 years of age in males and 18 years of age in females. Generally, for both males and females, MIMS units were successively higher from 3 to 6 years of age, declined from 6 to  $\approx 15$  years of age, and then plateaued.

### **Physical Education Classes and Organized Sports**

- In 2019, 25.9% of high school students attended physical education classes in school daily (28.9% of males and 22.8% of females).<sup>13</sup>
- Daily physical education class participation was lower with successively higher grades from the 9th grade (34.7%) through the 12th grade (19.7%).<sup>15</sup> Daily physical education for 9th to 12th graders was higher among Hispanic youth (29.9%) compared with NH Black (23.8%) and NH White (24.3%) youth.<sup>13</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>14</sup> However, the prevalence of attending physical education classes on all 5 days of the week decreased from 41.6% in 1991 to 25.9% in 2019.

### **Organized Sports**

- In 2019, 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 females and 60.2% of males); this number was lower in

12th grade (49.8%) compared with 9th grade (61.9%).<sup>13,15</sup>

- The prevalence of high school students playing  $\geq 1$  team sports in the past year did not substantively change between 1999 (55.1%) and 2019 (57.4%).<sup>14</sup>

### **Sedentary Behavior**

(See Charts 4-3 and 4-4)

- Nationwide in 2019, 46.1% of high school students used a computer, tablet, or smartphone for activities other than schoolwork (eg, video games, texting, social media) for  $\geq 3$  h/d on an average school day (Chart 4-3).<sup>15</sup> The prevalence differed by race and ethnicity and was high among both males (47.5%) and females (44.6%).
- Nationwide in 2019, 19.8% of high school students watched television  $\geq 3$  h/d (Chart 4-4).<sup>15</sup> The prevalence varied by race and ethnicity (highest among American Indian/Alaska Native students, followed by Black, Hispanic, White, and Asian students) and was higher among males than females.
- Among high school students in 2019, the prevalence of computer, tablet, or smartphone use for activities other than schoolwork or using a computer  $\geq 3$  h/d increased from 22.1% in 2003 to 46.1% in 2019.<sup>14</sup> However, watching television for  $\geq 3$  h/d decreased from 42.8% in 1999 to 19.8% in 2019.

### **Adults**

(See Charts 4-5 through 4-8)

#### **Physical Activity**

- According to NHIS 2018, the age-adjusted proportion of adults who reported meeting the aerobic PA guidelines for Americans ( $\geq 150$  min/wk of moderate PA,  $\geq 75$  min/wk of vigorous PA, or an equivalent combination) through leisure-time activities was 54.2% (Chart 4-5).<sup>17</sup> 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>17</sup>
- From BRFSS 2017 to 2020, the prevalence of self-reported physical inactivity varied by geography, ranging from the lowest in Colorado (17.7%), Utah (18.2%), and Washington (18.4%) to the highest in Kentucky (32.5%), Mississippi (33.2%), and Puerto Rico (49.4%; Chart 4-6).<sup>18</sup>
- The prevalence of self-reported physical inactivity among adults  $\geq 18$  years of age, overall and by sex, decreased from 1998 to 2018 (Chart 4-7).<sup>17</sup>
- 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>19</sup> The percentage of US adults who reported meeting the aerobic guidelines increased from 43.5% in 2008 to 54.2% in 2018.<sup>19</sup> The increase in those meeting the aerobic guidelines may be explained in part by the increased prevalence in self-reported walking for transportation, from 28.4% to 31.7%, and for leisure, from 42.1% to 52.1%, between 2005 and 2015.<sup>20</sup>

- 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 addition, the prevalence of engaging in any activity or meeting aerobic recommendations among adults  $\geq 18$  years of age was higher among those with higher household incomes compared with those with middle or lower household incomes across White, Black, and Hispanic groups.<sup>21</sup>
- 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>22</sup>
- Using 1 week of wrist-worn accelerometry data from 8675 participants  $\geq 20$  years of age in NHANES 2011 to 2014 showed that the median daily MIMS units (eg, indicator of total volume of PA) peaked at 20 years of age for males and 36 years of age for females.<sup>16</sup> For both males and females, PA levels represented by MIMS were the lowest at 80 years of age.

### Sedentary Behavior

- According to NHANES, mean daily sitting time increased by 19 min/d from 2007 to 2008 (332 min/d) to 2017 to 2018 (351 min/d).<sup>23</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 a computer), higher than in January 2018 (11 hours 6 minutes) and January 2019 (11 hours 27 minutes).<sup>24</sup> These habits affect time available for PA and contribute to sedentary behavior.

## COVID-19 Pandemic

### Impact on PA

- From a nonrepresentative sample of US parents of youth 5 to 13 years of age, there was indication that PA declined from February 2020 (before COVID-19) to April/May 2020.<sup>25</sup>
- Activity tracker companies 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, ranging from on average 4% declines in Australia to 38% declines in Spain.<sup>26</sup> Steps from users from the United States declined on average by 12%. 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>27</sup> The total number of steps decreased by 7.3% from 2019 to 2020 for Garmin users.<sup>28</sup> It is important to note that those who own and wear activity trackers are not representative of the general population.<sup>29,30</sup>

- In a nationally representative sample of 3829 US adults surveyed between March 19 and April 9, 2020, 30.4% of respondents reported less PA during the pandemic, whereas 20.3% reported more PA, 42.7% reported no change, and 6.6% reported not engaging in PA.<sup>31</sup> Among those reporting PA, the location of the PA was mostly inside their home (61.1%), around their neighborhood (51.1%), or at a park or public trail (16.7%).
- In a nationally representative sample of 2011 US adults conducted June 17–29, 2020, respondents reported a 10.4% decrease in local travel relative to prepandemic levels, including public transit use, personal vehicle use, and walking.<sup>32</sup> However, there was no change in reported bicycle use when the prepandemic period was compared with the pandemic period.
- Longitudinal data from the Understanding America Study indicated that self-reported exercise frequency decreased between April 2020 and January 2021 and then increased from January to July 2021.<sup>33</sup> More restrictive state-level COVID-19 policies were inversely associated with exercise frequency between April 2020 and December 2020.
- Among 311 patients with implanted cardiac devices and most with HF (92.2%), PA data from the device were compared for 4 weeks before the lockdown and 4 weeks after the lockdown in the United Kingdom.<sup>34</sup> A reduction of 20.8 active min/d was observed when the postlockdown and prelockdown periods were compared.
- The COVID-19 pandemic affected walking and bicycling for transportation and leisure through environmental and policy changes designed to limit or accommodate shifting users such as on roads, trails, and transit and in public parks.<sup>35,36</sup> The short- and long-term impacts of the environmental and policy changes on representative patterns of walking and bicycling are not yet known.

### Association of PA With COVID-19 Risks

- Among 48 440 adult patients with a COVID-19 diagnosis between January and October 2020, those who consistently did not meet PA recommendations (0–10 min/wk for each assessment during the study period) had a greater odds of hospitalization (OR, 2.26 [95% CI, 1.81–2.83]), admission to the ICU (OR, 1.73 [95% CI, 1.18–2.55]), and death (OR, 2.49 [95% CI, 1.33–4.67]) compared with those who consistently met PA recommendations (>150 min/wk of PA for each assessment during the study period).<sup>37</sup> The odds of hospitalization (OR, 1.20 [95% CI, 1.10–1.32]), admission to the ICU (OR, 1.10 [95% CI, 0.93–1.29]), and death (OR, 1.32 [95% CI, 1.09–1.60]) were also higher for those doing some PA (11–149 min/wk or those with variability for each assessment during the study period) compared with those who consistently met PA guidelines.
- In a case-control study, Korean patients (N=6288) who tested positive for severe COVID-19 were compared with age- and sex-matched controls (N=125 772). For every 1-SD-higher MET-min/wk of leisure-time PA, cases had a lower odds of COVID-19 infection (OR, 0.96 [95% CI, 0.93–0.99]) and a lower odds of mortality (OR, 0.65 [95% CI, 0.48–0.88]) compared with controls.<sup>38</sup>

### Risk Factors for PA and Cardiovascular/Metabolic Health

#### Youth

(See Chart 4-9)

- 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>39</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.
- Nationwide in 2019 to 2020, 10.6% of neighborhoods of youth 0 to 17 years of age did not contain any of the 4 health-promoting amenities (eg, parks, recreation centers, sidewalks, and libraries; Chart 4-9).<sup>12</sup> The prevalence of youth living in neighborhoods without any health-promoting amenities varied by race and ethnicity of the child: 4.5% for NH Asian, 6.9% for Hispanic, 7.3% for NH Black, 8.6% for other, and 14.0% for NH White.
- Nationwide in 2019 to 2020, 4.5% of neighborhoods of youth 0 to 18 years of age lived with all 3 detracting elements (eg, litter or garbage on the street or sidewalk, poorly kept or rundown housing, and vandalism such as broken windows and

graffiti; Chart 4-9).<sup>12</sup> The prevalence of youth living in neighborhoods with detracting elements also varied by race and ethnicity of the child: 1.9% for Asian NH, 2.9% for White NH, 5.5% for other NH, 6.2% for Hispanic, and 7.6% for Black NH.

#### Adults

- 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>40</sup>
- 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>41</sup>
- Multisession behavioral counseling can improve PA among those with elevated lipid levels or BP and reduce LDL, BP, adiposity, and cardiovascular events.<sup>42</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.”<sup>43</sup>
- In a meta-analysis of 11 studies investigating the role of exercise among individuals with MetS, aerobic exercise significantly improved DBP ( $-1.6$  mm Hg;  $P=0.01$ ), WC ( $-3.4$  cm;  $P=0.01$ ), fasting glucose ( $-0.15$  mmol/L;  $P=0.03$ ), and HDL-C ( $0.05$  mmol/L;  $P=0.02$ ).<sup>44</sup>
- In a meta-analysis of 38 RCTs of participants with cardiometabolic conditions (eg, prediabetes, diabetes, obesity, CVD), the use of wearable PA trackers was associated with increased levels of PA compared with the control condition of not wearing a PA tracker.<sup>45</sup> A similar review conducted among participants with CVD found that smartphone applications were effective at increasing PA.<sup>46</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–steps/d increase) and MetS (29% reduction in 6-year metabolic score per 2000–steps/d increase).<sup>47</sup>
- In the WHI/OPACH study of 4838 females without physician-diagnosed diabetes, each additional 2000–steps/day increment (as measured by 1 week of hip-worn accelerometry) was associated with a lower hazard for incident diabetes (HR, 0.88 [95% CI, 0.78–1.00]).<sup>48</sup>

#### Risk Prediction

##### Cardiovascular Events Among Adults

- A systematic review reported a favorable dose-response relationship between daily step counts and cardiovascular events (defined as cardiovascular

- death, nonfatal MI, or nonfatal stroke; 8% yearly rate reduction per 2000–steps/d increase).<sup>47</sup>
- In the WHI/OPACH study, 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 risk of CVD (HR, 0.92 [95% CI, 0.85–0.99]).<sup>49</sup> For every 1 hour of daily life movement (eg, standing and moving in a confined space), the HR for CVD was 0.86 (95% CI, 0.80–0.92).<sup>50</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 (ie, ≥13.2 MET-h/wk or a walk at 3 mph for 48 min/day for 5 d/wk) 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>51</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>52</sup>
  - A meta-analysis summarizing 10 studies found that the pooled adjusted risk of VTE was 0.87 (95% CI, 0.79–0.95) when the most physically active group was compared with the least physically active group.<sup>53</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>54,55</sup>
- GWASs in >377 000 individuals have identified 10 loci associated with PA phenotypes, including *CADM2*, *EXOC4*, and *APOE*.<sup>54</sup>
- A GWAS of 91 105 individuals with device-measured PA identified 14 significant loci.<sup>56</sup>
- Multiethnic analysis of >20 000 individuals identified several loci associated with leisure-time PA in individuals of European and African ancestry.<sup>57</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.
- Variants in 9 candidate genes (*ACE*, *CASR*, *CYP19A*, *FTO*, *DRD2*, *CNR1*, *LEPR*, *MC4R*, *NPC1*) have been identified to be associated with PA or

sedentary behavior. However, their replication in larger unbiased GWASs is warranted.<sup>58</sup>

## Awareness, Treatment, and Control

- Exercise and resistance training are recommended for adults after stroke.<sup>59</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>60</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>61</sup>
- A meta-analysis of RCTs reporting on the effects of PA among participants with HF found that the specific features indicative of a more successful intervention included a center-based group-oriented delivery format that combined exercise with behavioral change strategies.<sup>62</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>63</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>64</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>65</sup>
- An umbrella review of 24 systematic reviews of older adults concluded that those who are physically active are at 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>66</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>67</sup>
- In a meta-analysis of 29 prospective observational studies, the RR of HF was lower among those in

higher levels of total PA (RR, 0.74 [95% CI, 0.68–0.81]), leisure-time PA (RR, 0.66 [95% CI, 0.59–0.74]), and cardiorespiratory fitness (RR, 0.31 [HR, 0.19–0.49]).<sup>68</sup> Favorable associations were also found with vigorous activity, occupational activity, and walking and bicycling combined.

- 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]).<sup>69</sup> 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 had higher mortality risk (HR, 1.15 [95% CI, 1.05–1.27]).
- According to NHIS data, the prevalence of meeting the minimal aerobic PA guideline among US adults increased in a step-wise fashion from 1998 to 2000 to 2016 to 2018 for diabetes (31.6% to 43.5%), hypertension (36.6% to 47.6%), CHD (33.5% to 39.6%), stroke (27.5% to 41.1%), and cancer (40.3% to 53.1%).<sup>70</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>71</sup>
- In a prospective cohort study of 3307 individuals with CHD, participants who maintained high PA levels had a lower risk of mortality than those who remained inactive over time (HR, 0.64 [95% CI, 0.50–0.83]).<sup>72</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>73</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, respectively, compared with adults in the lowest category.<sup>74</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 a higher risk of all-cause mortality, stroke, and MI.<sup>75</sup>
- Among participants 40 to 79 years of age in the population-based EPIC–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>76</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>77</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>78</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>79</sup>
- A comprehensive review found that longer time in all-day standing was associated with a lower risk of mortality.<sup>80</sup> However, longer time spent in work-related standing had either adverse or null associations with both subclinical and incident CVD.
- In an analysis of 1718 MESA participants, substituting 30 minutes of sedentary time for sleep, light PA, or moderate to vigorous PA was associated with a more favorable CVH score.<sup>81</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>47,82</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>83</sup>
- In a harmonized meta-analysis of 15 international cohort studies that included 47 471 adults and 3013 deaths, the HR comparing with the lowest quartile of average steps per day was as follows: quartile 2 HR, 0.60 (95% CI, 0.51–0.71), quartile 3 HR, 0.55 (95% CI, 0.49–0.62), and quartile 4 HR, 0.47 (95% CI, 0.39–0.57).<sup>84</sup>
- According to accelerometry data from NHANES 2003 to 2006, if US adults ≥40 years of age increased their moderate to vigorous PA by ≈10 min/d, an estimated 110 000 deaths per year could be prevented.<sup>85</sup>
- In a retrospective observational study from 2014 to 2016, Medicare beneficiaries with an implantable

cardioverter defibrillator who attended cardiac rehabilitation had a lower all-cause mortality risk (HR, 0.76 [95% CI, 0.69–0.85]) at 1 year of follow-up, and differences remained at 2 and 3 years of follow-up.<sup>86</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>87</sup>
- Increasing population levels of PA could increase productivity, particularly through presenteeism, and lead to substantial economic gains.<sup>88</sup>

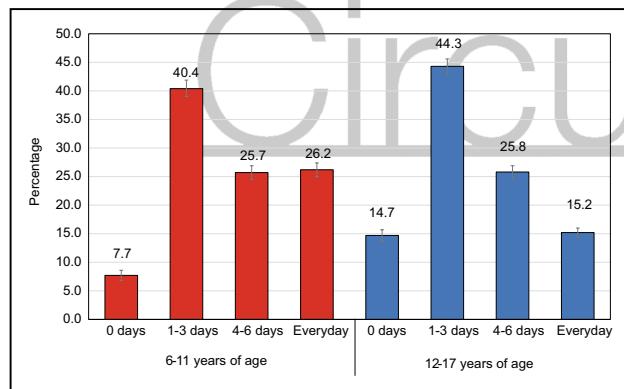
## Global Burden

### (See Chart 4-10)

- 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>89</sup>

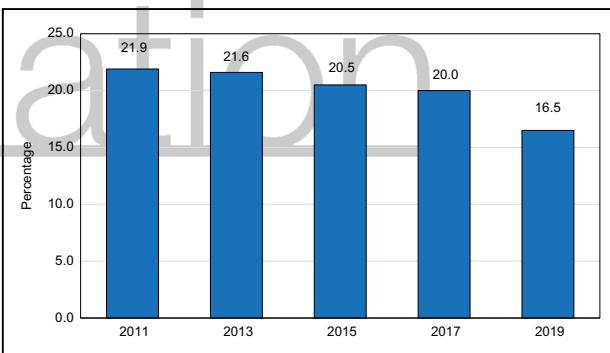
- The GBD 2020 study produces comprehensive and comparable estimates of disease burden for 370 reported causes and 88 risk factors for 204 countries and territories from 1990 to 2020.<sup>90</sup>
  - In 2020, age-standardized mortality rates attributable to low PA were highest in North Africa and the Middle East and southern sub-Saharan Africa (Chart 4-10).
  - 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>91</sup>



**Chart 4-1. Percentage of US youth 6 to 11 and 12 to 17 years of age who were physically active for at least 60 minutes, 2019 to 2020.**

Error bars represent 95% CIs.

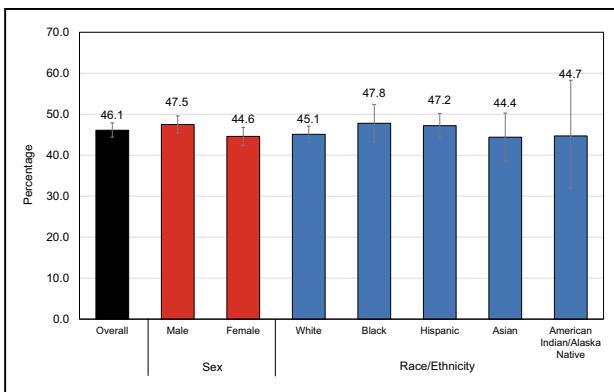
Source: Data derived from National Survey of Children's Health.<sup>12</sup>



**Chart 4-2. Percentage of US youth in grades 9 to 12 who met both aerobic and muscle strengthening PA recommendations, 2011 to 2019.**

PA indicates physical activity.

Source: Data derived from Youth Risk Behavior Survey.<sup>13</sup>

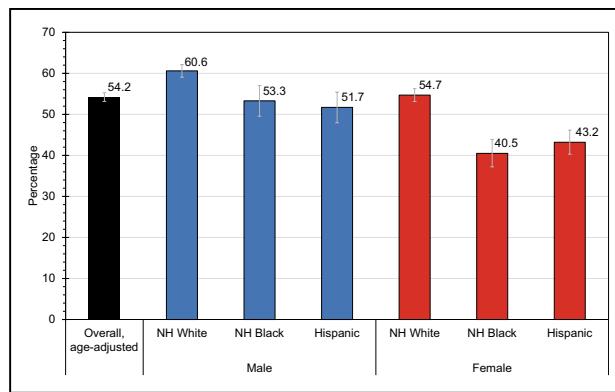


**Chart 4-3. Percentage of US students in grades 9 through 12 who played video or computer games or used a computer\* for ≥3 hours on an average school day, overall and by sex and race and ethnicity, 2019.**

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.

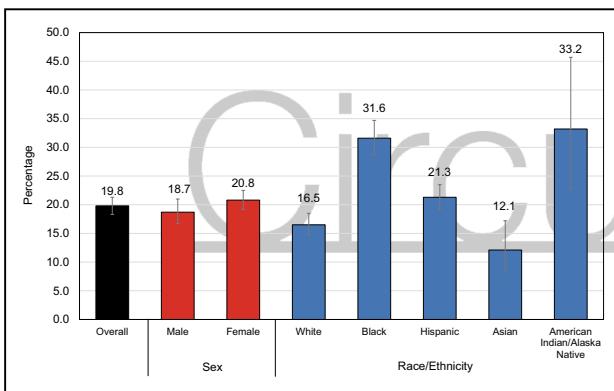
Source: Data derived from Youth Risk Behavior Surveillance System.<sup>92</sup>



**Chart 4-5. Percentage 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<sup>3</sup> 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>17</sup>

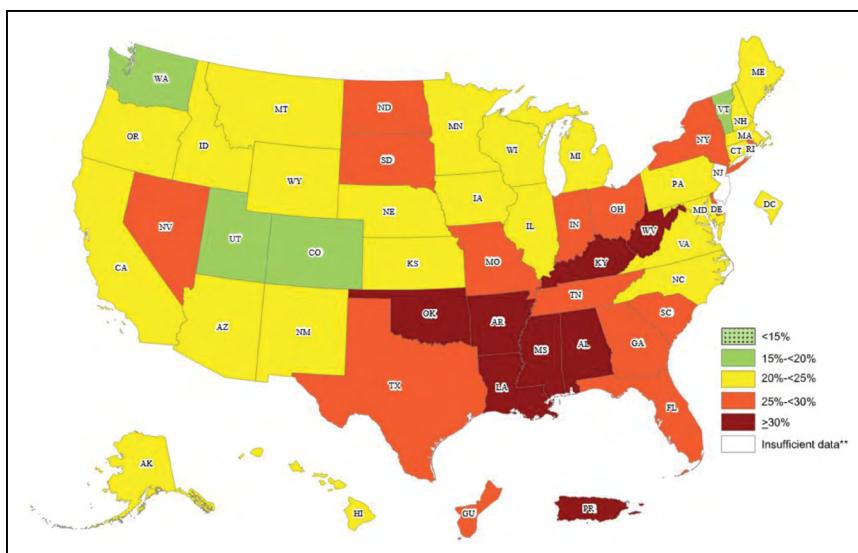


**Chart 4-4. Percentage of US students in grades 9 through 12 who watched television for ≥3 hours on an average school day, overall and by sex and race and ethnicity, 2019.**

Error bars represent 95% CIs.

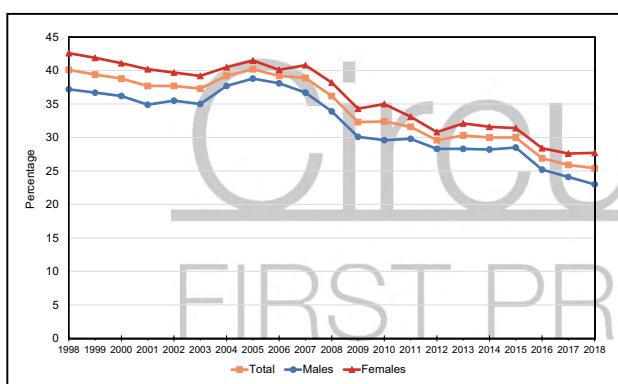
Source: Data derived from Youth Risk Behavior Surveillance System.<sup>92</sup>





**Chart 4-6. Prevalence of self-reported physical inactivity among US adults  $\geq 18$  years of age by state and territory, 2017 to 2020.**

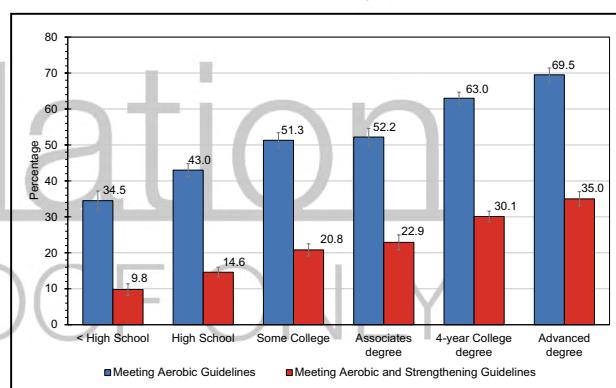
States in white had insufficient data, defined as a sample size  $<50$ , a relative SE  $\geq 30\%$ , or no data in at least 1 year.  
Source: Reprinted from Centers for Disease Control and Prevention, Behavioral Risk Factor Surveillance System.<sup>18</sup>



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

Data are age adjusted to the year 2000 standard population for adults  $\geq 18$  years of age. Physical inactivity is defined as reporting no engagement in leisure-time physical activity in bouts lasting  $\geq 10$  minutes.

Source: Data derived from Healthy People 2020<sup>93</sup> using the National Health Interview Survey.<sup>17</sup>

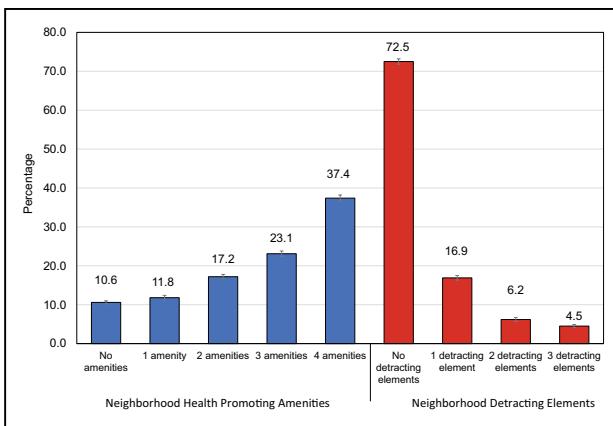


**Chart 4-8. Percentage meeting the aerobic PA guidelines among US adults  $\geq 25$  years of age, by educational attainment, 2018.**

Data are age adjusted to the year 2000 standard population for adults  $\geq 18$  years of age. The 2018 Physical Activity Guidelines for Americans<sup>3</sup> recommend engaging in moderate leisure-time PA for  $\geq 150$  min/wk, vigorous activity for  $\geq 75$  min/wk, or an equivalent combination (eg, aerobic guideline). The 2018 Physical Activity Guidelines for Americans also recommend engaging in muscle-strengthening activities  $\geq 2$  d/wk (eg, muscle-strengthening guideline). Error bars represent 95% CIs.

PA indicates physical activity.

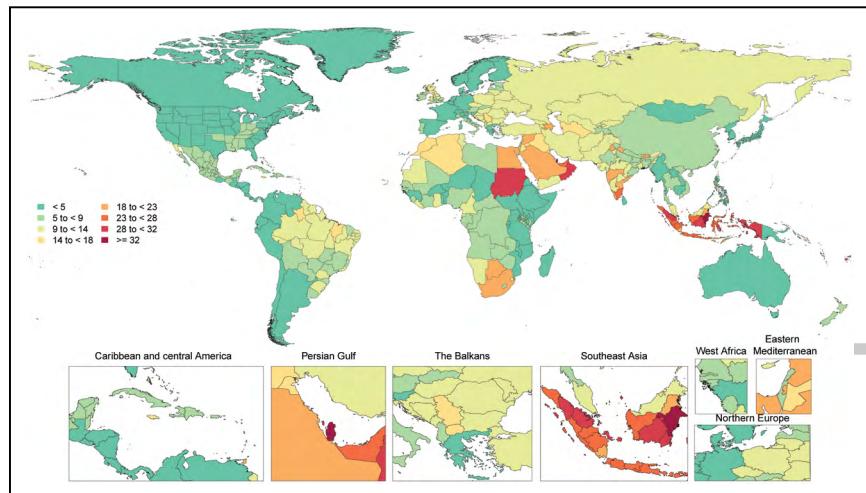
Source: Data derived from Healthy People 2020<sup>93</sup> using the National Health Interview Survey.<sup>17</sup>



**Chart 4-9. Presence of health-promoting amenities and detracting elements in neighborhoods of US youth 0 to 17 years of age, 2019 to 2020.**

Error bars represent 95% CIs. Health-promoting amenities included parks, recreation centers, sidewalks, and libraries. Health-detracting elements included litter or garbage on the street or sidewalk, poorly kept or rundown housing, and vandalism such as broken windows or graffiti.

Source: Data derived from National Survey of Children's Health.<sup>12</sup>



**Chart 4-10. Age-standardized global mortality rates attributable to low PA per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Disease; and PA, physical activity. Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>90</sup>

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# Circulation



## 5. NUTRITION

**See Tables 5-1 through 5-4 and Charts 5-1 through 5-4**

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This chapter highlights national dietary intake and habits with a focus on key foods, nutrients, patterns, and other dietary factors related to cardiometabolic health. It examines current intakes, trends and changes in intakes, and estimated effects on disease to support and further stimulate efforts to monitor and improve dietary habits in relation to CVH.

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

(See Tables 5-1 through 5-3)

On June 29, 2022, the AHA debuted Life's Essential 8, an updated algorithm for quantifying CVH.<sup>1</sup> This update was in response to extensive evidence that gives insights into the strengths and limitations of the original approach to quantifying CVH (Life's Simple 7). In Life's Essential 8, diet was 1 of the 4 items updated to reflect new evidence and to provide a guide to assess diet quality for adults and children at the population level (Table 5-1) and individual level (Table 5-2). At the population level, diet is assessed on the basis of DASH-style eating patterns. At the individual level, the Mediterranean Eating Pattern for Americans is used to assess and monitor CVH. A DASH-style pattern emphasizes vegetables, fruits, nuts and legumes, whole grains, and low-fat dairy and is reduced in sodium, red and processed meats, and sweetened beverages (Table 5-2). The items included in the Mediterranean Eating Pattern for Americans are shown in Table 5-3.<sup>1</sup>

The first study to use the AHA's Life's Essential 8 to quantify the CVH levels of adults and children in the United States included data from 23 409 individuals 2 through 79 years of age (13 521 adults and 9 888 children) participating in NHANES.<sup>2</sup> The adults in the study population represent 201 728 000 adults, and the children in the study represent 74 435 000 children.

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

This cross-sectional analysis of data from the NHANES 2013 to 2018 survey cycles revealed that 1 in 5 people in the United States have CVH scores indicative of optimal heart health and that there are differences across age and sociodemographic groups.<sup>2</sup> The scoring system for the AHA's Life's Essential 8 allows 100-point scores for each of the 8 metrics (0 is lowest, 100 is highest). The scores on the 8 metrics are used to generate a composite CVH score (the unweighted average of all components) that ranges from 0 to 100 points.

The mean overall CVH scores from this analysis revealed significant differences by age (range of mean values, 62.2–68.7), sex (women, 67.0; men, 62.5), and racial and ethnic group (range, 59.7–68.5).<sup>2</sup> Diet was among the 4 metrics with the lowest scores; the range for diet across demographic groups was 23.8 to 47.7. Among children 2 to 5 years of age, a mean diet score of 61.1 was observed. The score for children 12 to 19 years of age was 28.5.

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

#### Adults

(See Table 5-4 and Charts 5-1 and 5-2)

The average dietary consumption by US adults of selected foods and nutrients related to cardiometabolic health based on data from NHANES 2017 to 2018 is detailed below by sex and race and ethnicity (Table 5-4):

- 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/d. For each of these groups, <10% of adults met guidelines of ≥3 servings/d.
- 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/d. For each of those groups except Mexican American females, <10% of adults met guidelines of ≥2 cups/d. When 100% fruit juices were included, the number of servings increased, and the proportions of adults consuming ≥2 cups/d increased.
- Nonstarchy vegetable consumption ranged from 1.5 (NH Black males) to 2.3 (NH White females) servings/d. The proportion of adults meeting guidelines of ≥2.5 cups/d was <10%.
- Consumption of fish and shellfish ranged from 1.0 (NH White individuals) to 1.9 (NH Black females) servings/wk. The proportions of adults meeting guidelines of ≥2 servings/wk were ≈18% of NH White adults, ≈28% of NH Black adults, and ≈19% of Mexican American adults.
- Weekly consumption of nuts and seeds was ≈6 servings among NH White adults, ≈3 servings among NH Black adults, and ≈4 servings among Mexican

American adults. Approximately 1 in 3 White adults, 1 in 5 NH Black adults, and 1 in 4 Mexican American adults met guidelines of  $\geq 4$  servings/wk.

- Consumption of processed meats was lowest among Mexican American females (1.0 servings/wk) and highest among NH White males ( $\sim 2.5$  servings/wk). Between 59% (NH White males) and 87% (Mexican American females) of adults consumed  $\leq 2$  servings/wk.
- Consumption of SSBs was lowest among NH White females (6.4 servings/wk) and highest among NH Black individuals and Mexican American males ( $\approx 10$  servings/wk). 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/wk among Mexican American females to 3.3 servings/wk among NH Black males. The majority of NH White, NH Black, and Mexican American adults consumed  $<2.5$  servings/wk.
- 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 5-1 and 5-2. Sodium added to food outside the home accounts for more than two-thirds of total sodium intake in the United States (Chart 5-2).<sup>3</sup> The average daily sodium consumption for Americans  $\geq 1$  year of age is  $>3400$  mg, and the top 10 food categories accounted for 40% of sodium consumed.<sup>4</sup> These top 10 categories included

prepared foods with added sodium such as deli meat sandwiches, pizza, burritos, and tacos. During 2015 to 2016, the percentage of adults in the United States with sodium intake above the chronic disease risk reduction intake level was 86.7%.<sup>5</sup> This is noteworthy because the chronic disease risk reduction intake for sodium was established from evidence of the beneficial effect of reducing sodium intake on CVD risk, hypertension risk, SBP, and DBP. In apparently healthy populations, when reductions in intake of sodium exceed the chronic disease risk reduction, it is expected that there will be reductions in chronic disease risk.

### **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>6</sup>:

- Whole grain consumption was low with an estimated average intake of 0.95 serving/d (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/d (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/d (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/d (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/d (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/d (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/d (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/d (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/d (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 mg/d [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 useful in determining diet quality. The 2020 US Dietary Guidelines Advisory Committee summarized the evidence for benefits of healthful diet patterns on a range of cardiometabolic and other disease outcomes.<sup>7</sup> They concluded that the core elements of a healthy dietary pattern are (1) vegetables of all types; (2) fruits, especially whole fruit; (3) grains, of which at least half are whole grains; (4) dairy, including fat-free or low-fat milk, yogurt, and cheese, or lactose-free versions and fortified soy beverages and yogurt as alternatives; (5) protein foods, including lean meats, poultry and eggs, seafood, beans, peas, lentils, nuts, seeds, and soy products; and (6) oils, including vegetable oils and oils in food such as seafood and nuts. A healthy dietary pattern is also limited in foods and beverages high in added sugars, saturated fat, sodium, and alcoholic beverages. The Dietary Guidelines for Americans are published every 5 years, and adherence to them is measured with the HEI.

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];  $P_{\text{trend}} < 0.001$ ).<sup>8</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 compared with older adults and in those with a higher compared with a 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>6</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.

Patterns and trends in diet quality of foods from major sources, including grocery stores, restaurants, schools, and worksites, were examined in a study including children 5 to 19 years of age and adults  $\geq 20$  years of age in a serial, cross-sectional survey of data from 8 NHANES cycles from 2003 to 2018.<sup>9</sup>

The association between duration of participation in WIC and diet quality in children 24 months of age was examined.<sup>10</sup> Those who received benefits from WIC had better diet quality at 24 months (adjusted mean, 59.3 [95% CI, 58.6–60.1]) than children who discontinued WIC benefits (adjusted mean, 55.3 [95% CI, 51.6–59.0]) while they were infants.

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>11</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 5-3)

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 the risks of CVD or death.<sup>12</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 5-3). Fifty-two percent of US adults reported using any supplement, including multivitamins/multiminerals (31%), vitamin D (38%), and omega-3 fatty acids (11%).<sup>13</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 of Dietary Intake

- 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>14,15</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>16,17</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>18</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 individuals categorized as NH-Hispanic Black and Mexican American and in households with the lowest income.<sup>19</sup>

## Genetics/Family History

- Genetic factors may contribute to food preferences and modulate the association between dietary components and adverse CVH outcomes.<sup>20–23</sup> Nutrigenetics may also contribute to variation in the metabolism of specific dietary components (such as fatty acids) across individuals or ethnic and racial groups.<sup>24</sup> Nutritional epigenomics stipulates that epigenetic alterations induced by environmental exposures such as diet and bioactive compounds may mediate the impact of diet on CVH outcomes.<sup>25,26</sup> However, there is a paucity of gene-diet interaction studies with independent replication to support personalizing dietary recommendations according to genotype.
- A recent GWAS identified 26 loci associated with dietary carbohydrate, fat, and protein intake.<sup>23</sup> The study noted an enrichment of genes with a higher expression in specific neurons (GABAergic, dopaminergic, and glutamatergic), indicating neural mechanisms contributing to dietary patterns.<sup>23</sup>

- 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 a glucose challenge) modified the effects of diet on weight loss.<sup>27</sup>
- The interactions between a GRS composed of 97 BMI-associated variants and 3 diet-quality scores were examined in a pooled analysis of 30 904 participants from the Nurses' Health Study, the 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>28</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 ≈9000 females 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>29</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>30</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/d) 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>31</sup>

- NHANES III (1988–1994) data from 3733 overweight/obese (BMI  $\geq 25$  kg/m $^2$ ) adults (20–90 years of age) were analyzed to assess the relationship between the DII score and mortality. 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];  $P_{trend}=0.008$ ; HR<sub>1-SD increase<sup>a</sup></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];  $P_{trend}<0.001$ ; HR<sub>1-SD increase<sup>a</sup></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];  $P_{trend}=0.004$ )<sup>32</sup> and PREDIMED (HR, 1.42 [95% CI, 1.00–2.02];  $P_{trend}=0.009$ ). 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>32,33</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>34</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/d) 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>35</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>36</sup>

- A systematic review of 18 cohort studies (N=251 497) examined the relationship of 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>37</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>38</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/d) 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>39–41</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>42–44</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 AD- 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>45</sup>
- Moderate egg consumption and all-cause and cause-specific<sup>46</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>46</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>47</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>47</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>48</sup> The PREDIMED trial

demonstrated an ≈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 extravirgin olive oil or mixed nuts,<sup>48</sup> without changes in body weight.<sup>49</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>50</sup>
- In a systematic review and meta-analysis of 29 observational studies, the RR for the highest versus 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>51</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>52</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>53</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>53</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>54</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>55</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>55</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>56</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, triglycerides by 16 mg/dL, and 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>57</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>58</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>59</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>60</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>61</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>62</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>63</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>64</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>65</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>65</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>66</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>27</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, although the effects are modest in general and the sustainability is uncertain.<sup>67</sup>
- A study of NHANES 1999 to 2010 data from 24 144 participants comparing those in the fourth and 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 PUFAs (0.81 [95% CI, 0.78–0.84]) but an increased association between SFAs (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 PUFAs 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>68</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>69</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>70</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>71</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 the 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>72</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% 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>73</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>74</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>75</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>76</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>77</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>78</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>79</sup> In a prospective study of 512 891 adults in China (only 18% consumed fresh fruit daily), individuals who ate fresh fruit daily had 40% lower risk of CVD death (RR, 0.60 [95% CI, 0.54–0.67]), 34% lower risk of incident CHD (RR, 0.66 [95% CI, 0.58–0.75]), 25% lower risk of ischemic stroke (RR, 0.75 [95% CI, 0.72–0.79]), and 36% lower risk of hemorrhagic stroke (RR, 0.64 [95% CI, 0.56–0.74]).<sup>80</sup>

- In a meta-analysis of 22 RCTs, whole grain oats improved TC (standardized mean difference, 0.54, [95% CI, -0.95 to -0.12]) and LDL-C (standard mean difference, 0.57 [95% CI, -0.84 to -0.31]), whole grain rice improved triglycerides (standard mean difference, 0.22 [95% CI, -0.44 to -0.01]), and whole grains of all types improved HbA1c (standard mean difference, -0.33 [95% CI, -0.61 to -0.04]) and CRP (standard mean difference, -0.22 [95% CI, -0.44 to -0.00]).<sup>81</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>82</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>83</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>84</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>85</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/d of processed meats was associated with a higher incidence of CHD (RR, 1.42 [95% CI, 1.07–1.89]).<sup>86</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>87</sup>
- In a study of 169 310 female nurses and 41 526 male health professionals, consumption of 1 serving

of nuts ≥5 times per week was associated with lower risk of CVD (HR, 0.86 [95% CI, 0.79–0.93]) and CHD (HR, 0.80 [95% CI, 0.72–0.89]) compared with never or almost never consuming nuts. Results were largely consistent for peanuts, tree nuts, and walnuts.<sup>88</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>89</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>90</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 (≈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>91</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>92</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>93</sup>
- In a cross-sectional study of 12285 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>94</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>95</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>94</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>95</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>96</sup> The effects of sodium reduction on BP appear to be stronger in individuals who are older, hypertensive, and Black.<sup>97,98</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>99</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>100–104</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>104</sup>
- In a meta-analysis of 133 RCTs with 12197 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>105</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 mm Hg/100 mg [95% CI, 0.36–2.12]) and DBP (0.83 mm Hg/100 mg [95% CI, 0.22–1.44]). An increase in urinary phosphorus excretion was significantly associated with an increase in DBP (0.14 mm Hg/100 mg [95% CI, 0.01–0.28]).<sup>106</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>107</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>108</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>109</sup>
- A meta-analysis of 77 917 participants in 10 RCTs with ≥500 participants treated for ≥1 year found that fish oil supplementation (EPA dose range, 226–1800 mg/d; DHA dose range, 0–1700 mg/d) had no significant effect on CHD death (RR, 0.94 [95% CI, 0.81–1.03]), nonfatal MI (RR, 0.97 [95% CI, 0.87–1.08]), or any CHD events (RR, 0.97 [95% CI, 0.93–1.01]).<sup>110</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>111</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 years (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>112</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]), triglyceride (−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>113</sup>
- In an RCT of 25 871 adults (males ≥50 years of age and females ≥55 years of age), the effects of daily supplementation of 2000 IU vitamin D and 1 g marine n-3 fatty acids on the prevention of cancer and CVD were examined.<sup>114</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>115</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 ≥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>116</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>117</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 ≈25% of the sample was lost to follow-up.<sup>118</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>119</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 synergist effect of calcium and vitamin D and hormone therapy on LDL-C was observed ( $P=0.03$ ).<sup>120</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>121</sup> Another review article similarly reported that vitamin D supplementation had no beneficial effects on SBP and DBP in children and adolescents.<sup>122</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>123</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>124</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]) and 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>125</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>126</sup>

## Cost

The US Department of Agriculture reported that the Consumer Price Index for all food, not seasonally adjusted, increased by 7.9% from February 2021 to February 2022.<sup>127</sup> Prices for foods eaten at home increased by 8.6% over the same period, whereas prices for foods eaten away from home increased by 6.8%. 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>128</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>129</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>130</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>131</sup>
- Based on combined data from NHANES 2013 to 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>132</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>133</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>134</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>135</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>136</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 13890 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>137</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>138</sup> A number of countries and US cities have implemented SSB taxes. In Mexico, a 1-peso/L 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>139</sup> Data from 3 waves (2004–2018) of the Health Workers Cohort Study Mexico were used to examine the change in probability of belonging to 1 of 4 categories of soft drink consumption (non, low, medium, high) after the tax was implemented.<sup>140</sup> After the tax, the prevalence of medium or high consumers decreased from 50% to 43%, and the prevalence of nonconsumers increased from 10% to 14%. The probability of being a nonconsumer of soft drinks increased by 4.7% (95% CI, 0.3%–9.1%) and that of being a low consumer increased by 8.3% (95% CI, 0.6%–16.0%) compared with the pretax period. The probability of being in the medium and high levels of soft drink consumption decreased by 6.8% (95% CI, 0.5%–13.2%) and 6.1% (95% CI, 0.4%–11.9%), respectively. In Berkeley, CA, a 1-cent/oz SSB excise tax was implemented in January 2015.<sup>141</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. Three years after the tax was implemented, these declines were sustained across demographically diverse Berkeley neighborhoods compared with sales in the neighboring locales of San Francisco and Oakland.<sup>142</sup>

In 2010, the mean sodium intake among adults worldwide was 3950 mg/d.<sup>143</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, a reduction in mean sodium intake occurred in 5 of 10 initiatives.<sup>144</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>145</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 5-4)

- 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 5-4).
- 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>146</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 scores 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 scores 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.** Population-Level Measurement of Diet in the Essential 8 for CVH

Domain	CVH metric	Method of measurement	Quantification of CVH metric—adults ( $\geq 20$ y)	Quantification of CVH metric—children* ( $2\text{--}19$ y)																																																
Health behaviors	Diet	Measurement: Self-reported daily intake of a DASH-style eating pattern  Example tools for measurement: DASH diet score <sup>147,148</sup> (populations); MEPA <sup>149</sup> (individuals)	Quantiles of DASH-style diet adherence or HEI-2015 (population)  Scoring (population):  <table border="1"> <thead> <tr> <th>Points</th> <th>Quantile</th> </tr> </thead> <tbody> <tr> <td>100</td> <td><math>\geq 95</math>th percentile (top/ideal diet)</td> </tr> <tr> <td>80</td> <td>75th–94th percentile</td> </tr> <tr> <td>50</td> <td>50th–74th percentile</td> </tr> <tr> <td>25</td> <td>25th–49th percentile</td> </tr> <tr> <td>0</td> <td>1st–24th percentile (bottom/least ideal quartile)</td> </tr> </tbody> </table> Scoring (individual):  <table border="1"> <thead> <tr> <th>Points</th> <th>MEPA score (points)</th> </tr> </thead> <tbody> <tr> <td>100</td> <td>15–16</td> </tr> <tr> <td>80</td> <td>12–14</td> </tr> <tr> <td>50</td> <td>8–11</td> </tr> <tr> <td>25</td> <td>4–7</td> </tr> <tr> <td>0</td> <td>0–3</td> </tr> </tbody> </table>	Points	Quantile	100	$\geq 95$ th percentile (top/ideal diet)	80	75th–94th percentile	50	50th–74th percentile	25	25th–49th percentile	0	1st–24th percentile (bottom/least ideal quartile)	Points	MEPA score (points)	100	15–16	80	12–14	50	8–11	25	4–7	0	0–3	Quantiles of DASH-style diet adherence or HEI-2015 (population) or MEPA (individuals)*; 2–19 y of age (see <i>Supplemental Material</i> for younger ages)  Scoring (population):  <table border="1"> <thead> <tr> <th>Points</th> <th>Quantile</th> </tr> </thead> <tbody> <tr> <td>100</td> <td><math>\geq 95</math>th percentile (top/ideal diet)</td> </tr> <tr> <td>80</td> <td>75th–94th percentile</td> </tr> <tr> <td>50</td> <td>50th–74th percentile</td> </tr> <tr> <td>25</td> <td>25th–49th percentile</td> </tr> <tr> <td>0</td> <td>1st–24th percentile (bottom/least ideal quartile)</td> </tr> </tbody> </table> Scoring (individual):  <table border="1"> <thead> <tr> <th>Points</th> <th>MEPA score (points)</th> </tr> </thead> <tbody> <tr> <td>100</td> <td>9–10</td> </tr> <tr> <td>80</td> <td>7–8</td> </tr> <tr> <td>50</td> <td>5–6</td> </tr> <tr> <td>25</td> <td>3–4</td> </tr> <tr> <td>0</td> <td>0–2</td> </tr> </tbody> </table>	Points	Quantile	100	$\geq 95$ th percentile (top/ideal diet)	80	75th–94th percentile	50	50th–74th percentile	25	25th–49th percentile	0	1st–24th percentile (bottom/least ideal quartile)	Points	MEPA score (points)	100	9–10	80	7–8	50	5–6	25	3–4	0	0–2
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CVH indicates cardiovascular health; DASH, Dietary Approaches to Stop Hypertension; HEI, Healthy Eating Index; and MEPA, Mediterranean Eating Pattern for Americans.

\*Cannot meet these metrics until solid foods are being consumed.

#### Notes on implementation:

Diet: See *Supplemental Material Appendix 1*. For adults and children, a score of 100 points for the CVH diet metric should be assigned for the top (95th percentile) or a score of 15 to 16 on the MEPA (for individuals) or for those in the  $\geq 95$ th percentile on the DASH score or HEI-2015 (for populations). The 75th to 94th percentile should be assigned 80 points, given that there is likely improvement that can be made even among those in this top quartile. For individuals, the MEPA points are stratified for the 100-point scoring system approximately by quintiles. In children, a modified MEPA is suggested on the basis of age-appropriate foods. The writing group recognizes that the quintiles may need to be adjusted or recalibrated at intervals with population shifts in eating patterns. In children, the scoring applies only once solid foods are being consumed. For now, the reference population for quantiles of HEI or DASH score should be the National Health and Nutrition Examination Survey sample from 2015 to 2018. The writing group acknowledges that this may need to change or be updated over time. Clinicians should use judgment in assigning points for culturally contextual healthy diets. For additional notes on scoring in children, see *Supplemental Material Appendix 2*.

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**Table 5-2.** Scoring Criteria for the DASH-Style Diet Score

Component	Foods (NHANES 24-h recall)	Scoring criteria	Note
Fruits	All fruits and fruit juices	Quintile 1: 1 point Quintile 2: 2 points Quintile 3: 3 points Quintile 4: 4 points Quintile 5: 5 points	Higher score represents more ideal intake
Vegetables	All vegetables except potatoes and legumes		Quintile 1 is lowest consumption and quintile 5 is highest consumption
Nuts and legumes	Nuts and peanut butter, dried beans, peas, tofu		
Whole grains	Brown rice, dark breads, cooked cereal, whole grain cereal, other grains, popcorn, wheat germ, bran		
Low-fat dairy	Skim milk, yogurt, cottage cheese		
Sodium	Sum of sodium content of all foods reported as consumed	Quintile 1: 5 points Quintile 2: 4 points Quintile 3: 3 points Quintile 4: 2 points Quintile 5: 1 point	Reverse scoring as higher quintiles represent less ideal intake
Red and processed meats	Beef, pork, lamb, deli meats, organ meats, hot dogs, bacon		Quintile 1 is lowest consumption and quintile 5 is highest consumption
Sweetened beverages	Carbonated and noncarbonated sweetened beverages		

DASH indicates Dietary Approaches to Stop Hypertension; and NHANES, National Health and Nutrition Examination Survey.

The DASH diet score is assessed and points scored using the methods of Fung et al.<sup>150</sup> Quintiles of point score should be assigned using the most recent or most relevant NHANES data, appropriate to the question being addressed.

Source: Reproduced with permission from Fung et al.<sup>150</sup> Copyright © 2008, American Medical Association. All rights reserved.

**Table 5-3. Scoring Criteria for the Mediterranean Eating Pattern for Americans<sup>149</sup>**

Screener item	Question	Scoring criteria	Score
Olive oil	How much olive oil do you consume per day (including that used in frying, meals eaten away from home, salads, etc)?	≥2 servings of olive oil per day	1: If scoring condition met 0: If scoring condition not met (range, 0–16)
Green leafy vegetables	How many servings of green leafy vegetables do you consume per day?	≥7 servings of green leafy vegetables per week	
Other vegetables	How many servings of other vegetables do you consume per day?	≥2 servings of other vegetables per day	
Berries	How many servings of berries do you consume per week?	≥2 servings of berries per week	
Other fruit	How many servings of other fruit do you consume per week?	≥1 serving of other fruit per day	
Meat	How many servings of red meat, hamburger, bacon or sausage do you consume per week?	≤3 servings of red meat, hamburger, bacon or sausage per week	
Fish	How many servings of fish or shellfish/seafood do you consume per week?	≥1 serving of fish per week	
Chicken	How many servings of chicken do you consume per week?	≤5 servings of chicken per week	
Cheese	How many servings of full-fat or regular cheese or cream cheese do you consume per week?	≤4 servings of full-fat or regular cheese or cream cheese per week	
Butter/cream	How many servings of butter or cream do you consume per week?	≤5 servings of butter or cream per week	
Beans	How many servings of beans do you consume per week?	≥3 servings of beans per week	
Whole grains	How many servings of whole grains do you consume per day?	≥3 servings of whole grains per day	
Sweets and Pastries	How many servings of commercial sweets, candy bars, pastries, cookies, or cakes do you consume per week?	≤4 servings of commercial sweets, candy bars, pastries, cookies, or cakes per week	American Association
Nuts	How many servings of nuts do you consume per week?	≥4 servings of nuts per week	
Fast food	How many times per week do you consume meals from fast-food restaurants?	≤1 meal at a fast-food restaurant per week	
Alcohol	How much alcohol do you drink per week?	>0 or ≤2 servings of alcohol per day for men and >0 or ≤1 servings of alcohol per day for women	

Source: Reprinted from Lloyd-Jones et al.<sup>1</sup> Supplemental Material. Copyright © 2022, American Heart Association, Inc.

**Table 5-4. 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

(Continued)

**Table 5-4.** Continued

	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
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
Nutrients												
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-Linoleic 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 PUFA, % 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

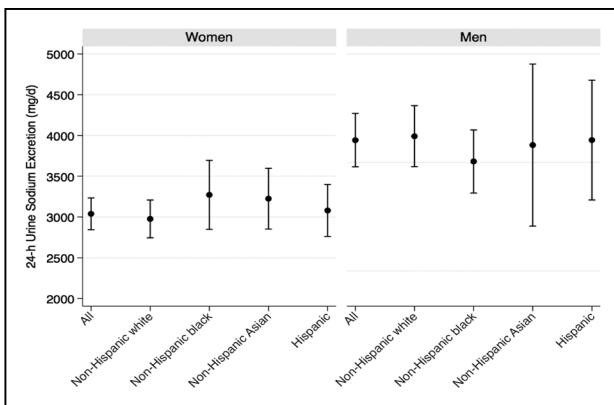
Values for average consumption are mean±SD. Data are from NHANES 2017 to 2018, derived from two 24-hour dietary recalls per person, with population SD adjusted for within-person versus between-person variation. All values are energy adjusted by individual regressions or percent energy, and for comparability,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

\*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 are 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>48</sup>; α-linoleic acid, ≥1.6/1.1 g/d (males/females); saturated fat, <10% energy; dietary cholesterol, <300 mg/d; dietary fiber, ≥28 g/d; sodium, <2.3 g/d; ratio of (PUFAs+MUFAs)/SFAs, ≥2.5; and added sugars, ≤6.5% total energy intake. No dietary targets are listed for starchy vegetables and unprocessed red meats because of their positive association with long-term weight gain and their positive or uncertain relation with diabetes and cardiovascular disease.

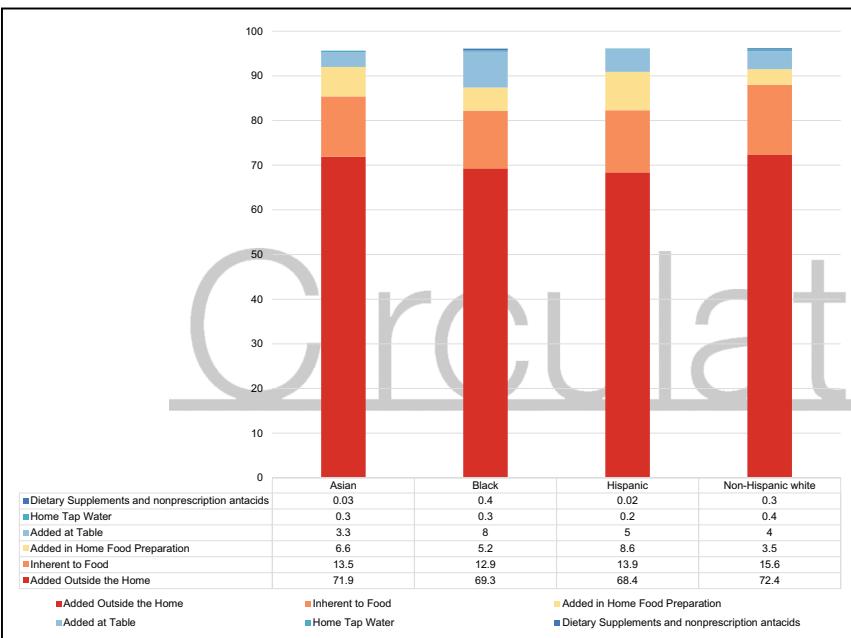
†Including white potatoes (chips, fries, mashed, baked, roasted, mixed dishes), corn, plantains, green peas, etc. Sweet potatoes, pumpkin, and squash are considered red-orange vegetables by the US Department of Agriculture and are included in nonstarchy vegetables.

Source: Unpublished analyses courtesy of Dr Junxiu Liu, Icahn School of Medicine at Mount Sinai, using NHANES.<sup>151</sup>



**Chart 5-1. Estimated mean sodium intake, by 24-hour urinary excretion, United States, 2013 to 2014.**

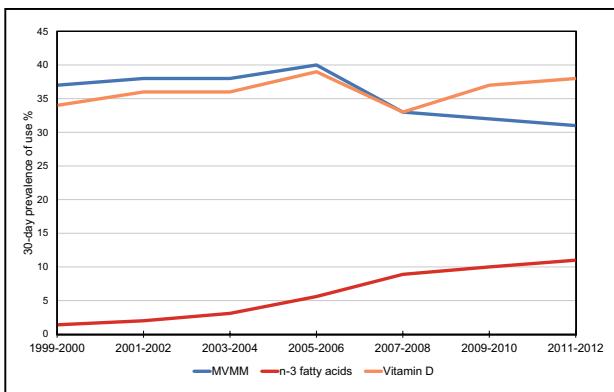
Estimates based on nationally representative sample of 827 nonpregnant, noninstitutionalized US adults 20 to 69 years of age who completed a 24-hour urine collection in NHANES 2013 to 2014. NHANES indicates National Health and Nutrition Examination Survey. Source: Data derived from Cogswell et al<sup>152</sup> using NHANES.<sup>151</sup>



**Chart 5-2. 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, and non-Hispanic White individuals).

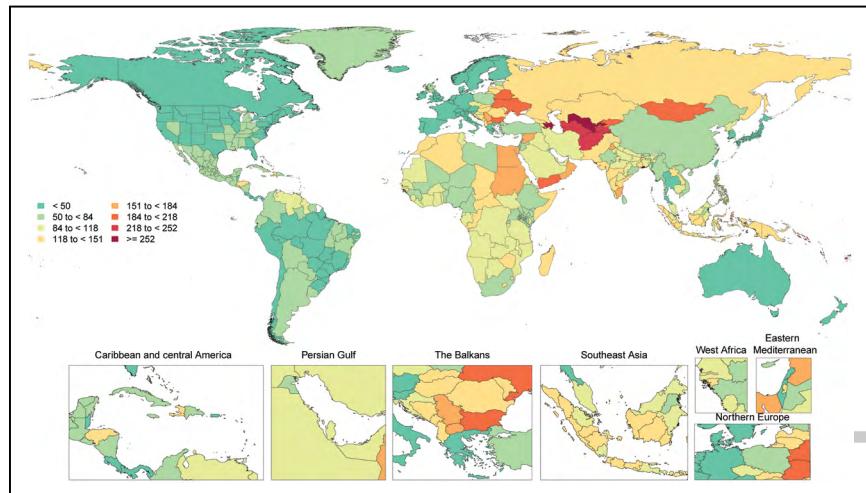
Source: Reprinted from Harnack et al.<sup>3</sup> Copyright © 2017 American Heart Association, Inc.



**Chart 5-3. 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>13</sup>



**Chart 5-4. Age-standardized global mortality rates attributable to dietary risks per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>153</sup>

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# Circulation

## 6. OVERWEIGHT AND OBESITY

**See Tables 6-1 and 6-2 and Charts 6-1 through 6-9**

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### Classification of Overweight/Obese

- BMI is calculated as weight in kilograms divided by height in meters squared. Obesity in adults is defined as  $\text{BMI} \geq 30.0 \text{ kg/m}^2$ , and severe obesity is usually defined as  $\text{BMI} \geq 40 \text{ kg/m}^2$ .<sup>1</sup> Overweight in adults is defined as  $\text{BMI} \geq 25.0 \text{ kg/m}^2$  but  $<30 \text{ kg/m}^2$ .
- Obesity in adults can be further subdivided into class 1 ( $\text{BMI } 30 < 35 \text{ kg/m}^2$ ), class 2 ( $\text{BMI } 35 < 40 \text{ kg/m}^2$ ); severe obesity is classified as class 3 ( $\text{BMI} \geq 40 \text{ kg/m}^2$ ).<sup>2</sup>
- For children and adolescents, obesity is defined as  $\text{BMI} \geq 95\text{th percentile}$  and severe obesity as a  $\text{BMI} \geq 120\%$  of the 95th percentile.<sup>3</sup> Overweight in children is defined as  $\text{BMI} \geq 85\text{th}$  but  $<95\text{th}$  percentile. Severe obesity in children is a  $\text{BMI} \geq 120\%$  of the 95th percentile.
- It should be noted that the cardiovascular risk conferred by BMI is not uniform across racial and ethnic groups and may overestimate risk among Black adults and underestimate risk in Asian people.<sup>4</sup> Even among different Asian populations, the BMI cut point for observed risk varies from 22 to 26  $\text{kg/m}^2$ , and for high risk, the BMI varies from 26 to 31  $\text{kg/m}^2$ .<sup>5</sup>

### Prevalence and Secular Trends

#### Youth

##### Prevalence in Children/Adolescents

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

- According to data from NHANES from 2017 until March 2020 (before the COVID-19 pandemic), among US children and adolescents 2 to 19 years of age, the prevalence of being either overweight or obese was 36.8%, with obesity prevalence of 19.8% (Table 6-1). The prevalence of overweight/obesity

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

(combined) and obesity was 37.3% and 21.1% for male youth and 36.2% and 18.6% for female youth. The highest prevalence of obesity was seen among Hispanic male and NH Black female youth.

- According to data from NHANES from 2017 to 2018, among US children and adolescents 2 to 19 years of age, the prevalence of being overweight (alone) was 16.1% overall and 14.7% and 17.6% for male and female youth, respectively. The prevalence of severe obesity was 6.1% overall and 6.9% and 5.2% for male and female youth, respectively.<sup>3</sup>
- There were significant disparities in obesity by racial and ethnic groups. Again, according to NHANES data from 2017 to March 2020, the prevalence of obesity for males and females was 17.7% and 15.3% for NH White, 18.3% and 30.5% for NH Black, 13.7% and 5.2% for NH Asian, and 30.1% and 23.3% for Hispanic children and adolescents 2 to 19 years of age, respectively (Table 6-1 and Chart 6-1).
- Among youth, percent body fat was not consistent by BMI categories. In NHANES data from 2011 to 2018 in youth 8 to 19 years of age, percent body fat was highest among Hispanic females (35.7%) and males (28.2%).<sup>6</sup> There was no difference in percent body fat between NH Black, White, or Asian females at 32.7%, 33.2%, and 32.7%, respectively. Percent body fat was lower among NH Black males at 23.9% compared with NH White or Asian males at 26.0% and 26.6%, respectively. Among female youth with obesity, NH Asian females had lower percent body fat (40.5%) than NH White females (42.8%;  $P=0.0072$ ).
- There are regional/geographical differences in prevalence of obesity in youth across the United States. According to NHANES data from 1999 to 2014 among adolescents 12 to 19 years of age, across 9 regions, the prevalence of obesity was lowest in the Mountain and New England areas (both  $<15\%$ ) and highest in the central United States (21%–24%), followed by the South and Mid-Atlantic regions (19%–20%) and the Pacific and West North Central regions (17%–18%).<sup>7</sup>

#### Youth Secular Trends

**(See Chart 6-2)**

- Comparing data across NHANES survey years shows that the prevalence of overweight, obesity, and severe obesity among all children and adolescents 2 to 19 years of age increased from 10.2%, 5.2%, and 1.0%, respectively, in 1971 to 1974 to 16.1%, 19.3%, and 6.1% in 2017 to 2018 (Chart 6-2). For males, the prevalence increased from 10.3%, 5.3%, and 1.0% in 1971 to 1974 to 14.7%, 20.5%, and 6.9% in 2017 to 2018. For females, the prevalence increased from 10.1%, 5.1%, and

1.0% in 1971 to 1974 to 17.6%, 18.0%, and 5.2% in 2017 to 2018.<sup>3</sup>

### Adults

#### Prevalence in Adults

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

- According to data from NHANES 2017 through March 2020 (before the pandemic), the age-adjusted prevalence of overweight or obesity among adults  $\geq 20$  years of age in the United States was 71.2%. The prevalence of obesity was 41.4% and was similar for males (41.2%) and females (41.4%; Table 6-1 and Chart 6-3). There were significant disparities by racial and ethnic groups with the highest prevalence of obesity among NH Black females (56.8%; Chart 6-3).
- This prevalence of obesity by age categories for adults  $\geq 20$  years of age in a prior NHANES analysis from 2017 to 2018 was 40.0% in younger adults 20 to 39 years of age, 44.8% in middle-aged adults 40 to 59 years of age, and 42.8% in adults  $\geq 60$  years of age (Chart 6-4).<sup>1</sup>
- In data from NHANES 2017 through March 2020 (before the pandemic), the age-adjusted prevalence of severe obesity among adults  $\geq 20$  years of age in the United States was 9.1% with greater prevalence in females (11.6%) than males (6.5%; Table 6-1 and Chart 6-5). Significant disparities were noted by racial and ethnic groups with the greatest prevalence of severe obesity among Black females (18.8%).
- The prevalence of severe obesity was similar to the prior NHANES report from 2017 to 2018, in which the age-adjusted prevalence of severe obesity stratified by age groups was 9.1%, 11.5%, and 5.8% for 20 to 39, 40 to 59, and  $\geq 60$  years of age, respectively.<sup>1</sup>
- According to data from BRFSS among adults  $\geq 18$  years of age in the United States in 2020, the age-adjusted prevalence by BMI categories was 31.9% for obesity ( $BMI \geq 30 \text{ kg/m}^2$ ), 35.2% for overweight ( $BMI 25\text{--}29.9 \text{ kg/m}^2$ ), 31.0% for normal weight ( $BMI 18.5\text{--}24.9 \text{ kg/m}^2$ ), and 1.8% for underweight ( $BMI <18.5 \text{ kg/m}^2$ ), with geographical variation across the United States (Chart 6-6).<sup>8</sup>
- In 1 meta-analysis, 70% of adults with obesity were not obese in childhood or adolescence.<sup>9</sup> Thus, additional strategies are needed to prevent obesity in adulthood.

#### Secular Trends in Adults

##### (See Chart 6-2)

- Comparing NHANES data from 1999 to 2000 to 2017 to 2018 shows that the prevalence of obesity increased from 27.5% (95% CI, 24.3%–30.8%) to 43% (95% CI, 37.6%–48.6%) among US males,

with severe obesity increasing from 3.1% to 6.9%. All racial and ethnic groups experienced an increase in obesity and severe obesity during this time frame except for Black males, for whom the obesity prevalence did not increase after 2005 to 2006 (Chart 6-7). The increase in obesity biennially was greater among Mexican American males (3%) than NH White males (1.4%;  $P<0.001$ ).<sup>10</sup>

- Among females, the prevalence of obesity increased from 33.4% (95% CI, 29.8%–37.1%) in 1999 to 2000 to 41.9% (95% CI, 37.8%–46.1%) in 2017 to 2018; severe obesity increased from 6.2% to 11.5%. This same pattern of increase was seen among NH White and NH Black females, whereas Mexican American females experienced a rise in obesity, but severe obesity increased only after 2009 to 2010.<sup>10</sup>

### Social Determinants of Health and Health Equity

#### Urbanization

- There are differences in obesity prevalence by urbanization status. In US data from NHANES 2013 to 2016, the age-adjusted prevalence of obesity for females living in nonmetropolitan statistical areas was greater at 47.2% than for females living in small ( $<250\,000$ ) or medium (250 000–999 999) metropolitan statistical areas at 42.5% or for females living in large metropolitan statistical areas ( $\geq 1$  million population) at 38.1%.<sup>11</sup> For males, the age-adjusted prevalence of obesity was higher for small or medium metropolitan statistical areas at 42.4% versus large metropolitan statistical areas at 31.8%, but the prevalence of obesity was similar to that of nonmetropolitan statistical areas at 38.9%. The prevalence of severe obesity, however, was higher in males living in nonmetropolitan statistical areas at 9.9% versus large metropolitan statistical areas at 4.1%, and for females, it was 13.5% versus 8.1%.

#### Income

- According to data from NHANES 2011 to 2014, the age-adjusted prevalence of obesity was lower in the highest income group ( $>350\%$  of federal poverty level) at 31.2% compared with the low- ( $\leq 130\%$  of federal poverty level) and middle- ( $>130\% \text{--} \leq 350\%$  federal poverty level) income groups with prevalence of 40.8% and 9.0%, respectively.<sup>12</sup> Among females, the prevalence of obesity was also lower in the highest income group (29.7%) compared with middle- (42.9%) and low- (45.2%) income groups, with a similar trend for NH White, NH Asian, and Hispanic females, but this was statistically significant only for NH White females. Among NH Black females, the prevalence of obesity did not differ

across income groups. In males, the prevalence of obesity was highest in the middle-income groups (38.5%) compared with the low- (31.5%) and high- (32.6%) income groups. This pattern was seen among both NH White and Hispanic males, but there was no difference in obesity prevalence by income groups among NH Asian males. Among NH Black males, the obesity prevalence was greater in the high-income (42.7%) compared with the low-income (33.8%) group.<sup>12</sup>

### **Education**

- In that same NHANES study from 2011 to 2014, there were also differences in obesity prevalence by education status. The age-adjusted prevalence of obesity was lower among college graduates (27.8%) compared with those with some college (40.6%) and those who had only a high school education or less (40.0%).<sup>12</sup> By sex-education groups, the prevalence of obesity for females and males was 28.8% and 27.9% for college graduates, 41.2% and 40.0% for individuals with some college, and 45.3% and 35.5% for those with a high school education or less. Among NH Asian adults and among Hispanic males, there was no difference in the prevalence of obesity by education level.<sup>12</sup>

### **Composite Social Determinants**

- According to data from the NHIS from 2013 to 2017, there was a graded association with increasing burden of social determinants of health being associated with a higher prevalence of obesity. For example, in adjusted models, for the fourth quartile of unfavorable social determinants of health compared with the first quartile, there was a 15%, 50%, and 70% higher prevalence of overweight, obesity class 1 or 2, and obesity class 3, respectively.<sup>13</sup>

### **Family History and Genetics**

- Although environmental factors certainly are a leading contributor to obesity and its growing rates, there are considerable genetic components in the tendency toward overweight and obesity status,<sup>14</sup> with heritability estimates ranging from 40% to 70%.<sup>15</sup>
- GWASs have estimated that common genetic variants may account for >20% of the variation in BMI.<sup>16</sup>
- Monogenic or mendelian causes of obesity include variants with strong effects in genes that control appetite and energy balance (eg, *LEP*, *MC4R*, *POMC*). Obesity that occurs in the context of genetic syndromes (eg, Prader-Willi syndrome) also can reflect monogenic or mendelian causes.<sup>17</sup>
- Many more GWASs, ≈60 to date, have identified >1100 independent loci associated with obesity traits.<sup>18</sup>

- In GWAS analyses targeting African ancestry, only <30% of loci associated with BMI and waist-to-hip ratio in European ancestry were also associated in African ancestry.<sup>19</sup>
- One GWAS conducted specifically in children identified 3 new loci with susceptibility for childhood BMI with a GRS (combining these 3 with 12 other previously identified loci) explaining 2% of variations in childhood BMI.<sup>20</sup>
  - One of the first loci to be identified was the *FTO* gene (first intron of fat mass and obesity),<sup>21</sup> which is relatively common among individuals of European ancestry with a minor allele frequency of 40% to 5%.<sup>18,22</sup> *FTO* has a relatively large effect on BMI of 0.35 kg/m<sup>2</sup> per allele, or ≈1 kg in weight for a person who is 1.7 m tall. The association of *FTO* SNPs on BMI was similar in populations of African or Asian ancestry but is less prevalent in these populations compared with European ancestry.<sup>18,22</sup> This locus has been replicated in diverse populations and across different age groups.<sup>22–26</sup> The mechanisms underlying the association between variation at *FTO* and obesity remain incompletely elucidated but could be related to mitochondrial thermogenesis or food intake.<sup>21</sup>

- 
- Monogenic obesity inherited in a mendelian pattern is generally rare and associated with other organ-specific abnormalities,<sup>17</sup> whereas polygenic obesity has a heritability pattern similar to other that of complex diseases.<sup>18</sup>
  - A PRS comprising 2.1 million common variants was tested in a cohort of >300 000 individuals from birth to middle age and showed that among middle-aged adults there was a 13-kg gradient in weight and a 25-fold gradient in risk of severe obesity across increasing deciles of polygenic scores.<sup>27</sup> Similarly, a weight gradient was seen after birth to early childhood of up to 12-kg difference by 18 years of age. However, obesity-related genetic risks are not deterministic; in the same analysis, 17% of people of normal weight were in the top decile of polygenic risk.<sup>27</sup>
  - Polygenic risk associated with higher BMI is associated with increased risk for CAD, HF, and mortality.<sup>27</sup> A mendelian randomization study has shown that a high-BMI GRS is associated with shorter life span in the UK Biobank (HR per 1-SD BMI GRS for increase in mortality, 1.07 [95% CI, 1.05–1.09]).<sup>28</sup>
  - Mendelian randomization analysis also was used to evaluate the health consequences of obesity across a spectrum of human diseases. In data from the UK Biobank, a high GRS for obesity was associated with a 70% increased risk for diabetes (OR, 1.70 [95% CI, 1.62–1.79]), a 35% increased risk for hypertension (OR, 1.35 [95% CI, 1.31–1.38]),

a 27% increased risk for CAD (OR, 1.27 [95% CI, 1.19–1.36]), a 23% increased risk for ischemic stroke (OR, 1.23 [95% CI, 1.02–1.48]), a 33% increased risk for HF (OR, 1.33 [95% CI, 1.14–1.54]), and a 40% increased risk for VTE (OR, 1.40 [95% CI, 1.30–1.49]).<sup>29</sup>

- In another analysis, PRS explained 5.2% of BMI variance, and gene-by-environment interaction explained an additional 1.9%.<sup>30</sup>
  - Genetic variants may also influence responsiveness to weight loss interventions.<sup>31</sup> A GWAS (N=1166) conducted in a low-caloric diet intervention trial identified 2 loci, *NKX6.3/MIR486* and *RBSG4*, that were associated with degree of weight loss.<sup>31</sup> Both loci were replicated in a second low-caloric diet intervention study (N=789).
  - Genetic variants also may affect weight loss or weight gain in the context of a behavioral intervention. For example, *MTIF3* lead variant rs1885988, a previously identified BMI locus, was consistently associated with greater weight loss after lifestyle behavioral interventions in 2 RCTs with each copy of the minor G allele being associated with a mean of –1.14-kg (95% CI, –1.75 to –0.53) weight loss in the lifestyle arm compared with a mean of 0.33-kg weight gain (95% CI, –0.30 to 0.95) in the comparison arm.<sup>32</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>33</sup>
  - However, there is considerable uncertainty in obesity GRSs. A study of N=291 273 unrelated White British UK Biobank participants reported that only 0.4% of participants assigned to the 90% BMI GRS threshold had corresponding 95% credible intervals fully contained in the top decile.<sup>34</sup>

## Obesity Prevention

- A prior meta-analysis suggested that school-based interventions aimed at promoting healthy weights were generally, albeit modestly, effective in reducing excessive weight gain in children (average BMI reduction, –0.14 kg/m<sup>2</sup> [95% CI, –0.21 to –0.06] for single-component interventions).<sup>35</sup>
- Another meta-analysis of technology-based interventions in youth (telemedicine or digital technology mHealth tools) found only small effects on pediatric obesity, with a standardized difference in weight outcomes of only –0.13 and 79% of included studies

not demonstrating a significant difference between treatment and comparator groups.<sup>36</sup>

- A systematic review and meta-analysis of RCTs demonstrated that lifestyle interventions did prevent cumulative weight gain among nonobese adults (–1.15 kg [95% CI, –1.50 to –0.80]); however, further study is needed to determine the feasibility for implementation and cost-effectiveness for these programs.<sup>37</sup>

## Obesity Treatment

### Diet and Surgery

- A meta-analysis of 54 RCTs with >30 000 participants with obesity found that diets for the intention of weight reduction, usually low in total fat and saturated fat with or without exercise advice, were associated with a reduction in all-cause mortality (RR, 0.82 [95% CI, 0.71–0.95]) but no statistically significant reduction in CVD mortality or CVD events.<sup>38</sup>
- A systematic review of 122 RCTs and 2 observational studies indicated that behavior-based weight loss interventions conferred modest but significantly greater weight loss at 12 to 18 months (–2.39 kg [95% CI, –2.86 to –1.93]) and less weight regain (–1.59 kg [95% CI, –2.38 to –0.79]) than control groups.<sup>39</sup>

American Heart Association
- Modern bariatric surgery procedures have strong evidence for efficacy and safety for individuals and should be considered in patients with BMI ≥40 kg/m<sup>2</sup> or ≥35 kg/m<sup>2</sup> if serious obesity-related comorbidities are present.<sup>40</sup> One meta-analysis including studies with >10-year follow-up showed that gastric bypass conferred 57% excess weight loss, laparoscopic adjustable gastric band conferred 46%, and sleeve gastrectomy conferred 58%, but reoperations were common across all 3 procedures.<sup>41</sup>
- In 1 large meta-analysis of prospective controlled trials and matched control studies, bariatric surgery was associated with a lower rate of mortality (HR, 0.51 [95% CI, 0.48–0.54]) and longer life expectancy (median, 6.1 years) than usual care for obesity management. There were greater survival benefits among individuals with diabetes (HR for mortality, 0.41 [95% CI, 0.37–0.45]) than those without diabetes (HR, 0.71 [95% CI, 0.59–0.84]).<sup>42</sup>
- In another observational analysis of patients with obesity and type 2 diabetes, there were significantly improved cardiovascular and kidney outcomes among bariatric surgery-treated patients compared with those who did not have surgery with a reduction in HF (HR, 0.33 [95% CI, 0.24–0.46]), cardiovascular mortality (HR, 0.36 [95% CI, 0.22–0.58]), and composite kidney disease (HR, 0.56 [95% CI, 0.44–0.71]) outcomes.<sup>43</sup>

## Pharmacotherapy

- Metformin has weight-reduction effects. In a meta-analysis of 21 trials, metformin compared with control conferred a modest reduction in BMI overall with a WMD of  $-0.98 \text{ kg/m}^2$  (95% CI,  $-1.2$  to  $-0.72$ ), which was greater among individuals with simple obesity (WMD,  $-1.31$  [95% CI,  $-2.07$  to  $-0.54$ ]) compared with those with obesity with type 2 diabetes (WMD,  $-1.00$  [95% CI,  $-1.30$  to  $-0.70$ ]), although both groups were statistically significant.<sup>44</sup>
- A 2016 meta-analysis of weight loss trials showed that orlistat, lorcaserin, naltrexone-bupropion, phentermine-topiramate, and liraglutide all conferred a greater likelihood of achieving at least a 5% weight loss at 52 weeks compared with placebo among adults with overweight and obesity. In this analysis, phentermine-topiramate (OR, 9.22 [95% CI, 6.63–12.85]) and liraglutide (OR, 5.54 [95% CI, 4.15–7.78]) were the agents most likely to confer at least 5% weight loss.<sup>45</sup> Since that study publication, lorcaserin has been removed from the US market given concerns about possible risk of cancer.
- SGLT-2 inhibitor medications can confer modest weight loss.<sup>46</sup> In a recent meta-analysis of 116 RCTs, including patients with and without type 2 diabetes, SGLT2 inhibitors conferred a mean weight reduction of  $-1.79 \text{ kg}$  (95% CI,  $-1.93$  to  $-1.66$ ) compared with placebo. This effect was seen for all SGLT2 inhibitor drugs and across diabetes status.<sup>47</sup>
- Among patients with type 2 diabetes, meta-analyses of trials have shown that all GLP1-RAs conferred weight loss, albeit with some differences among type and dose of GLP1-RAs.<sup>48,49</sup> In a 2017 meta-analysis, the greatest weight loss was with liraglutide ( $-1.96 \text{ kg}$  [95% CI,  $-2.67$  to  $-1.25$ ]), followed by twice-daily exenatide ( $-1.67 \text{ kg}$  [95% CI,  $-2.29$  to  $-1.05$ ]), dulaglutide ( $-1.57 \text{ kg}$  [95% CI,  $-2.48$  to  $-0.66$ ]), once-weekly exenatide ( $-1.49 \text{ kg}$  [95% CI,  $-2.58$  to  $-0.40$ ]), and lixisenatide ( $-0.78 \text{ kg}$  [95% CI,  $-1.48$  to  $-0.09$ ]).<sup>48</sup> More recently, GLP1-RAs have emerged as effective pharmacological options for weight loss with cardiovascular safety among patients with overweight/obesity with or without type 2 diabetes.<sup>50–52</sup> In the STEP 3 trial, semaglutide 2.4 mg/wk reduced weight from baseline by 10% more than placebo at 68 weeks in adults with overweight/obesity as an adjunct to a low-calorie diet and intensive behavioral therapy.<sup>52</sup> In the STEP 1 trial among patients with overweight/obesity, semaglutide 2.4 mg/wk conferred 12.4% greater weight reduction, which is a treatment difference of  $-12.7 \text{ kg}$  (28 lb) compared with placebo.<sup>50</sup> In both trials, there were more gastrointestinal side effects, leading to discontinuation in the GLP1-RA-treated group.
- In another meta-analysis, greater weight loss compared with placebo was conferred by semaglutide

2.4 mg/wk and  $<2.4 \text{ mg/wk}$  subcutaneous and liraglutide  $>1.8 \text{ mg/d}$  subcutaneous than was seen with other types of GLP-1RAs.<sup>53</sup>

- Semaglutide and liraglutide are approved by the FDA for long-term weight management in adults with overweight or obesity who had at least 1 weight-related condition such as type 2 diabetes, hypertension, or dyslipidemia, in conjunction with a reduced-calorie diet and increased PA.<sup>54</sup>
- It is notable that among patients with type 2 diabetes and obesity, GLP1-RAs also significantly reduce major adverse cardiovascular events (RR, 0.88 [95% CI, 0.81–0.96]).<sup>55</sup>
- Among patients with type 2 diabetes and NAFLD, a meta-analysis showed that GLP1-RAs significantly reduced BMI (WMD,  $-1.57 \text{ kg/m}^2$  [95% CI,  $-2.72$  to  $-0.39$ ]), as well as WC and body weight.<sup>56</sup>
- In a meta-analysis of 9 studies including 574 children and adolescents with obesity, GLP1-RAs conferred modest reductions in BMI (WMD,  $-1.24 \text{ kg/m}^2$  [95% CI,  $-1.71$  to  $0.77$ ]) and reductions in body weight (WMD,  $-1.50 \text{ kg}$  [95% CI,  $-2.50$  to  $-0.50$ ]), showing efficacy and safety in youth with obesity.<sup>57</sup>
- Dual agonists of glucose-dependent insulinotropic peptide and glucagon-like peptide 1 are also emerging pharmacotherapies for weight loss. Tirzepatide, a dual glucose-dependent insulinotropic peptide/glucagon-like peptide 1 agonist, was studied in the SURMOUNT-1 trial of 2539 adult patients without type 2 diabetes who were obese ( $\text{BMI} \geq 30 \text{ m/kg}^2$ ) or overweight ( $\text{BMI} \geq 27 \text{ m/kg}^2$ ) with a history of weight-related comorbidities and showed that this drug achieved significant weight loss in a dose-dependent manner.<sup>58</sup> The highest dose of tirzepatide (15 mg) conferred 22.5% weight reduction with mean weight loss of 23.6 kg (52.0 lb) at 72 weeks compared with placebo.

## Mortality

- In the SPRINT trial, there was a J-shaped relationship between BMI and mortality; however, this was no longer statistically significant after adjustment for traditional CVD risk factors.<sup>59</sup>
- In contrast, a large meta-analysis of 230 cohort studies including  $>30$  million individuals found a statistically significant J-shaped relationship of BMI with mortality, with both underweight and increasing BMI being associated with an increased risk of death.<sup>60</sup> The RR for mortality for a 5-unit increment in BMI was 1.04 (95% CI, 1.04–1.07) for all participants and 1.27 (95% CI, 1.21–1.33) among healthy nonsmokers. The lowest mortality rates were seen at a BMI of 23 to 24  $\text{kg/m}^2$  among never-smokers and at 20 to 22  $\text{kg/m}^2$  in cohort studies with longer durations of follow-up.<sup>60</sup>

- Being overweight or obese was associated with a 21% (RR, 1.21 [95% CI, 1.08–1.35]) and 52% (RR, 1.52 [95% CI, 1.31–1.77]) increased risk of SCD compared with normal weight in a meta-analysis of >10 studies.<sup>61</sup>
- An analysis from the Organization for Economic Co-Operation and Development that examined the impact of obesity on morbidity, mortality, and health expenditure in 52 countries estimated that over the next 30 years (2020–2050) 3 million premature deaths globally will be attributed to overweight/obesity with a reduction in life expectancy by 2.7 years.<sup>62</sup>

## Complications of Obesity

### **Cardiovascular Disease**

- Obesity is associated with increased risk of adverse cardiovascular outcomes. A recent umbrella review examined 12 systematic reviews including 53 meta-analyses, >500 cohort studies, and 12 mendelian randomization studies.<sup>63</sup> This study found that for every 5-kg/m<sup>2</sup> increase in measured BMI, the RR was 1.07 (95% CI, 1.02–1.12) for stroke, 1.15 (95% CI, 1.12–1.20) for CHD, 1.23 (95% CI, 1.17–1.30) for AF, 1.41 (95% CI, 1.32–1.50) for HF, and 1.49 (95% CI, 1.40–1.60) for hypertension.<sup>63</sup> Mendelian randomization analyses suggest that obesity is causally related to CVD, that for each 5-kg/m<sup>2</sup> increase in genetically determined BMI, the RR was 1.19 (95% CI, 1.03–1.37) for CHD, 1.23 (95% CI, 1.13–1.33) for PAD, 1.64 (95% CI, 1.47–1.82) for hypertension, and 1.92 (95% CI, 1.12–3.30) for HF, but no association with stroke was seen.
- In an analysis pooling data from 10 large US prospective cohorts, lifetime risks for incident CVD were higher in middle-aged adults with overweight and obesity compared with individuals with normal weight.<sup>64</sup> The HR for incident CVD in males was 1.21 (95% CI, 1.14–1.28) for overweight, 1.67 (95% CI, 1.55–1.79) for obesity, and 3.14 (95% CI, 2.48–3.07) for morbid obesity. The HR for incident CVD in females was 1.32 (95% CI, 1.24–1.40) for overweight, 1.85 (95% CI, 1.72–1.99) for obesity, and 2.53 (95% CI, 2.20–2.91) for morbid obesity. Although the overweight group had a longevity similar to that of the normal BMI group, an increased risk of developing CVD at an earlier age translates to a greater proportion of years lived with CVD morbidity.<sup>64</sup>

### **Coronary Heart Disease**

- Mendelian randomization studies suggest a causal role of obesity and CAD (OR, 1.49 [95% CI, 1.39–1.60]) per 1 SD of genetically predicted BMI, although this is accounted for in part by intermediate

factors such as hypertension, lipids, and diabetes.<sup>65</sup> After accounting for these potential cardiovascular risk mediators, the OR for CAD per 1-SD increase in genetically predicted BMI was attenuated to 1.14 (95% CI, 1.04–1.26).

- In a meta-analysis pooling data from 1.8 million participants, each 5-kg/m<sup>2</sup> higher BMI was associated with a 27% increased risk for CHD (HR, 1.27 [95% CI, 1.23–1.31]) after adjustment for confounders.<sup>66</sup> Approximately half of the excess risk of CHD associated with overweight/obesity status was mediated by BP, cholesterol, and glucose.
- Among patients with CAD, fluctuations in body weight were associated with an increased risk of cardiovascular events and mortality that was independent of traditional CVD risk factors.<sup>67</sup> Among >9500 participants in the Treating to New Target trial, for the highest quintile of weight fluctuation compared with the lowest, there was a 64% greater risk of coronary events, 85% greater risk of cardiovascular events, 117% higher risk of MI, 136% higher risk of stroke, and 124% increased risk of death.<sup>67</sup>

### **Stroke**

- A meta-analysis including 4.4 million participants indicated a J-shaped relationship of BMI with stroke, with the nadir observed at a BMI of 23 to 24 kg/m<sup>2</sup>.<sup>68</sup> The pooled RR for stroke was 1.10 (95% CI, 1.06–1.13) for each 5-unit increment in BMI.
- In another meta-analysis, the HR of incident stroke for each 5-kg/m<sup>2</sup> higher BMI was 1.18 (95% CI, 1.14–1.22) after adjustment for confounders.<sup>66</sup> Approximately three-quarters of the excess risk of CHD associated with overweight/obesity status was mediated by BP, cholesterol, and glucose.

### **Heart Failure**

- In a meta-analysis, a J-shaped relationship was noted between BMI and HF risk. Compared with normal weight, the OR for incident HF was 1.22 (95% CI, 0.95–1.58) for underweight, 1.11 (95% CI, 0.97–1.27) for overweight, 1.62 (95% CI, 1.32–1.99) for obesity, and 1.73 (95% CI, 1.30–2.21) for severe obesity.<sup>69</sup> In that same analysis, intentional weight loss with bariatric surgery was associated with improvement in measures of cardiac structure and function among patients with obesity with a reduction in left atrial size ( $P=0.02$ ) and improvement in LV diastology ( $P<0.0001$ ).<sup>69</sup>
- Data from the ARIC cohort showed that the association of severe obesity (BMI  $\geq 35$  kg/m<sup>2</sup>) with incident HF was greater than for the other subtypes of CVD, including CHD and stroke (HR, 3.74 [95% CI, 3.24–4.31] for HF versus 2.00 [95% CI, 1.67–2.40] and 1.75 [95% CI, 1.40–2.20] for CHD and stroke, respectively) over a 23-year follow-up.<sup>70</sup>

- The stronger association of higher BMI with incident HF compared with other CVD subtypes was also noted in a pooled analysis across 10 cohorts. For males, compared with normal weight, the lifetime risk of HF was an HR of 1.22 (95% CI, 1.07–1.40) for overweight, 1.95 (95% CI, 1.68–2.27) for obesity, and 5.26 (95% CI, 3.65–7.57) for severe obesity. For females, the HR for HF was 1.37 (95% CI, 1.21–1.55) for overweight, 2.28 (95% CI, 2.00–2.60) for obesity, and 4.32 (95% CI, 3.39–5.19) for severe obesity.<sup>64</sup>
- Cumulative weight (ie, BMI-years) over a lifetime has a stronger association with incident HF. In an analysis from MESA, BMIs at 20 and 40 years of age were more strongly associated with increased risk of incident HF than BMI measured in mid to late adulthood. Even after accounting for present weight at later adulthood, higher BMI per 5 kg/m<sup>2</sup> (determined by self-reported weight) at 20 years of age was independently associated with an HR of incident HF of 1.27 (95% CI, 1.07–1.50), and at 40 years of age, the HR was 1.36 (95% CI, 1.18–1.57).<sup>71</sup>
- Regionality of fat distribution influences HF risk.<sup>72</sup> Visceral adipose tissue, but not subcutaneous fat, was associated with incident HFpEF in the MESA cohort.<sup>73</sup>
- NAFLD, which is also strongly linked to obesity, is associated with incident HF with a 60% higher odds of incident HF according to a recent meta-analysis (OR, 1.60 [95% CI, 1.24–2.05]).<sup>74</sup>

### Atrial Fibrillation

- Obesity is a strong risk factor for AF; it is associated with incident AF and persistent AF.<sup>75</sup> A mendelian randomization study supported a causal relationship between BMI and AF risk.<sup>76</sup> A BMI gene score per 1-unit increase conferred an HR of 1.15 (95% CI, 1.04–1.26) in an age- and sex-adjusted analysis, which was similar to the meta-analysis of observed BMI with an HR of 1.05 (95% CI, 1.04–1.06) for 1-kg/m<sup>2</sup> higher BMI.<sup>76</sup>
- In a meta-analysis of 16 cohort studies, obese status was associated with a 49% increased risk of developing AF compared with nonobese status (RR, 1.49 [95% CI, 1.36–1.64]). There was a graded relationship between increasing weight categories and increased risk of AF.<sup>77</sup>
- In a large meta-analysis of 25 studies including >2 million participants, each 5-kg increase in weight was associated with a 28% greater risk of AF (RR, 1.28 [95% CI, 1.20–1.38]).<sup>78</sup> The association between BMI and AF was not linear, although there was a generally stronger association with AF with increasing BMI levels. However, even a BMI of 22.5 to 24.0 kg/m<sup>2</sup> (HR, 1.09 [95% CI, 1.04–1.13])

compared with 20 to 22.5 kg/m<sup>2</sup> (reference) also had an increased risk with greatest risk of AF for BMI ≥40 kg/m<sup>2</sup> (HR, 3.45 [95% CI, 2.56–4.64]).

- As demonstrated in a recent meta-analysis, among patients with a history of catheter ablation for AF, those who lost weight experienced a lower risk of recurrent AF than those who did not (RR, 0.35 [95% CI, 0.18–0.67]).<sup>79</sup> The reduced risk of AF after ablation was seen predominantly among patients who lost ≥10% of weight (RR, 0.18 [95% CI, 0.03–0.89]) but not for patients with <10% of weight loss (RR, 1.00 [95% CI, 0.51–1.96]). There was also a lower risk of recurrent AF among patients who lost weight before the ablation procedure.<sup>79</sup>
- For patients with overweight/obesity and AF, current guidelines recommend a ≥10% reduction in weight, a BMI <27 kg/m<sup>2</sup>, and at least a 2-MET increase in PA. Bariatric surgery could be considered in appropriate candidates.<sup>75</sup>

### Coronavirus Disease 2019

- Obesity is a risk factor for severe COVID-19 and COVID-19-associated mortality.<sup>80</sup> In a meta-analysis of 186 studies including >1.3 million patients, the RR of mortality in COVID-19 associated with obesity was 1.45 (95% CI, 1.31–1.61) compared with those with a BMI <30 kg/m<sup>2</sup>, with an increased risk of death of 1.12 (95% CI, 1.08–1.18) for every 5-kg/m<sup>2</sup> increase in BMI. This relationship was J shaped with lowest risk of COVID-19-associated mortality around a BMI of 22 to 24 kg/m<sup>2</sup>.<sup>81</sup>
- In the AHA COVID-19 registry, obese patients were more likely to be hospitalized with COVID-19 than nonobese patients and had greater multivariable-adjusted risk for the composite outcome of in-hospital death or mechanical ventilation (OR for class I, II, and III obesity: 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). There was a significant interaction with age, with severe obesity being associated with a greater risk of in-hospital death only for individuals ≤50 years of age (HR, 1.36 [95% CI, 1.01–1.84]).<sup>82</sup> Obese patients also had greater risk of VTE (HR, 1.81 [95% CI, 1.22–2.98]).

### Complications in Youth

- Overweight and obesity in youth frequently track into adulthood. In a meta-analysis including >200 000 participants, children and adolescents with obesity were ≈5 times more likely to have obesity in adulthood. Approximately 55% of children with obesity will have obesity in adolescence, and ≈80% of adolescents with obesity will still have obesity in adulthood, with ≈70% remaining obese after 30 years of age.<sup>9</sup>
- In an analysis from NHANES, obesity in youth (3–19 years of age) was associated with increased

prevalence of cardiometabolic risk factors, including greater SBP and DBP, lower HDL-C, and higher levels of triglycerides and HbA1c, particularly in males.<sup>83</sup>

- Childhood obesity is associated with cardiometabolic risk factors in adulthood such as BP elevation and dyslipidemia.<sup>84</sup> In a meta-analysis, high BMI in childhood was associated with an increased risk of diabetes (OR, 1.70 [95% CI, 1.30–2.22]) and CHD (1.20 [95% CI, 1.10–1.31]) in adulthood.<sup>85</sup> However, only 31% of later-life adulthood diabetes and 22% of adulthood hypertension and CHD occurred in children ≥12 years who were overweight or obese.
- In another meta-analysis of 22 studies including >5 million youth 2 to 19 years of age, childhood and adolescent BMI per 1-SD increment conferred a 12% increased risk of CHD in adulthood (HR, 1.12 [95% CI, 1.01–1.25]).<sup>86</sup> The associations did not significantly change after adjustment for SES or differ by sex.
- In another analysis using longitudinal data from 2.3 million adolescents 16 to 19 years of age who were followed up for 40 years, overweight status and obesity status were strongly associated with increased cardiovascular mortality in adulthood. The HRs for CHD mortality and CVD mortality were 4.9 (95% CI, 3.9–6.1) and 3.5 (95% CI, 2.9–4.1) for BMIs ≥95th percentile compared with the 5th to 24th age-sex BMI percentile, respectively, after adjustment for sex, age, birth year, and sociodemographic characteristics.<sup>87</sup> There was also a graded increase in CHD and CVD deaths for BMIs in the 50th to 74th, 75th to 84th, and 85th to 94th percentiles, which includes BMI percentiles within a normal acceptable range.<sup>87</sup> For example, for CHD deaths, the HRs were 1.11 (95% CI, 0.94–1.31), 1.49 (95% CI, 1.27–1.76), 2.17 (95% CI, 1.78–2.64), and 3.02 (95% CI, 2.50–3.65), for BMIs in the 25th to 49th, 50th to 74th, 75th to 84th, and 85th to 94th percentiles, respectively, compared with the 5th to 24th percentile (reference group).

## Health Care Use and Cost

- Adjusted to 2019 US dollars, a study using data from MEPS, a nationally representative US sample, and controlling for confounders estimated that obesity was associated with \$1861 (95% CI, \$1656–\$2053) in excess costs per person annually among obese compared with normal-weight individuals.<sup>88</sup> Severe obesity was associated with excess annual costs of \$3097 (95% CI, \$2777–\$3413) per person among adults. Each 1-unit increase in BMI over 30 kg/m<sup>2</sup> was associated with an additional \$253 (95% CI, \$167–\$347) cost per year per person.
- In that same MEPS analysis, obesity in children was associated with \$116 (95% CI, \$14–\$201) in

excess costs per child and \$1.32 billion in medical spending with severe obesity costing \$310 (95% CI, \$124–\$474) more per child.<sup>88</sup>

- In that same MEPS analysis, medical expenditures associated with higher BMI were greater among females.<sup>88</sup> There was a J-shaped relationship between medical expenditures and BMI with the lowest expenditures seen at a BMI of 20.5 kg/m<sup>2</sup> for adult females and 23.5 kg/m<sup>2</sup> for adult males.<sup>88</sup>
- In another analysis, it was established that the total direct medical cost attributed to obesity for noninstitutionalized adults in the United States was \$260.0 billion in 2016, more than double that of 2001 (\$124.2 billion).<sup>89</sup>

## Global Burden of Disease

### (See Table 6-2 and Charts 6-8 and 6-9)

- Worldwide, between 1975 and 2016, the prevalence of obesity has tripled in adults according to data from the Non-Communicable Disease Risk Factor Collaboration from the WHO.<sup>90</sup> According to the WHO, in 1975, the global prevalence of obesity (BMI ≥30 kg/m<sup>2</sup>) and overweight (BMI ≥25 kg/m<sup>2</sup>) was 4.7% and 21.5%, respectively, which increased to 13.1% and 38.9%, respectively, in 2016.<sup>90</sup>
- In 2016, >1.9 billion adults (39% of world's adult population) were overweight and >650 million (13% of world's adult population, including 11% males and 15% females) were obese.<sup>18,90,91</sup>
- In that same Non-Communicable Disease Risk Factor Collaboration analysis, the prevalence of obesity in children and adolescents increased from <1% in 1975 to >7% (6% of females, 8% of males) in 2016, which is >124 million children and adolescents.<sup>18,90,91</sup>
- Thirty-nine million children <5 years of age were overweight or obese in 2020 globally.<sup>90</sup>
- For youth 5 to 19 years of age, the prevalence of overweight and obesity increased substantially from 4% in 1975 to >18% (18% of females, 19% of males) in 2016. In 2016, >340 million children and adolescents 5 to 19 years of age were either overweight or obese.<sup>90</sup>
- It is estimated that by 2025, 1 in 5 adults globally will be obese.<sup>92</sup>
- It is estimated that 8% of deaths globally in 2017 were attributable to obesity with a death rate from obesity of 60 per 100 000.<sup>93</sup>
- There is an ≈10-fold difference in death rates from obesity across the world, ranging from <5% in low-income countries such as sub-Saharan Africa to 8% to 10% in high-income countries such as Western Europe, East Asia, Asia Pacific, South Asia, and Australasia, with the highest obesity-related death rates ≥15% in middle-income countries such as Eastern Europe, Central

Asia, Latin American, and North Africa. The higher death rates attributable to obesity in middle-income countries likely stem from having not only a high prevalence of obesity but also poorer health and health care infrastructure relative to high-income countries that have similarly high levels of obesity.<sup>93</sup>

- Globally, it is estimated that the absolute number of deaths attributed to high BMI (defined as  $>25 \text{ kg/m}^2$  and above normal weight for children) was 5.02 million (95% UI, 3.22–7.11 million) and 160 million (95% UI, 106–209 million) DALYs lost.<sup>94</sup> This was an increase from 2.20 million (95% UI, 1.21–3.43 million) deaths and 67.3 million (95% UI, 38.0–104 million) DALYs in 1990.
- Age-standardized DALY rates attributed to high BMI in 2019 were highest in Oceania, Central Asia, North Africa and the Middle East, southern sub-Saharan Africa, Eastern Europe, Central Latin America, the Caribbean, and Central Europe (Chart 6–8). The global DALY rates attributed to high BMI were generally similar between males and females, although age-standardized DALY rates were higher for males in Central Asia, Central Europe, and Eastern Europe.
- 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 6–9).
- High BMI was attributed to 2.40 million (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 the rate of increase in obesity prevalence seems to be declining in most high-income countries, the prevalence rate continues to rise in many low- and middle-income countries.<sup>18,91</sup> Data from the Non-Communicable Disease Risk Factor Collaboration reported that increases in BMI in rural areas accounted for >55% of the global rise in mean BMI from 1985 to 2017 and >80% of the rise in some low- and middle-income regions.<sup>95</sup> These data challenge the notion that urbanization is responsible for the obesity epidemic and call attention to the need for improvement in prevention strategies and CVH in rural areas.



**Table 6-1. Prevalence of Overweight, Obesity, and Severe Obesity in Youth and Adults, United States, 2017 to March 2020**

	Prevalence of over-weight and obesity,* 2–19 y of age		Prevalence of obesity,* 2–19 y of age		Prevalence of over-weight and obesity,* ≥20 y of age		Prevalence of obesity,* ≥20 y of age		Prevalence of severe obesity,* ≥20 y of age	
	nt	%	nt	%	nt	%	nt	%	nt	%
Total	26 866 283	36.8	14 494 961	19.8	172 770 797	71.2	98 396 677	41.4	21 094 352	9.1
Male	13 809 774	37.3	7 799 977	21.1	87 635 019	75.7	47 427 779	41.2	7 328 333	6.5
Female	13 056 509	36.2	6 694 984	18.6	85 135 778	68.8	50 968 898	41.4	13 766 018	11.6
NH White										
Male	6 646 223	35.3	3 334 177	17.7	54 760 252	74.8	30 692 341	42.7	4 572 520	6.8
Female	5 869 786	32.9	2 732 850	15.3	52 509 500	66.7	30 798 467	39.4	8 673 380	12.0
NH Black										
Male	1 553 207	31.7	895 364	18.3	8579 865	69.9	4 795 740	39.3	948 077	7.7
Female	2 396 250	49.3	1 482 834	30.5	11 744 519	79.2	8 406 985	56.8	2 747 956	18.8
Hispanic										
Male	4 321 470	46.7	2 788 722	30.1	16 205 625	86.0	8 473 190	44.6	1 158 444	5.9
Female	3 910 923	43.5	2 098 804	23.3	14 066 744	75.4	8 239 980	44.1	1 616 973	8.5
NH Asian										
Male	464 241	26.0	244 486	13.7	4 080 624	61.8	1 162 842	17.3	162 897	2.4
Female	306 146	16.5	96 723	5.2	3 493 698	45.9	1 094 535	14.4	86 750	1.1

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>96</sup>

COVID indicates coronavirus disease 2019; NHANES, National Health and Nutrition Examination Survey; and NH, non-Hispanic.

\*Overweight and obesity in adults are defined as body mass index (BMI)  $\geq 25 \text{ kg/m}^2$ . Obesity in adults is defined as BMI  $\geq 30 \text{ kg/m}^2$ . Severe obesity is defined as BMI  $\geq 40 \text{ kg/m}^2$ . Prevalence estimates for adults were age adjusted with the direct method to standardize estimates to the projected 2000 US census population with 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  $\geq 85^{\text{th}}$  percentile of the 2000 Centers for Disease Control and Prevention (CDC) growth charts. In children, obesity is based on BMI-for-age values  $\geq 95^{\text{th}}$  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 NHANES.<sup>97</sup>

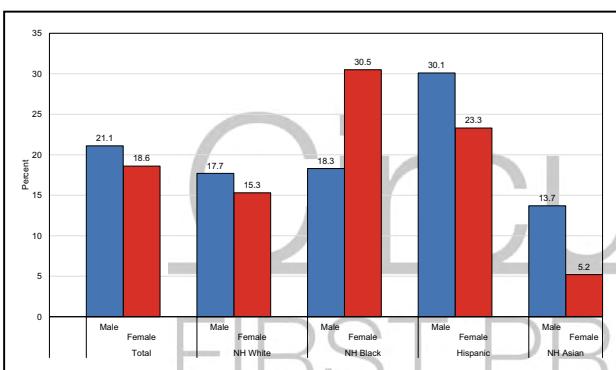
**Table 6-2.** Deaths Caused by High BMI Worldwide by Sex, 2020

	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)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

BMI indicates body mass index; GBD, Global Burden of Disease Study; PAF, population attributable fraction; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>98</sup>

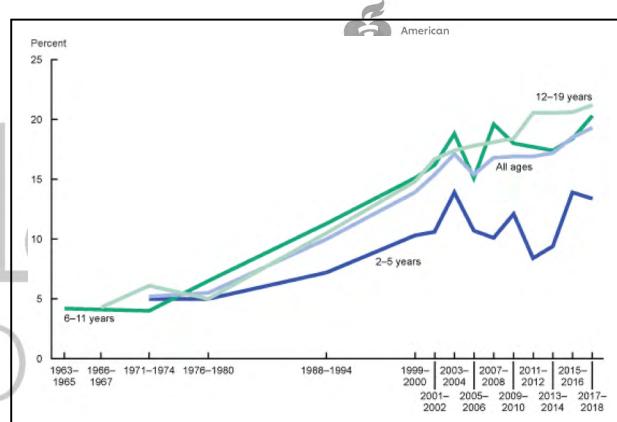


**Chart 6-1.** Prevalence of obesity among youth 2 to 19 years of age by sex, race, and Hispanic origin, United States, 2017 to March 2020.

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>96</sup>

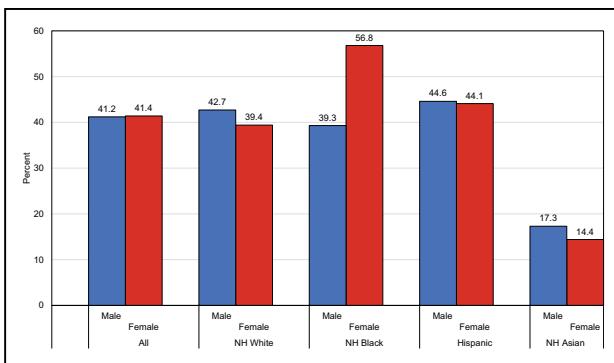
COVID-19 indicates coronavirus disease 2019; NHANES, National Health and Nutrition Examination Survey; and NH, non-Hispanic.

Source: Unpublished tabulation using NHANES.<sup>97</sup>



**Chart 6-2.** Trends in obesity among children and adolescents 2 to 19 years of age by age, United States, 1963 to 1965 through 2017 to 2018.

Source: Reprinted from Fryar et al<sup>9</sup> using National Health and Nutrition Examination Survey.<sup>97</sup>

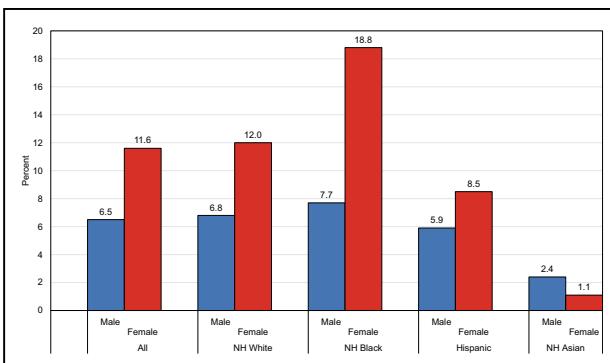


**Chart 6-3. Age-adjusted prevalence of obesity among adults  $\geq 20$  years of age by sex, race, and Hispanic origin, United States, 2017 to March 2020.**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>96</sup>

COVID-19 indicates coronavirus disease 2019; NHANES, National Health and Nutrition Examination Survey; and NH, non-Hispanic.

Source: Unpublished tabulation using NHANES.<sup>97</sup>

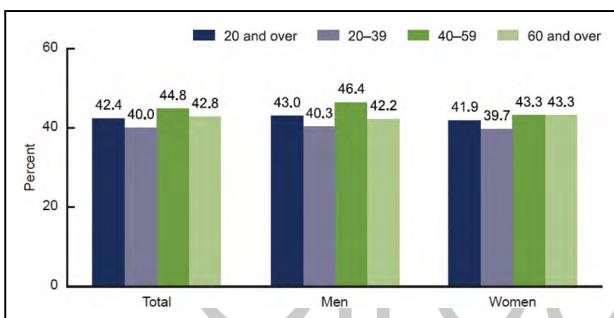


**Chart 6-5. Age-adjusted prevalence of severe obesity among adults  $\geq 20$  years of age, by sex, race, and Hispanic origin, United States, 2017 to March 2020.**

In March 2020, the COVID-19 pandemic halted NHANES field operations. As data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>96</sup>

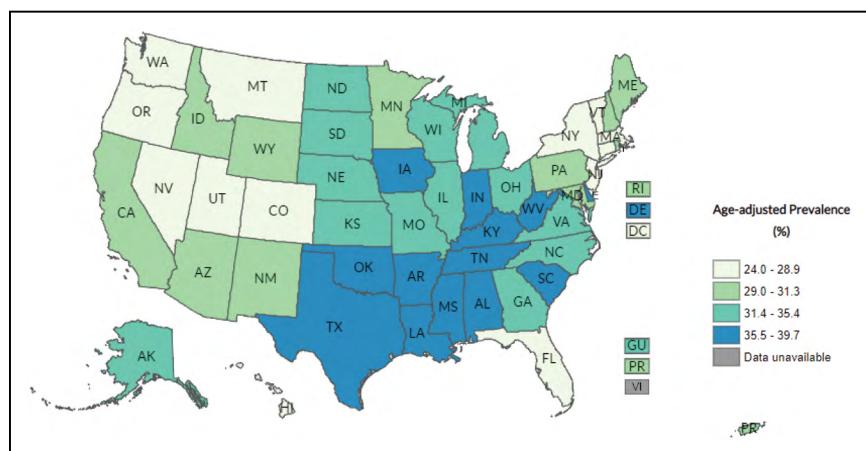
COVID-19 indicates coronavirus disease 2019; NHANES, National Health and Nutrition Examination Survey; and NH, non-Hispanic.

Source: Unpublished tabulation using NHANES.<sup>97</sup>



**Chart 6-4. Prevalence of obesity among adults  $\geq 20$  years of age by age and sex, United States, 2017 to 2018.**

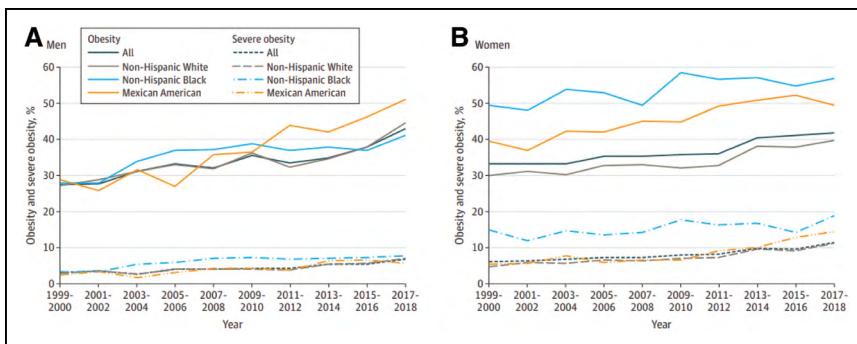
Source: Reprinted from Hales et al<sup>1</sup> using National Health and Nutrition Examination Survey.<sup>97</sup>



**Chart 6-6. Age-adjusted prevalence of obesity (body mass index  $\geq 30$  kg/m $^2$ ) for US adults  $\geq 18$  years of age, United States, 2020.**

White space and drop-down menus have been removed from the original chart.

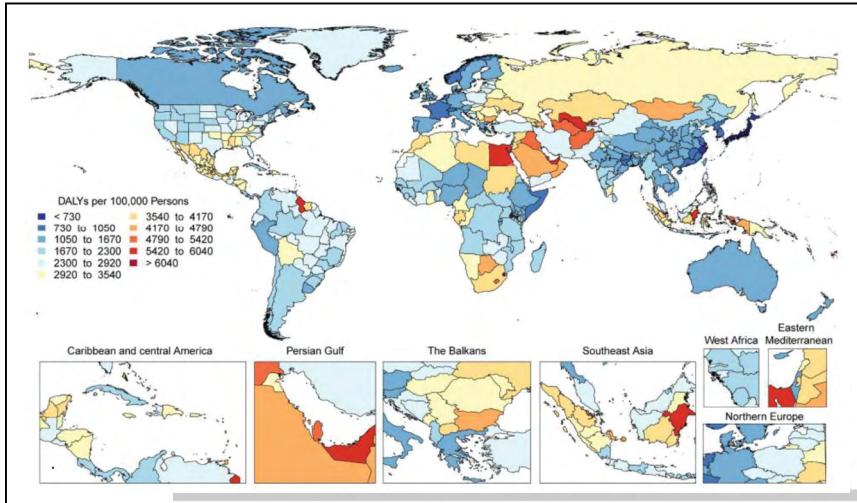
Source: Reprinted from Centers for Disease Control and Prevention, Obesity Prevalence Map using Behavioral Risk Factor Surveillance System prevalence and trends data.<sup>8</sup>



**Chart 6-7. Age-adjusted prevalence of obesity and severe obesity in US adults.**

**A**, Men. **B**, Women.

Source: Reproduced with permission from Ogden et al.<sup>10</sup> Copyright © 2020 American Medical Association. All rights reserved.



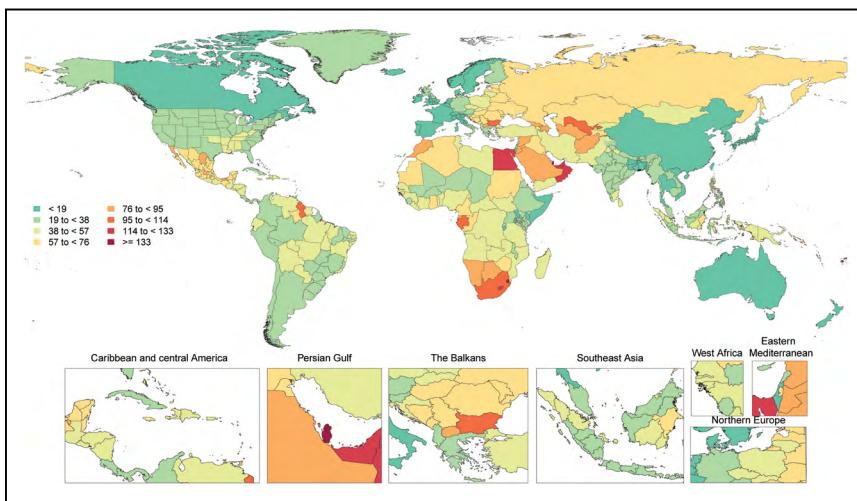
**Chart 6-8. Age-standardized global rates of DALYs attributable to high body mass index per 100 000, both sexes, 2019.**

DALY indicates disability-adjusted life-year.

Source: Reprinted from Roth et al.<sup>94</sup>

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**Chart 6-9. Age-standardized global mortality rates attributable to high body mass index per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease. Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>98</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. TC levels in the blood are one of the primary metrics used to define CVH in children and adults. LDL-C is the component of TC that is most closely associated with CVD risk and is therefore the target of both lifestyle and pharmacological treatment. HDL-C is inversely associated with CVD risk, and high triglyceride levels are associated with increased risk. A full lipid panel, including TC, LDL-C, HDL-C, and triglycerides, is normally recommended to best assess lipid-related CVD risk. Lipoprotein(a), an LDL particle with an added apolipoprotein(a), is a genetically determined factor with elevated levels associated with increased CVD risk. The multisociety 2018 Cholesterol Clinical Practice Guideline and the 2019 AHA/ACC CVD Primary Prevention Clinical Practice Guidelines focus predominantly 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 2017 to 2020 was 157.4 mg/dL. For males, it was 157.5 mg/dL; for females, it was 157.2 mg/dL. Mean TC levels among racial and ethnic groups in NHANES 2017 to 2020 were as follows (unpublished NHLBI tabulation using NHANES<sup>3</sup>):
  - For NH White children, 156.3 mg/dL for males and 159.5 mg/dL for females
  - For NH Black children, 159.3 mg/dL for males and 155.3 mg/dL for females
  - For Hispanic children, 156.5 mg/dL for males and 153.1 mg/dL for females

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

- For NH Asian children, 169.6 mg/dL for males and 166.0 mg/dL for females
- Among adolescents 12 to 19 years of age, the mean TC level in 2017 to 2020 was 154.8 mg/dL; for males, it was 150.1; for females, it was 159.7 mg/dL. Mean TC levels among racial and ethnic groups in NHANES 2017 to 2020 were as follows (unpublished NHLBI tabulation using NHANES<sup>3</sup>):
  - For NH White adolescents, 148.8 mg/dL for males and 162.4 mg/dL for females
  - For NH Black adolescents, 153.1 mg/dL for males and 156.8 mg/dL for females
  - For Hispanic adolescents, 149.8 mg/dL for males and 154.9 mg/dL for females
  - For NH Asian adolescents, 156.3 mg/dL for males and 161.0 mg/dL for females
- Among youth 6 to 19 years of age, the prevalence of elevated TC levels (TC  $\geq$ 200 mg/dL) in 2009 to 2016 was 7.1% (95% CI, 6.4%–7.8%; Chart 7-1A). 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)

- 
- American Heart Association
- Among adults  $\geq$ 20 years of age, the mean TC level in 2017 to 2020 was 187.2 mg/dL. For males, it was 183.9 mg/dL; for females, it was 190.0 mg/dL. Across 3 NHANES time periods (1999–2002, 2007–2010, and 2017–2020), NH Black adults had the lowest serum TC compared with NH White adults and Mexican American adults (Chart 7-2). Mean TC levels among racial and ethnic groups in 2017 to 2020 were as follows (unpublished NHLBI tabulation using NHANES<sup>3</sup>):
    - For NH White adults, 183.3 mg/dL for males and 191.6 mg/dL for females
    - For NH Black adults, 179.5 mg/dL for males and 182.6 mg/dL for females
    - For Hispanic adults, 185.3 mg/dL for males and 187.4 mg/dL for females
    - For NH Asian adults, 191.4 mg/dL for males and 190.8 mg/dL for females
  - The prevalence of moderately and significantly elevated TC levels  $\geq$ 200 and  $\geq$ 240 mg/dL among US adults  $\geq$ 20 years of age in 2017 to 2020 (unpublished NHLBI tabulation using NHANES<sup>3</sup>) is shown overall and by sex and race and ethnicity in Table 7-1 and Charts 7-3 and 7-4.
  - The Healthy People 2030 target is a mean population TC level of 186.4 mg/dL for adults,<sup>5</sup> which has been achieved by NH Black US adults (males and females combined) and Mexican American US

adults (males and females combined) in NHANES 2017 to 2020 (Chart 7-2).<sup>3,5</sup>

## Prevalence of Abnormal Levels of Lipid Subfractions

### *LDL-C and Lipoprotein(a)*

#### *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 2017 to 2020 was 88.1 mg/dL (males, 85.1 mg/dL; females, 91.3 mg/dL). Mean LDL-C levels among racial and ethnic groups were as follows (unpublished NHLBI tabulation using NHANES<sup>3</sup>):
  - For NH White adolescents, 83.2 mg/dL for males and 92.0 mg/dL for females
  - For NH Black adolescents, 84.8 mg/dL for males and 97.6 mg/dL for females
  - For Hispanic adolescents, 89.0 mg/dL for males and 88.1 mg/dL for females
  - For NH Asian adolescents, 83.0 mg/dL for males and 83.2 mg/dL for females; however, these values are based on data from small sample sizes (39 NH Asian males and 27 NH Asian females)
- LDL-C levels  $\geq 130$  mg/dL occurred in 5.0% of male adolescents and 4.6% of female adolescents during 2017 to 2020 (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)**

- A desirable LDL-C level in adults without ASCVD is  $< 100$  mg/dL. In 2017 to 2020 (unpublished NHLBI tabulation using NHANES<sup>3</sup>), the mean level of LDL-C for American adults  $\geq 20$  years of age was 110.1 mg/dL. The racial and ethnic breakdown was as follows:
  - Among NH White adults, 109.5 mg/dL for males and 109.3 mg/dL for females
  - Among NH Black adults, 109.8 mg/dL for males and 106.0 mg/dL for females
  - Among Hispanic adults, 110.5 mg/dL for males and 111.5 mg/dL for females
  - Among NH Asian adults, 114.8 mg/dL for males and 109.6 mg/dL for females
- In 2017 to 2020, the age-adjusted prevalence of high LDL-C ( $\geq 130$  mg/dL) was 25.5% (unpublished NHLBI tabulation using NHANES<sup>3</sup>; Table 7-1).
- Elevated lipoprotein(a), which is defined as  $\geq 125$  nmol/L or  $\geq 50$  mg/dL and is present in up to 20%

of the population, is associated with increased ASCVD risk and is defined as a risk-enhancing factor by the 2018 Cholesterol Clinical Practice Guideline. Among  $\approx 460\,000$  middle-aged adults in the UK Biobank enrolled between 2006 and 2010, median serum lipoprotein(a) concentrations were 19.6 nmol/L (25th–75th percentile, 7.6–74.8 nmol/L) overall, with median values of 21.8 nmol/L in females and 17.4 nmol/L in males, and 19 nmol/L in White, 31 nmol/L in South Asian, 75 nmol/L in Black, and 16 nmol/L in Chinese adults.<sup>6</sup>

### *HDL Cholesterol*

#### *Youth*

##### **(See Chart 7-1)**

- Among children 6 to 11 years of age, the mean HDL-C level in 2017 to 2020 was 55.5 mg/dL. For males, it was 56.6 mg/dL, and for females, it was 54.3 mg/dL. Mean HDL-C levels among racial and ethnic groups were as follows (unpublished NHLBI tabulation using NHANES<sup>3</sup>):
  - For NH White children, 56.8 mg/dL for males and 54.8 mg/dL for females
  - For NH Black children, 58.5 mg/dL for males and 55.9 mg/dL for females
  - For Hispanic children, 55.6 mg/dL for males and 51.3 mg/dL for females
  - For NH Asian children, 59.3 mg/dL for males and 58.1 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 8.9% of females in 2017 to 2020 (unpublished NHLBI tabulation using NHANES<sup>3</sup>).
- Among adolescents 12 to 19 years of age, the mean HDL-C level was 51.7 mg/dL. For males, it was 49.0 mg/dL, and for females, it was 54.6 mg/dL. Mean HDL-C levels among racial and ethnic groups were as follows (NHANES,<sup>3</sup> unpublished NHLBI tabulation):
  - For NH White adolescents, 48.2 mg/dL for males and 55.2 mg/dL for females
  - For NH Black adolescents, 53.8 mg/dL for males and 55.9 mg/dL for females
  - For Hispanic adolescents, 48.2 mg/dL for males and 52.2 mg/dL for females
  - For NH Asian adolescents, 51.1 mg/dL for males and 55.3 mg/dL for females
- Low levels of HDL-C ( $< 40$  mg/dL) occurred in 19.3% of male adolescents and 8.6% of female adolescents in 2017 to 2020 (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)**

- HDL-C is considered low and associated with increased ASCVD risk if <40 mg/dL in males or <50 mg/dL in females. In 2017 to 2020 (unpublished NHLBI tabulation using NHANES<sup>3</sup>), the mean level of HDL-C for American adults ≥20 years of age was 53.6 mg/dL. Mean HDL-C levels among racial and ethnic groups were as follows:
  - Among NH White adults, 48.4 mg/dL for males and 59.5 mg/dL for females
  - Among NH Black adults, 52.7 mg/dL for males and 59.2 mg/dL for females
  - Among Hispanic adults, 45.4 mg/dL for males and 55.4 mg/dL for females
  - Among NH Asian adults, 46.8 mg/dL for males and 59.8 mg/dL for females
- Age-adjusted prevalence rates of low HDL-C (<40 mg/dL) for 2017 to 2020 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 2017 to 2020 was 62.3 mg/dL. For males, it was 61.6 mg/dL, and for females, it was 63.1 mg/dL. Levels among racial and ethnic groups were as follows (unpublished NHLBI tabulation using NHANES<sup>3</sup>):
  - Among NH White adolescents, 65.0 mg/dL for males and 66.8 mg/dL for females
  - Among NH Black adolescents, 48.1 mg/dL for males and 44.5 mg/dL for females
  - Among Hispanic adolescents, 63.1 mg/dL for males and 70.7 mg/dL for females
  - Among NH Asian adolescents, 52.8 mg/dL for males and 67.9 mg/dL for females
- Triglycerides (≥130 mg/dL) occurred in 7.2% of male adolescents and 6.2% of female adolescents during 2017 to 2020 (unpublished NHLBI tabulation using NHANES<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**

- Triglyceride levels of 150 to 199 mg/dL are generally considered borderline, and levels ≥200 mg/dL are considered elevated, although increases in risk of ASCVD have been demonstrated at levels even <100 mg/dL.<sup>7</sup> Among American adults ≥20

years of age, the geometric mean triglyceride level in 2017 to 2020 was 91.6 mg/dL (unpublished NHLBI tabulation using NHANES<sup>3</sup>). The geometric mean triglyceride levels were 98.5 mg/dL for males and 85.5 mg/dL for females. Levels among racial and ethnic groups were as follows:

- Among NH White adults, 99.0 mg/dL for males and 85.9 mg/dL for females
- Among NH Black adults, 74.1 mg/dL for males and 67.5 mg/dL for females
- Among Hispanic adults, 108.2 mg/dL for males and 96.2 mg/dL for females
- Among NH Asian adults, 110.2 mg/dL for males and 84.3 mg/dL for females
- In 2017 to 2020, 19.9% of adults had high triglyceride levels (≥150 mg/dL; unpublished NHLBI tabulation using NHANES<sup>3</sup>).

**Secular Trends in TC and Lipid Subfractions****Youth****(See Chart 7-1)**

- Between 1999 and 2016, there were favorable trends in mean levels of TC, HDL-C, and non-HDL-C among youth 6 to 19 years of age. There were also favorable trends in levels of LDL-C, triglycerides, and 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 (≥20 Years of Age)****(See Chart 7-2)**

- The prevalence of high TC (≥240 mg/dL) has decreased over time, from 18.3% of adults in 1999 to 2000 to 10.5% in 2017 to 2018.<sup>8</sup>
  - From 1999 to 2020, mean serum TC for adults ≥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>9</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>10</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>8</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 ( $P_{\text{interaction by sex}} = 0.872$ ).<sup>10</sup>
- Geometric mean levels of triglycerides declined from 123 mg/dL in 1999 to 2000 to 97 mg/dL in 2013 to 2014.<sup>11</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>12</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>13</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 the 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 identified >200 lipid loci.<sup>14–18</sup>
- A recent multiancestry GWAS in 1.65 million individuals has identified 941 lipid-associated genomic regions harboring >1700 distinct variants, with 355 novel genomic loci identified.<sup>19</sup> The notable findings also highlight that multiancestry PRSSs leveraging the GWAS findings from multiple ethnicities

are more informative for lipid traits across multiple population groups.<sup>19</sup>

- Lipoprotein(a), a causal risk factor for CAD, is a highly heritable trait. Whole-genome sequencing (which provides a comprehensive coverage of the entire genome, including both coding and noncoding regions) analysis combining structural variants (mainly LPA KIV2-CN) with sequence variations has elucidated that genetic heritability of lipoprotein(a) is  $\approx 85\%$  in Black individuals and  $\approx 75\%$  in European individuals.<sup>20</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>21</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>22–27</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>28,29</sup> Fewer than 10% of patients with FH have actually been diagnosed.
- 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>30</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>31</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>32</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>33</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 individuals with LDL-C  $\geq 190$  mg/dL without pathogenic variants.<sup>28</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 ≥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>34</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>35</sup> Among participants with a pathogenic variant associated with FH compared with those without a pathogenic variant associated with FH, risk of premature ASCVD (≤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 risk factors for ASCVD (age [30–59 years versus <30 years: 2.92 (95% CI, 1.14–7.52); ≥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>36</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>37</sup>
  - In NHANES 1999 to 2014, 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>30</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>38</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>39</sup> These figures are similar to the medians reported for 8 European countries, although there is substantial variation between countries.<sup>40</sup>
- Cascade screening, meaning 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>41</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>42</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>43</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/xanthelomas), and 3 were diagnosed after screening on the basis of family history of biallelic FH. Diet and medications alone reduced LDL-C by 32.2% (SD, 18.0%) to a mean (SD) of 510 mg/dL (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>44</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. Familial combined hyperlipidemia remains underdiagnosed.<sup>45</sup>

## Screening

- About 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>46</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 were in the District of Columbia (92.4%) and Puerto Rico (92.3%), whereas the state with the lowest percentage was South Dakota (77.1%).<sup>47</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>1,48</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>49</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 ( $\text{LDL-C} \geq 190 \text{ mg/dL}$  or  $\text{LDL-C} \geq 160 \text{ mg/dL}$  plus family history) or any hyperlipidemia ( $\text{LDL-C} \geq 130 \text{ mg/dL}$ ) 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>50</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 during the COVID-19 pandemic compared with the same time frame in 2018 to 2019.<sup>51</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>52</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>47</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 ( $P_{\text{linear trend}}=0.07$ ).<sup>9</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>53</sup> Independent predictors of awareness included older age (OR, 2.35 [95% CI, 1.53–3.61] for 30–39 years of age 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

- The Healthy People 2030 target for cholesterol treatment is 54.9% of eligible adults treated. In 2013 to 2016, 44.9% of eligible adults  $\geq 21$  years of age received treatment for blood cholesterol.<sup>5</sup>
- 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>54</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>55</sup>
- 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>10</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>56</sup>
- Among US adults with diabetes, statin use increased from 48.3% to 60.2% between 2005 to 2006 and 2015 to 2016.<sup>9</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>9</sup>
- In the US nationally representative Prognos LDL-C Registry linked to IQVIA longitudinal and prescription claims data for 4 652 468 patients with a history of ASCVD, 58.3% were on any lipid-lowering therapy (of these, 93.1% were on statin only, 4.7% were on statin and ezetimibe, 1.4% were on ezetimibe only, and 0.8% were on PCSK9 inhibitor alone or in combination with statin).<sup>57</sup>
- Among 2963 unweighted visits of patients with a history of stroke or TIA in the NAMCS, statin therapy was initiated or continued in 35.7% of office visits.<sup>58</sup> Among factors associated with statin prescription, office visits in rural areas were associated with a lower likelihood of statin prescription compared with office visits in urban areas (OR, 0.64 [95% CI, 0.41–0.99]).

## Control

- 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>59</sup>
- In NHANES 2011 to 2012, cholesterol control in adults with a history of MI (defined as TC  $< 200$  mg/dL among those receiving treatment) was achieved in 72% of females and 85% of males, and 82% of NH White, 64% of NH Black, and 66% of Hispanic adults.<sup>60</sup>

## Mortality and Complications

- Among 18 288 healthy young and middle-aged adults in 4 US cohorts (ARIC, FHS Offspring, CARDIA, MESA) followed up for a median of 16 years, the highest quartiles of cumulative LDL-C exposure level and time-weighted average LDL-C were associated with incident CHD (aHR, 1.57 [95% CI, 1.10–2.23] for cumulative LDL-C level; aHR, 1.69 [95% CI, 1.23–2.31] for time-weighted average LDL-C), relative to the lowest quartile of each measure, adjusted for demographic and clinical risk factors and index visit LDL-C.<sup>61</sup>
- In 589 participants in the Cardiovascular Risk in Young Finns Study with non-HDL-C measured in adolescence (12–18 years of age), young adulthood (21–30 years of age), and midadulthood (33–45 years of age), a 38.61-mg/dL higher non-HDL-C at each life stage was associated with higher odds

of CAC in midadulthood, adjusted for cardiovascular risk factors (adolescence aOR, 1.16 [95% credible interval, 1.01–1.46]; young adulthood aOR, 1.14 [95% credible interval, 1.01–1.43]; midadulthood aOR, 1.12 [95% credible interval 1.01–1.34]), with an accumulated aOR for CAC of 1.50 (95% credible interval, 1.14–1.92).<sup>62</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×years [95% CI, 1.02–1.09]) and the slope of the LDL-C accumulation (0.797 per 1 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>63</sup>
- Among 28 024 participants in the WHS, in addition to significant associations per 1-SD increment of standard cholesterol measures such as TC (aHR, 1.39 [95% CI, 1.12–1.73]), LDL-C (aHR, 1.38 [95% CI, 1.10–1.74]), HDL-C (aHR, 0.39 [95% CI, 0.27–0.55]), and apolipoprotein B (aHR, 1.89 [95% CI, 1.52–2.35]) with premature CHD (onset <55 years of age), total LDL particles (aHR, 1.75 [95% CI, 1.42–2.15]), novel lipoprotein fractions such as small LDL particles (aHR, 2.25 [95% CI, 1.76–2.89]), and total triglyceride-rich lipoproteins (aHR, 1.74 [95% CI, 1.44–2.10]) were significantly associated with premature CHD.<sup>64</sup>
- In a prospective case-cohort study (N=480 cases and 496 controls) within the WHS, 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>65</sup>
- In a large study of the National Health Insurance Service in Korea (N=15 860 253) starting in 2009 to 2010 that evaluated 555 802 deaths resulting from all causes during a mean of 8.4 years of follow-up through 2018, a U-shaped association of HDL-C with all-cause mortality was observed. Relative to HDL-C levels of 50 to 59 mg/dL, individuals at the lowest HDL-C levels (<20 mg/dL) had higher risk for all-cause mortality (aHR for males, 3.03 [95% CI, 2.84–3.24]; aHR for females, 2.10 [95% CI, 1.84–2.40]), and individuals at the highest HDL-C levels (≥110 mg/dL) also had higher risk for all-cause mortality (aHR for males, 1.30 [95% CI 1.23–1.38]; aHR for females, 1.21 [95% CI, 1.11–1.31]).<sup>66</sup> A similar relationship was observed among N=14 478 participants of the UK Biobank and replicated in the Emory Cardiovascular Biobank: HDL-C levels

>80 mg/dL were associated with a higher risk for all-cause mortality (aHR, 1.96 [95% CI, 1.42–2.71]) and cardiovascular mortality (aHR, 1.71 [95% CI, 1.09–2.68]) compared with HDL-C of 40 to 60 mg/dL.<sup>67</sup>

- 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 triglyceride 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>26</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>68</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 ≥30 mg/dL at baseline or ≥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 ≥50 mg/dL, and 1.43 (95% CI, 1.15–1.76) for on-statin levels ≥50 mg/dL.<sup>69</sup>
- Among patients with ASCVD on statin therapy in the AIM-HIGH cohort, a 1-SD (37 nmol/L) higher lipoprotein(a) was associated with a 7% higher risk of recurrent ASCVD events (aHR, 1.07 [95% CI, 1.04–1.10]).<sup>70</sup>
- In >460 000 individuals from the UK Biobank, the risk of incident ASCVD per 50 nmol/L lipoprotein(a) was similar across ethnicity with an HR of 1.11 (95% CI, 1.10–1.12) in White, 1.10 (95% CI, 1.04–1.16) in South Asian, and 1.07 (95% CI, 1.00–1.15) in Black individuals.<sup>6</sup> Lipoprotein(a) ≥150 nmol/L was present in 12.2% of those without and 20.3% of those with preexisting ASCVD and was associated with an HR of 1.50 (95% CI, 1.44–1.56) and 1.16 (95% CI, 1.05–1.27) for incident ASCVD, respectively.



- Among 502 655 adults 40 to 69 years of age in the UK Biobank, a linear association between higher prepandemic HDL-C level and later COVID-19-related hospitalization was observed.<sup>71</sup> Each 0.2-mmol/L higher HDL-C level was associated with 7% lower odds of hospitalization (aOR, 0.93 [95% CI, 0.90–0.96]).

## 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>72</sup> Costs were split relatively evenly between younger and older adults (51.0% for 20–64 years of age, 48.4% for ≥65 years of age, 0.6% for <20 years of age), were higher for public versus private insurance (49.1% public insurance, 43.8% private insurance, 7.1% out-of-pocket payments), and were concentrated in prescription medications and ambulatory visits (45.6% prescribed pharmaceuticals, 33.4% ambulatory care, 5.9% inpatient care, 4.7% nursing care facility, 0.5% ED). Hyperlipidemia was among the conditions with highest annual spending growth for public insurance from 1999 to 2016 at 9.3% (95% CI, 8.2%–10.4%) per year; annual spending

growth for hyperlipidemia was 5.2% overall, 4.0% for private insurance, and –0.9% for out-of-pocket payments.

- Among Medicare Part D beneficiaries in the United States from 2014 to 2018, Medicare expenditure for LDL-C-lowering therapy decreased 46% from \$6.3 billion in 2014 to \$3.3 billion in 2018.<sup>73</sup>

## Global Burden of Hypercholesterolemia

### (See Chart 7-5 and Table 7-2)

- Among the GBD data, global years of life lost attributable to high LDL-C totaled 5.71 million (95% UI, 3.68–8.27) in 2019. LDL-C was the third highest contributor to CVD DALYs in 2019, after high SBP and dietary risks.<sup>74</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-C 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), 2017 to 2020**

Population group	Prevalence of TC ≥200 mg/dL	Prevalence of TC ≥240 mg/dL	Prevalence of LDL-C ≥130 mg/dL	Prevalence of HDL-C <40 mg/dL
Both sexes	86 400 000 (34.7)	24 700 000 (10.0)	63 100 000 (25.5)	41 300 000 (16.9)
Males	38 900 000 (32.8)	11 000 000 (9.5)	30 300 000 (25.6)	29 900 000 (24.9)
Females	47 500 000 (36.2)	13 700 000 (10.4)	32 800 000 (25.4)	11 400 000 (9.3)
NH White males	32.5	9.6	25.0	25.0
NH White females	37.2	10.7	24.0	8.8
NH Black males	27.5	6.9	26.4	15.3
NH Black females	29.6	9.3	22.5	7.9
Hispanic males	32.8	9.3	23.7	29.5
Hispanic females	33.6	10.0	27.5	11.8
NH Asian males	40.7	13.0	31.5	25.4
NH Asian females	37.7	8.7	25.3	6.9

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. In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>75</sup>

COVID-19 indicates coronavirus disease 2019; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NH, 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> applied to 2020 population estimates.

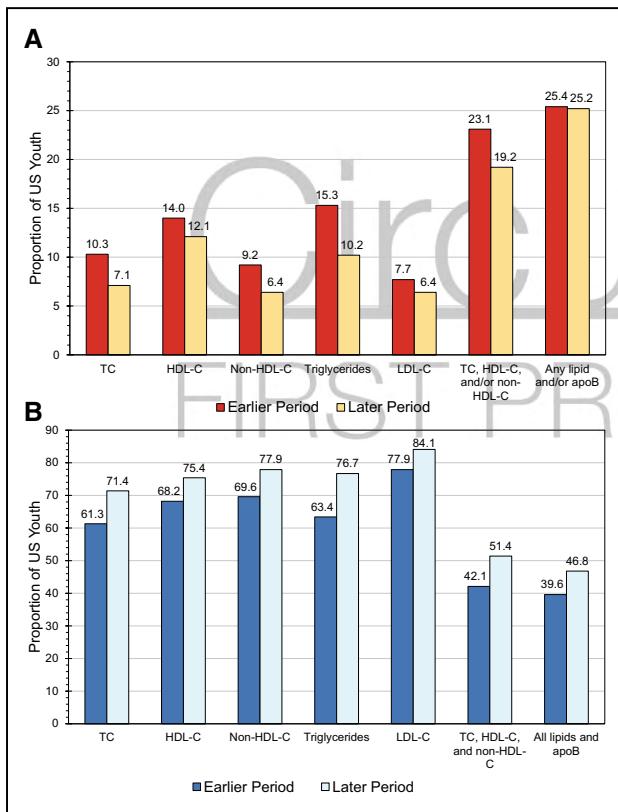
**Table 7-2.** Deaths Caused by High LDL-C Worldwide by Sex, 2020

	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)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; LDL-C, low-density lipoprotein cholesterol; PAF, population attributable fraction; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>76</sup>



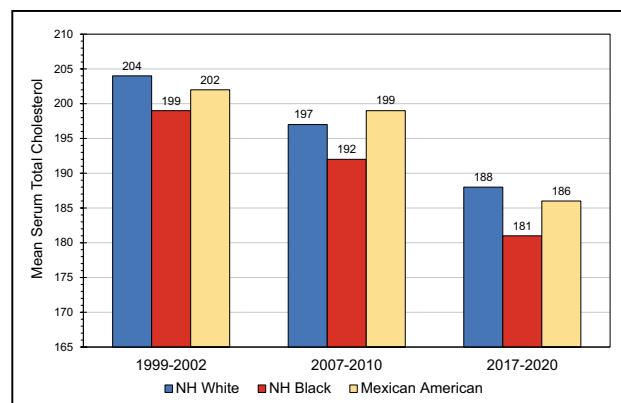
**Chart 7-1. Proportions of US youth with guideline-defined high (or, for HDL-C, low) and acceptable lipid levels in the period of 1999 to 2016, NHANES.**

**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 (Continued)

**Chart 7-1 Continued.** 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>48</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>



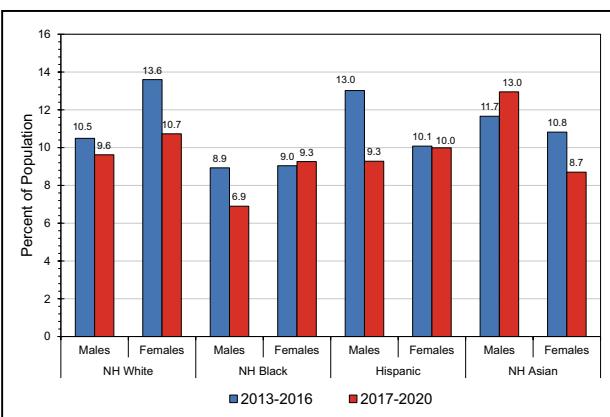
**Chart 7-2. Age-adjusted trends in mean serum TC among US adults ≥20 years of age by race and ethnicity and survey year (NHANES 1999–2002, 2007–2010, and 2017–2020).**

Values are in milligrams per deciliter. In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>75</sup>

COVID-19 indicates coronavirus disease 2019; NH, 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>

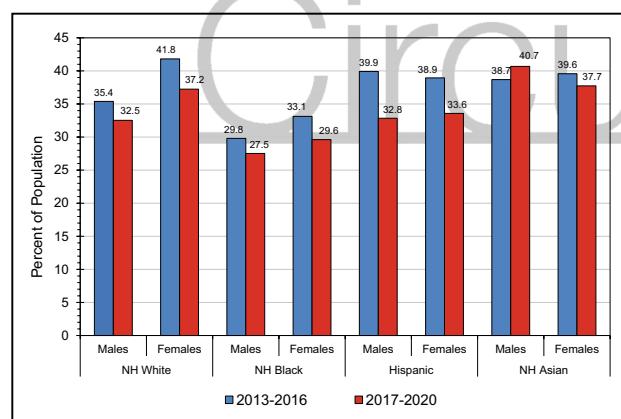


**Chart 7-4. Age-adjusted trends in the prevalence of serum TC ≥240 mg/dL in US adults ≥20 years of age, by race and ethnicity, sex, and survey year (NHANES 2013–2016 and 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>75</sup>

COVID-19 indicates coronavirus disease 2019; NH, 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>

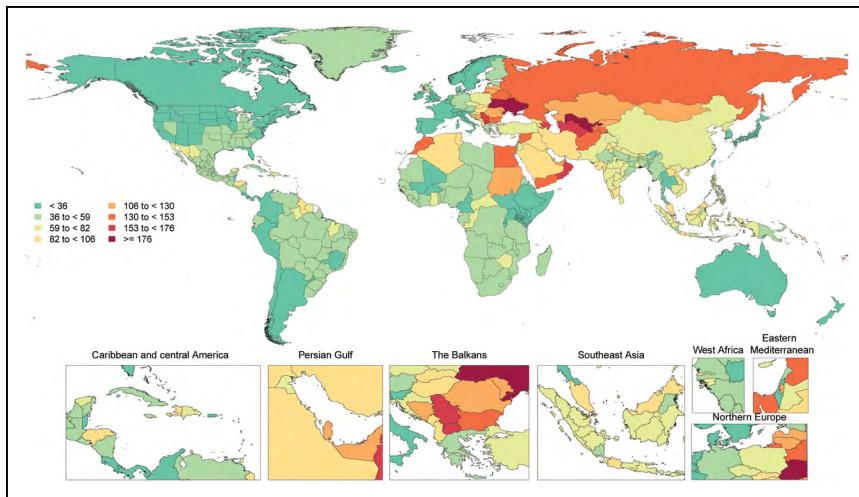


**Chart 7-3. Age-adjusted trends in the prevalence of serum TC ≥200 mg/dL in US adults ≥20 years of age by race and ethnicity, sex, and survey year (NHANES 2013–2016 and 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>75</sup>

COVID-19 indicates coronavirus disease 2019; NH, 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 7-5. Age-standardized global mortality rates attributable to high LDL-C per 100,000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and LDL-C, low-density lipoprotein cholesterol.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>76</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 mm Hg (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 mm Hg, DBP ≥80 mm Hg, or self-reported antihypertensive medicine use, or
  - Having been told previously, at least twice, by a physician or other health professional that one has HBP.
- Other important BP classifications, or phenotypes, assessed 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 46.7% in NHANES in 2017 to 2020 (50.4% for males and 43.0% for females). This equates to an estimated 122.4 million adults ≥20 years of age

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

who have HBP (62.8 million males and 59.6 million females; Table 8-1).

- In NHANES 2017 to 2020,<sup>6</sup> the prevalence of HBP was 28.5% among those 20 to 44 years of age, 58.6% among those 45 to 64 years of age, and 76.5% among those ≥65 years of age (unpublished NHLBI tabulation).
- In NHANES 2017 to 2020,<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 2017 to 2020<sup>6</sup> indicate that 38.0% 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 2017 to 2020 is shown in race and ethnicity and sex subgroups in Chart 8-2.
- In a cohort of 3367 patients with established kidney disease, 40.4% had resistant hypertension, which was defined as having SBP ≥140 mm Hg or DBP ≥90 mm Hg on ≥3 antihypertensive medications or use of ≥4 antihypertensive medications and SBP <140 mm Hg and DBP <90 mm Hg.<sup>7</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>8</sup>
- In NHANES 2015 to 2016, among youth 8 to 17 years of age, hypertension was more common among males (5.9%) than females (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 males (16.9%) than females (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>8</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>9</sup>
- In a systematic review of 60 studies of pediatric patients (defined as individuals  $\leq 18$  years of age) with type 2 diabetes, the prevalence of hypertension among 3463 participants was 25.3% (95% CI, 19.6%–31.5%).<sup>10</sup> Male participants had higher hypertension risk than female participants (OR, 1.42 [95% CI, 1.10–1.83]), with Pacific Islander and Indigenous (referring to the indigenous populations of North America) youth having the highest prevalence of all racial and ethnic groups (Pacific Islander youth, 26.7% [95% CI, 14.5%–40.7%]; Indigenous youth, 26.5% [95% CI, 17.3%–36.7%]; White youth, 21.0% [95% CI, 12.7%–30.6%]; Black youth, 19.0% [95% CI, 12.0%–27.2%]; Hispanic/Latino youth, 15.1% [95% CI, 6.6%–26.3%]; Asian youth, 18.4% [95% CI, 9.5%–29.2%]).
  - In an analysis from SHIP AHOY, a cross-sectional cohort study of 397 adolescents 11 to 19 years of age, the prevalence of hypertension with awake ambulatory BP using the 95th percentile was 17% and 11% for SBP and DBP, respectively.<sup>11</sup> With the use of the 2017 ACC/AHA adult thresholds of  $\geq 130/80$  mm Hg, the prevalence was higher at 27% and 13% for SBP and DBP, respectively.
  - 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>12</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 2017 to 2020 data,<sup>6</sup> the age-adjusted prevalence of hypertension among NH Black people was 55.8% among males and 56.9% 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>13</sup>

- Data from the NHIS 2018 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>14</sup>

### Incidence and Lifetime Risk

- 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  $\geq 130$  mm Hg, DBP  $\geq 80$  mm Hg, or self-reported antihypertensive medication use) by 55 years of age was 75.7% in Black females, 75.5% in Black males, 54.5% in White males, and 40.0% in White females.<sup>15</sup>
- 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>16</sup>
- In a study of the UK General Practice Research Datalink of 13 177 290 individuals on antihypertensive agents, the age-standardized incidence of resistant hypertension, defined as having SBP  $\geq 140$  mm Hg or DBP  $\geq 90$  mm Hg on  $\geq 3$  antihypertensive medications or use of  $\geq 4$  antihypertensive medications and SBP  $< 140$  mm Hg and DBP  $< 90$  mm Hg, increased from 0.93 cases per 100 person-years (95% CI, 0.87–1.00) in 1996 to a peak level of 2.07 cases per 100 person-years (95% CI, 2.03–2.12) in 2004 and then decreased to 0.42 cases per 100 person-years (95% CI, 0.40–0.44) in 2015.<sup>17</sup> The age-standardized prevalence increased from 1.75% (95% CI, 1.66%–1.83%) in 1995 to a peak of 7.76% (95% CI, 7.70%–7.83%) in 2007 and subsequently declined to 6.46% (95% CI, 6.38%–6.54%) in 2015. Compared with patients 65 to 69 years of age, those  $\geq 80$  years of age were more likely to have prevalent resistant hypertension throughout the study period.

### 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 ( $\geq 140/90$  mm Hg), 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 definition of hypertension ( $\geq 130/80$  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>18</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 ( $P_{\text{trend}} < 0.001$ ) and the prevalence of hypertension declined from 6.6% to 4.5% ( $P_{\text{trend}} = 0.005$ ).<sup>8</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 ( $P_{\text{trend}} = 0.03$ ) 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 ( $P_{\text{trend}} = 0.001$  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>8</sup>
- In NHDS data compiled by the CDC, chronic hypertension in pregnancy (defined as SBP  $\geq 140$  mmHg or DBP  $\geq 90$  mmHg 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>19</sup>

## Risk Factors

- 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-weight/underweight youth was 16.2% compared with 8.7%.<sup>8</sup>

- Among 60 027 participants in the Norwegian Mother and Child Cohort Study who were normotensive before pregnancy, the PAF for pharmaco logically 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>20</sup>
- In a cohort of 58 671 parous females participating in the Nurses' Health Study 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; HR, 2.2 [95% CI, 2.1–2.3] for preeclampsia).<sup>21</sup>
- In an analysis of the Australian Longitudinal Study on Women's Health, 9508 females were followed up for 145 159 person-years, and 1556 females (16.4%) developed hypertension during follow-up.<sup>22</sup> The incidence of hypertension was higher among females with polycystic ovarian syndrome (17 per 1000 person-years) compared with females without (10 per 1000 person-years). The incidence rate difference of hypertension was 4-fold higher (15.8 per 1000 person-years versus 4.3 per 1000 person-years) among obese females with polycystic ovarian syndrome compared with age-matched lean females with polycystic ovarian syndrome. Polycystic ovarian syndrome was independently associated with 37% greater risk of hypertension (HR, 1.37 [95% CI, 1.14–1.65]) after adjustment for BMI, family history of hypertension, occupation, and comorbidity with type 2 diabetes.
- In a systematic review of 11 cohort studies including 224 829 individuals, living or working in environments with noise exposure was significantly associated with increased risk of hypertension (RR, 1.18 [95% CI, 1.06–1.32]), and a linear dose-response was noted, with a risk ratio of hypertension of 1.13 (95% CI, 0.99–1.28) per 10-decibel higher ambient noise.<sup>23</sup>
- In a study from the China Health and Nutrition Survey of 12 080 adults 18 to 65 years of age who were enrolled from 1989 and 2011, compared with the referent group of those who worked 35 to 49 h/wk, participants who worked no more than 34 h/wk (HR, 1.21 [95% CI, 1.03–1.41]) and at least 56 h/wk (HR, 1.38 [95% CI, 1.19–1.59]) had a higher risk

- of developing hypertension during follow-up after adjustment for sociodemographics, lifestyle factors, and occupation type.<sup>24</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>25</sup>
  - In a meta-analysis of 133 studies with 12 197 participants, each 50-mmol reduction in 24-hour sodium excretion (a marker of sodium consumption) was associated with a 1.10-mm Hg (95% CI, 0.66–1.54) reduction in SBP and a 0.33-mm Hg (95% CI, 0.04–0.63) reduction in DBP.<sup>26</sup> Greater SBP and DBP lowering from the same amount of sodium reduction was seen in populations with older age ( $-3.33/-1.23$  mm Hg in those  $>65$  years of age compared with  $-0.39/-0.18$  mm Hg in those  $<35$  years of age), individuals with higher baseline SBP ( $-2.97/-1.41$  mm Hg in those with SBP  $>160$  mm Hg compared with  $-0.39/-0.07$  mm Hg in those with SBP  $<120$  mm Hg), and Black individuals ( $-4.07/-2.37$  mm Hg compared with  $-1.60/-0.82$  mm Hg in White individuals).
  - In an open-label, cluster-randomized trial involving 20 995 people from 600 villages in rural China, the use of a salt substitute (75% sodium chloride and 25% potassium chloride by mass) compared with the use of regular salt (100% sodium chloride) resulted in a lower incidence of stroke (RR, 0.86 [95% CI, 0.77–0.96]), all-cause mortality (RR, 0.88 [95% CI, 0.82–0.95]), and MACEs (RR, 0.87 [95% CI, 0.80–0.94]).<sup>27</sup> There was no increase in rates of hyperkalemia with use of the salt substitute (RR, 1.04 [95% CI, 0.80–1.37]).
  - 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>28</sup>
  - In a population-based study from the Australian Longitudinal Study on Women's Health, which included 6599 middle-aged and 6099 females of reproductive age, higher intakes of flavones (RR for highest versus lowest quintile of consumption, 0.82 [95% CI, 0.70–0.97]), isoflavones (RR, 0.86 [95% CI, 0.75–0.99]), and flavanones (RR, 0.83 [95% CI, 0.69–1.00]) were associated with a lower risk of hypertension in the middle-aged cohort.<sup>29</sup> In the cohort of reproductive age, higher intakes of flavanols (RR, 0.70 [95% CI, 0.49–0.99]) were associated with a lower risk of hypertension.

- In the JHS, intermediate and ideal levels versus a 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>30</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>31</sup>
- In an analysis of the electronic FHS participants, higher daily habitual PA as measured by a smart-watch was associated with lower home BP with every 1000-step increase in step count being associated with a 0.49-mm Hg lower home SBP ( $P=0.004$ ) and 0.36 mm Hg lower home DBP ( $P=0.003$ ), with no difference between males and females.<sup>32</sup>
- In a double-blind, placebo-controlled, crossover study (PATH-BP), 4 g/d acetaminophen given to 110 hypertensive individuals (both treated and untreated) resulted in a higher ambulatory BP compared with placebo of 4.7 mm Hg for SBP and 1.6 mm Hg for DBP.<sup>33</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>34</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>35</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>36</sup>

## Social Determinants

- 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>37</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>38</sup>

- In an analysis of the JHS cohort study of NH Black people, high (versus low) adult SES measures were associated with a lower prevalence of hypertension, with the exception of having a college degree (PR, 1.04 [95% CI, 1.01–1.07]) and upper-middle income (PR, 1.05 [95% CI, 1.01–1.09]).<sup>39</sup> Higher childhood SES was associated with a lower prevalence (PR, 0.83 [95% CI, 0.75–0.91]) and risk (HR, 0.76 [95% CI, 0.65–0.89]) of hypertension.
- 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>40</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 mm Hg per 1-SD increase [95% CI, 0.25–2.83]) in both sexes and lower levels of DBP (1.24 mm Hg [95% CI, 0.37–2.12]) among females only.<sup>41</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>42</sup>
- In a systematic review including 45 studies and involving 117 252 workers, an increase in both SBP and DBP among permanent night workers (2.52 mm Hg [95% CI, 0.75–4.29] and 1.76 mm Hg [95% CI, 0.41–3.12], respectively) compared with day workers was noted.<sup>43</sup> For rotational shift workers, both with and without night work, compared with day workers without rotations, an increase was noted only for SBP (0.65 mm Hg [95% CI, 0.07–1.22] and 1.28 mm Hg [95% CI, 0.18–2.39], respectively).

## Borderline Risk Factors/Subclinical/ Unrecognized Disease

- Among 17 747 participants in NHANES 2007 to 2012 who were 8 to 80 years of age, the yearly net transition probabilities for ideal BP (<90th percentile by age and sex for individuals 8–19 years of age; SBP <120 mm Hg and DBP <80 mm Hg for individuals 20–80 years of age) to prehypertension (90th–95th percentile or SBP  $\geq 120$  mm Hg or DBP  $\geq 80$  mm Hg for individuals 8–19 years of age; SBP 120–129 mm Hg or DBP 80–89 mm Hg for individuals 20–80 years of age) among Black 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>44</sup>

## Genetics/Family History

- Several large-scale GWASs and whole-exome and whole-genome sequencing studies in primarily European ancestry populations, with the 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>45–55</sup>
- Nine genetic loci have been identified for BP traits in African-ancestry populations.<sup>56</sup> Large-scale genomic discovery effort in non-European ancestry populations is needed to comprehensively understand the genetic architecture of hypertension.
- PRSs for hypertension are also associated with increased risk of CVD, CHD, and stroke,<sup>45,57</sup> and mendelian randomization analysis suggests a causal role for higher BP in 14 cardiovascular conditions, including IHD (SBP per 10 mm Hg: OR, 1.33 [95% CI, 1.24–1.41]; DBP per 5 mm Hg: OR, 1.20 [95% CI, 1.14–1.27]) and stroke (SBP per 10 mm Hg: OR, 1.35 [95% CI, 1.24–1.48]; DBP per 5 mm Hg: OR, 1.20 [95% CI, 1.12–1.28]).<sup>58</sup>
- Sex-specific genetic burden for early-onset hypertension is reported to be higher in females and may contribute to the rapid progression of BP measures over the lifetime among females.<sup>59,60</sup>
- Given the strong effects of environmental factors on hypertension, gene-environment interactions are important in the pathophysiology of hypertension. 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> In individuals of European ancestry, a high genetic risk for hypertension and CVD is offset by a favorable lifestyle. Large-scale gene-environment interaction

studies in multiethnic populations have not yet been conducted.

- The clinical implications and utility of hypertension genes remain unclear, although some genetic variants have been shown to influence response to anti-hypertensive agents.<sup>65</sup> Pharmacogenomic studies in ethnically diverse populations have the potential to recognize potential adverse events and to inform personalized drug efficacy.<sup>66</sup>

## Prevention

### Awareness, Treatment, and Control

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

- Based on NHANES 2017 to 2020 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, 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 2017 to 2020<sup>6</sup> found that hypertension awareness, treatment, and control increased in all racial and ethnic groups between 1999 to 2002 and 2007 to 2010. Changes in hypertension awareness, treatment, and control were more modest between 2007 to 2010 and 2017 to 2020, with some racial and ethnic subgroups experiencing declines (Table 8-2).
- In an analysis of 18262 adults  $\geq 18$  years of age with hypertension (defined as  $\geq 140/90$  mmHg) 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>18</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).
- 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  $\geq 130$  mmHg and increased cardiovascular risk.<sup>67</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>68</sup>

- 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  $\geq 140$  mmHg or DBP  $\geq 90$  mmHg (PR, 1.26 [95% CI, 1.16–1.37]).<sup>69</sup>
- 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>70</sup>
- In the UK Biobank among 99468 previously diagnosed, treated hypertensive individuals, 60 to 69 years of age (OR, 0.61 [95% CI, 0.58–0.64] compared with 40–50 years of age), alcohol consumption  $>30$  units per week (OR, 0.61 [95% CI, 0.58–0.64] compared with no alcohol use), Black ethnicity (OR, 0.73 [95% CI, 0.65–0.82] compared with White ethnicity), and obesity (OR, 0.73 [95% CI, 0.71–0.76] compared with normal BMI) were associated with lack of hypertension control.<sup>71</sup> Comorbidities associated with lack of BP control included CVD (OR, 2.11 [95% CI, 2.04–2.19]), migraines (OR, 1.68 [95% CI, 1.56–1.81]), diabetes (OR, 1.32 [95% CI, 1.27–1.36]), and depression (OR, 1.27 [95% CI, 1.20–1.34]).
- In an analysis of 269010 US veterans with apparent treatment-resistant hypertension from 2000 to 2017, 4277 (1.6%) were tested for primary aldosteronism.<sup>72</sup> Testing was associated with a 4-fold higher likelihood of initiating mineralocorticoid antagonist therapy (HR, 4.10 [95% CI, 3.68–4.55]). After adjustment for patient-, health care professional-, and center-level covariates (including baseline BP), compared with no testing, testing for primary aldosteronism was associated with an average 1.47-mmHg (95% CI, –1.64 to –1.29 mmHg) lower SBP over time.
- 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>73</sup>

## Mortality

(See Table 8-1)

- According to data from the NVSS, in 2020,<sup>74</sup> 119 997 deaths were attributable primarily to HBP

(Table 8-1). The 2020 age-adjusted death rate attributable primarily to HBP was 29.1 per 100 000. Age-adjusted death rates attributable to HBP (per 100 000) in 2020 were 29.1 for NH White males, 69.0 for NH Black males, 27.7 for Hispanic males, 20.7 for NH Asian/Pacific Islander males, 41.3 for NH American Indian/Alaska Native males, 23.5 for NH White females, 46.9 for NH Black females, 20.5 for Hispanic females, 16.6 for NH Asian/Pacific Islander females, and 26.3 for NH American Indian/Alaska Native females (unpublished NHLBI tabulation using CDC WONDER<sup>75</sup>).

- From 2010 to 2020, the death rate attributable to HBP increased 54.8%, and the actual number of deaths attributable to HBP rose 90.1%. During this 10-year period, in NH White people, the HBP age-adjusted death rate increased 63.0%, whereas the actual number of deaths attributable to HBP increased 88.4%. In NH Black people, the HBP death rate increased 29.7%, whereas the actual number of deaths attributable to HBP increased 73.3%. In Hispanic people, the HBP death rate increased 38.7%, and the actual number of deaths attributable to HBP increased 135.3% (unpublished NHLBI tabulation using CDC WONDER<sup>75</sup>).
- When any mention of HBP was present, the overall age-adjusted death rate in 2020 was 162.0 per 100 000. Death rates were 175.7 for NH White males, 325.3 for NH Black males, 129.1 for NH Asian or Pacific Islander males, 235.9 for NH American Indian or Alaska Native males (underestimated because of underreporting), and 199.4 for Hispanic males. In females, rates were 127.9 for NH White females, 216.1 for NH Black females, 88.5 for NH Asian or Pacific Islander females, 157.6 for NH American Indian or Alaska Native females (underestimated because of underreporting), and 132.1 for Hispanic females (unpublished NHLBI tabulation using CDC WONDER<sup>75</sup>).
- The elimination of hypertension could reduce CVD mortality by 30.4% among males and 38.0% among females.<sup>76</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>76</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>77</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>78</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 (HR, 2.09 [95% CI, 1.23–4.48]) mortality compared with normotension.<sup>79</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>80</sup>

## Complications

- In the Blood Pressure Lowering Treatment Trialists Collaboration individual patient-level meta-analysis of 48 RCTs and 344 716 participants, a 5-mmHg reduction of SBP reduced the risk of major cardiovascular events by ≈10%, regardless of previous diagnoses of CVD.<sup>81</sup> This effect was also seen at normal and high-normal BP values.
- In a meta-analysis that included 93 772 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>82</sup>
- In a cross-sectional analysis from SHIP AHOY of 397 adolescents 11 to 19 years of age, absolute mean systolic ambulatory BP cut points of 125 mmHg during wake hours, 110 mmHg during sleep, and 120 mmHg over 24 hours were observed to have a balance of sensitivity (67%) and specificity (60%) for predicting LVH.<sup>11</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>83</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 mm Hg or DBP 80–89 mm Hg) per 1000 person-years compared with 1.37 (95% CI, 1.07–1.75) among those who retained normal BP through 40 years of age.<sup>83</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>84</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>85</sup>
- Among 5236 adults in the REGARDS study ≥65 years of age currently taking antihypertensive medications and enrolled in Medicare fee-for-service, having more indicators of frailty (low BMI, cognitive impairment, depressive symptoms, exhaustion, impaired mobility, and history of falls) was associated with an increased risk for serious fall injuries. The HR associated with 1 versus 0 indicators of frailty was 1.18 (95% CI, 0.99–1.40), with 2 versus 0 indicators was 1.49 (95% CI, 1.19–1.87), and with ≥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>86</sup>
- In an RCT of 8511 older Chinese hypertensive patients (60–80 years of age), randomizing to a BP target of 110 to <130 mm Hg (intensive treatment) compared with a target of 130 to <150 mm Hg (standard treatment) reduced MACEs (HR, 0.74 [95% CI, 0.60–0.92]).<sup>87</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 mm Hg) had a 26% lower risk of developing AF over the 5.2 years of follow-up (28 322 person-years) than those in the standard BP-lowering arm (target SBP <140 mm Hg; HR, 0.74 [95% CI, 0.56–0.98];  $P=0.037$ ).<sup>88</sup>
- In 1034 adults from the JHS cohort of NH Black participants completing ambulatory BP monitoring, each 1-SD higher level of mean daytime SBP (13.5 mm Hg) was also associated with an increased incidence of CVD events (HR, 1.53 [95% CI, 1.24–1.88]) after multivariable adjustment that included clinic BP. Adjusted findings were similar for nighttime SBP (HR, 1.48 [95% CI, 1.22–1.80]) per 15.5 mm Hg, daytime DBP (HR, 1.25 [95% CI, 1.02–1.51]) per 9.3 mm Hg, and nighttime DBP (HR, 1.30 [95% CI, 1.06–1.59]) per 9.5 mm Hg.<sup>80</sup>
- A meta-analysis (23 cohorts with 20 445 participants) showed that white-coat hypertension is associated with an increased risk for CVD among untreated individuals (aHR, 1.38 [95% CI, 1.15–1.65]) but not among treated individuals (HR, 1.16 [95% CI, 0.91–1.49]).<sup>89</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>7</sup>
- In an analysis from the CRIC study of 3873 participants, 180 participants (4.6%) had orthostatic hypotension and 81 (2.1%) had orthostatic hypertension.<sup>90</sup> Orthostatic hypotension was associated with high risk for cardiovascular outcomes, including HF, MI, stroke, or PAD (HR, 1.12 [95% CI, 1.03–1.21]), but not kidney outcomes or mortality. Orthostatic hypertension was independently associated with high risk for kidney outcomes, including incident ESRD or 50% decline in eGFR (HR, 1.51 [95% CI, 1.14–1.97]), but not cardiovascular outcomes or mortality.
- In a prospective follow-up of the REGARDS, MESA, and JHS cohorts (N=31 856), 63.0% (95% CI, 54.9%–71.1%) of the 2584 incident CVD events occurred in participants with SBP <140 mm Hg and DBP <90 mm Hg.<sup>91</sup>
- Among 3319 adults ≥65 years of age from the SAGES 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.
  - In a meta-analysis of 20 studies and 7 899 697 participants, higher SBP variability (OR, 1.25 [95% CI, 1.16–1.35]), mean SBP (OR, 1.12 [95% CI, 1.02–1.29]), DBP variability (OR, 1.20 [95% CI, 1.12–1.29]), and mean DBP (OR, 1.16 [95% CI, 1.04–1.29]) were associated with dementia and cognitive impairment.<sup>94</sup>
  - In an analysis of the ONTARGET study, the lowest risk of ESRD or doubling of serum creatinine (707 events overall) was seen at achieved SBP of 120 to <140 mm Hg; risk increased with higher (HR, 3.06 [95% CI, 1.90–3.32]) and lower (HR, 1.97 [95% CI, 1.7–3.32]) SBP, with similar RRs reported with or without diabetes.<sup>95</sup>
  - In an analysis from the CKiD cohort, high mean arterial pressure >90th percentile was associated with progression, defined as time to renal replacement therapy or 50% decline in baseline renal function, in children (HR, 1.88 [95% CI, 1.03–3.44]) only after 4 years of follow-up.<sup>96</sup> Among those with glomerular CKD, higher risk for progression was noted from baseline with the highest risk in those with mean arterial pressure >90th percentile (HR, 3.23 [95% CI, 1.34–7.79]).
  - In an individual patient meta-analysis of 33 trials including 260 447 participants with 15 012 cancer events, no associations were identified between any antihypertensive drug class and risk of any cancer (HR, 0.99 [95% CI, 0.95–1.04] for ACE inhibitors; HR, 0.96 [95% CI, 0.92–1.01] for angiotensin receptor blockers; HR, 0.98 [95% CI, 0.89–1.07] for  $\beta$ -blockers; HR, 1.01 [95% CI, 0.95–1.07] for thiazides), except for calcium channel blockers (HR, 1.06 [95% CI, 1.01–1.11]).<sup>97</sup> In a network meta-analysis comparing each drug class with placebo, no drug class was associated with an excess cancer risk (HR, 1.00 [95% CI, 0.93–1.09] for ACE inhibitors; HR, 0.99 [95% CI, 0.92–1.06] for angiotensin receptor blockers; HR, 0.99 [95% CI, 0.89–1.11] for  $\beta$ -blockers; HR, 1.04 [95% CI, 0.96–1.13] for calcium channel blockers; HR, 1.00 [95% CI, 0.90–1.10] for thiazides).

## 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 2009 to 2019, the number of inpatient discharges from short-stay hospitals with HBP as the principal diagnosis increased from 291 000 to 1 413 000 (Table 8-1). The number of discharges with any listing of HBP increased from 15 292 000 to 18 196 000.
- In 2019, there were 10 000 principal diagnosis discharges for essential hypertension (HCUP,<sup>98</sup> unpublished NHLBI tabulation).
- In 2019, there were 9 613 000 all-listed discharges for essential hypertension (HCUP,<sup>98</sup> unpublished NHLBI tabulation).
- In 2018, 336 100 000 of 860 386 000 physician office visits had a primary diagnosis of essential hypertension (*ICD-9-CM* 401; NAMCS,<sup>99</sup> unpublished NHLBI tabulation). There were 916 000 ED discharges with a principal diagnosis of essential hypertension in 2019 (HCUP,<sup>98</sup> unpublished NHLBI tabulation), and 3 743 000 of 125 721 000 hospital outpatient visits in 2011 were for essential hypertension (NHAMCS,<sup>100</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>101</sup>

## Cost

### (See Table 8-1)

- The estimated direct and indirect cost of HBP for 2018 to 2019 (annual average) was \$52.2 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>102</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>103</sup>
- According to data from MEPS for 2011 to 2014, among individuals with a diagnosis code for hypertension who were ≥18 years of age (n=26 049), the mean annual costs of hypertension ranged from \$3914 (95% CI, \$3456–\$4372) for those with no comorbidities to \$13 920 (95% CI, \$13 166–\$14 674) for those with ≥3 comorbidities.<sup>104</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>105</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>106</sup>
- In a meta-analysis of population-based studies conducted in Africa that included 91 studies from 1989 to 2016, the prevalence of hypertension was 55.2% among adults ≥55 years of age.<sup>107</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>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. 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 ≥140 mmHg was estimated to be 20 526 per 100 000. This represents an increase from 17 307 per 100 000 in 1990.<sup>109</sup> In addition, the prevalence of SBP 110 to 115 mmHg 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 mmHg or higher in 2015. Of this group, 874 million had SBP ≥140 mmHg.<sup>109</sup>
- It has been estimated that 7.834 million deaths and 143.037 million DALYs in 2015 could be attributed to SBP ≥140 mmHg.<sup>109</sup> In addition, 10.7 million deaths and 211 million DALYs in 2015 could be attributed to SBP of 110 to 115 mmHg or higher.
- Between 1990 and 2015, the number of deaths related to SBP ≥140 mmHg 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>109</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>110</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>111</sup>
- In a cross-sectional study of 12 926 individuals from the Bangladesh Demographic and Health Survey, the overall prevalence of hypertension was 27.4%, being higher in females (28.4%) than males (26.2%). Of those with hypertension, 42.4% (n=1508) of people were aware of being hypertensive.<sup>112</sup>
- In a systematic review of 15 cross-sectional studies from the United Arab Emirates involving 139 907 adults, the pooled prevalence of hypertension was 31% (95% CI, 27%–36%).<sup>113</sup> Among those with hypertension, the level of awareness was 29% (95% CI, 17%–42%). The pooled proportion being treated was 31% (95% CI, 18%–44%); among those taking antihypertensive medications, 38% (95% CI, 19%–57%) had controlled BP (defined as <140/90 mmHg).
- In an analysis of LASI, the estimated hypertension prevalence among adults ≥45 years of age was 45.9% (95% CI, 45.4%–46.5%).<sup>114</sup> Among those with hypertension, 55.7% (95% CI, 54.9%–56.5%) had been diagnosed, 38.9% (95% CI, 38.1%–39.6%) were taking antihypertensive medication, and 31.7% (95% CI, 31.0%–32.4%) achieved BP control.
- 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>115</sup>
- In a systematic review of 64 studies among children <18 years of age in India, the pooled prevalence was 7% (95% CI, 6%–8%) for hypertension, 4% (95% CI, 3%–4.1%) for sustained hypertension, and 10% (95% CI, 8%–13%) for prehypertension.<sup>116</sup> The pooled prevalence was 29% in children with obesity compared with 7% in normal-weight children.
  - In an analysis from the CREOLE study, which included 721 Black people from sub-Saharan Africa

between 30 and 79 years of age with uncontrolled hypertension and a baseline 24-h ambulatory BP monitoring, the prevalence of nondipping pattern was 78%.<sup>117</sup>

- In an analysis of the GBD Study using an age-period-cohort model from 1990 to 2017, the high SBP-attributable stroke mortality rate per 100 000 population declined from 164.7 to 108.7 in males and from 129.1 to 55.5 in females in China.<sup>118</sup> In Japan, the corresponding rates also declined from 63.7 and 24.7 in males and 35.9 and 8.9 in females, respectively.

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

Population group	Prevalence, 2017–2020, age ≥20 y	Mortality,* 2020, all ages	Hospital discharges,† 2019, all ages	Estimated cost, 2018–2019
Both sexes	122 400 000 (46.7%) (95% CI, 44.2%–49.3%)	119 997	1 413 000	\$52.2 Billion
Males	62 800 000 (50.4%)	58 423 (48.7%)‡	...	...
Females	59 600 000 (43.0%)	61 574 (51.3%)‡	...	...
NH White males	48.9%	38 801	...	...
NH White females	42.6%	43 308	...	...
NH Black males	57.5%	12 033	...	...
NH Black females	58.4%	11 216	...	American Heart Association.
Hispanic males	50.3%	4 964	...	...
Hispanic females	35.3%	4 498	...	...
NH Asian males	50.2%	1854§	...	...
NH Asian females	37.6%	2 026§	...	...
NH American Indian/Alaska Native people	...	873	...	...

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>119</sup> Hypertension is defined in terms of NHANES BP 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>120</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. In March 2020, the COVID-19 pandemic halted NHANES field operations.

BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, 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. The large increase in hospital discharges is attributable to *International Classification of Diseases, 10th Revision* coding changes for heart failure (HF) using Agency for Healthcare Research and Quality Prevention Quality Indicator 08, HF admission rate.

‡These percentages represent the portion of total HBP mortality that is for males versus 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 (for underlying cause of HBP): Unpublished NHLBI tabulation using National Vital Statistics System.<sup>74</sup> These data represent underlying cause of death only. Mortality for NH Asian people includes Pacific Islander people. Hospital discharges (with a principal diagnosis of HBP): Unpublished NHLBI tabulation using HCUP.<sup>98</sup> Cost: Unpublished NHLBI tabulation using Medical Expenditure Panel Survey<sup>121</sup>; includes estimated direct costs for 2018 to 2019 (annual average) and indirect costs calculated by NHLBI for 2018 to 2019 (annual average).

**Table 8-2. Hypertension Awareness, Treatment, and Control: NHANES 1999 to 2002, 2007 to 2010, and 2017 to 2020 Age-Adjusted Percent With Hypertension in US Adults by Sex and Race and Ethnicity**

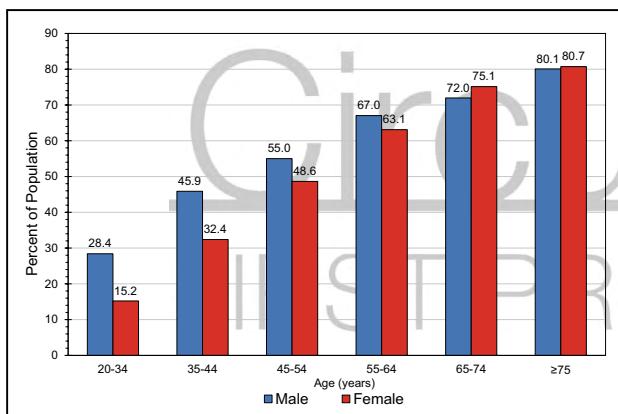
	Awareness, %			Treatment, %			Control, %		
	1999–2002	2007–2010	2017–2020	1999–2002	2007–2010	2017–2020	1999–2002	2007–2010	2017–2020
Overall	48.9	61.2	62.0	37.7	52.5	52.6	12.0	24.1	25.7
NH White males	42.7	58.0	62.0	31.4	48.7	50.4	10.9	22.2	26.7
NH White females	56.7	66.1	62.9	45.9	59.2	56.4	14.8	28.7	27.6
NH Black males	46.0	60.5	61.5	33.0	47.6	48.4	9.1	18.2	17.3
NH Black females	67.7	73.5	71.2	54.9	64.3	61.0	16.4	28.2	25.6
Mexican American males*	25.9	40.6	47.7	14.0	30.5	36.2	4.1	12.7	20.6
Mexican American females*	50.4	55.6	60.5	35.4	49.3	49.9	10.4	21.2	23.9

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>119</sup> Hypertension is defined in terms of NHANES BP measurements and health interviews. A subject was considered to have hypertension if SBP was  $\geq 130$  mm Hg, DBP was  $\geq 80$  mm Hg, or the subject said "yes" to taking antihypertensive medication. Controlled hypertension is considered to be SBP  $< 130$  mm Hg or DBP  $< 80$  mm Hg. Total includes race and ethnicity groups not shown (other Hispanic, other race, and multiracial).

BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

\*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).

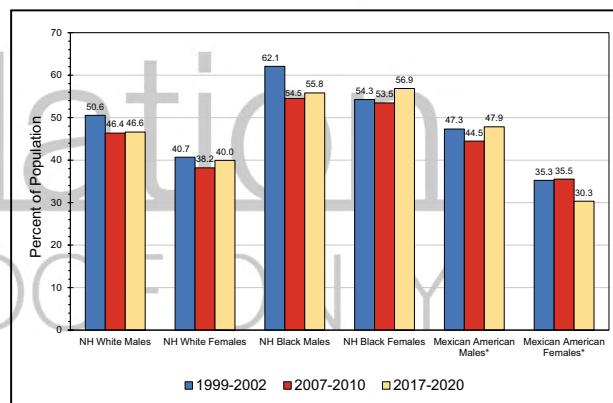
Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>6</sup>

**Chart 8-1. Prevalence of hypertension in US adults  $\geq 20$  years of age by sex and age (NHANES 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>119</sup> Hypertension is defined in terms of NHANES BP measurements and health interviews. A person was considered to have hypertension if he or she had SBP  $\geq 130$  mm Hg or DBP  $\geq 80$  mm Hg, if he or she said "yes" to taking antihypertensive medication, or if the person was told on 2 occasions that he or she had hypertension.

BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

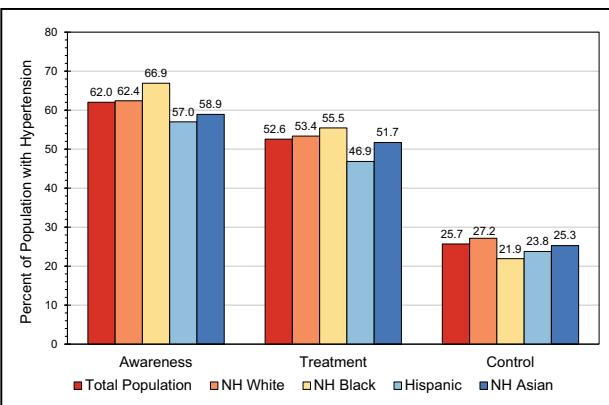
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>6</sup>

**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 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>119</sup> Hypertension is defined in terms of NHANES BP measurements and health interviews. A person was considered to have hypertension if he or she had SBP  $\geq 130$  mm Hg or DBP  $\geq 80$  mm Hg or if he or she said "yes" to taking antihypertensive medication. BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

\*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.

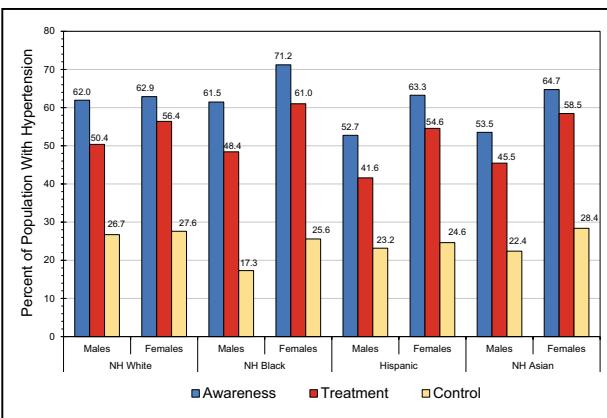
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>6</sup>



**Chart 8-3. Extent of awareness, treatment, and control of HBP by race and ethnicity, United States (NHANES 2017-2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>119</sup> Hypertension is defined in terms of NHANES BP measurements and health interviews. A person was considered to have hypertension if he or she had SBP  $\geq 130$  mmHg or DBP  $\geq 80$  mmHg or if he or she said "yes" to taking antihypertensive medication. BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; HBP, high blood pressure; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

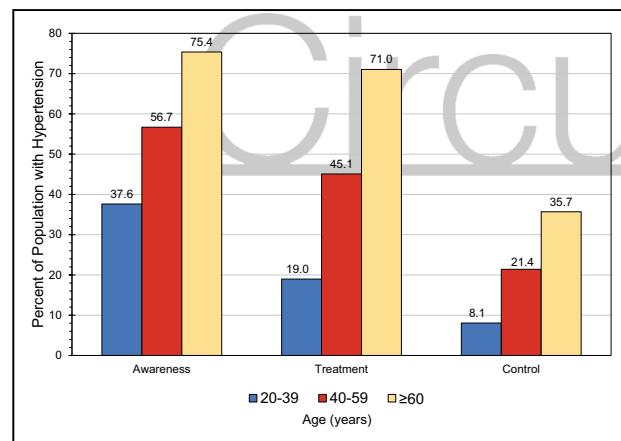
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>6</sup>



**Chart 8-5. Extent of awareness, treatment, and control of HBP by race and ethnicity and sex, United States (NHANES, 2017-2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>119</sup> Hypertension is defined in terms of NHANES BP measurements and health interviews. A person was considered to have hypertension if he or she had SBP  $\geq 130$  mmHg or DBP  $\geq 80$  mmHg or if he or she said "yes" to taking antihypertensive medication. BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; HBP, high blood pressure; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

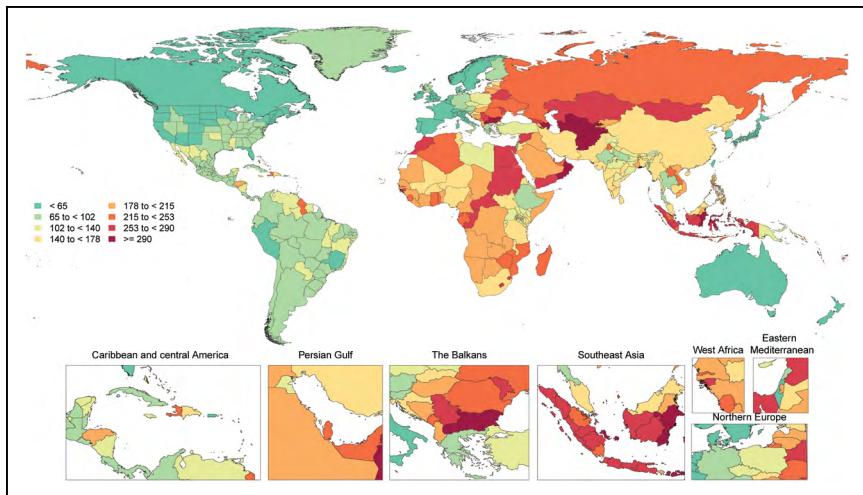
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>6</sup>



**Chart 8-4. Extent of awareness, treatment, and control of HBP by age, United States (NHANES 2017-2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>119</sup> Hypertension is defined in terms of NHANES BP measurements and health interviews. A person was considered to have hypertension if he or she had SBP  $\geq 130$  mmHg or DBP  $\geq 80$  mmHg or if he or she said "yes" to taking antihypertensive medication. BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; HBP, high blood pressure; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

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 SBP per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and SBP, systolic blood pressure.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>122</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 an 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, HF, PAD, 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

- In 2019, 283 000 children and adolescents  $<20$  years of age, or 35 per 10 000 US youths, had diagnosed diabetes. This includes 244 000 with type 1 diabetes.<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

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

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)

- On the basis of NHANES 2017 to 2020 data,<sup>8</sup> 29.3 million adults (10.6%) had diagnosed diabetes, 9.7 million adults (3.5%) had undiagnosed diabetes, and 115.9 million adults (46.4%) had prediabetes (Table 9-1).
- After adjustment for population age differences, NHANES 2017 to 2020<sup>8</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 2018 to 2019 data from the US Indian Health Service, the age-adjusted prevalence of diagnosed diabetes among American Indian/Alaska Native people was 14.4% for males and 14.7% for females.<sup>5</sup>
- On the basis of NHANES 2017 to 2020 data,<sup>8</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 (7.9%), and Hispanic adults with less than a high school education had the highest prevalence (16.2%; 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>9</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>10</sup>
- Geographic variations in diabetes prevalence have been reported in the United States:
  - From state-level data from BRFSS<sup>11</sup> 2020, Guam (16.1%), Puerto Rico (13.3%), and Mississippi (13.2%) had the highest age-adjusted prevalence of diagnosed diabetes, and Vermont (6.7%) had the lowest prevalence (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 youth <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>12</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>12</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>12</sup>

### Adults

#### (See Table 9-1)

- Approximately 1.4 million US adults ≥18 years of age were diagnosed with incident diabetes in 2019 (Table 9-1). This included ≈723 000 males and 675 000 females, 71 000 NH Asian individuals, 181 000 NH Black individuals, 261 000 Hispanic individuals, and 860 000 NH White individuals.<sup>5</sup>
- During 2018 to 2019, adults with less than a high school education had a higher age-adjusted incidence rate for diagnosed diabetes (8.2 per 1000 [95% CI, 5.8–11.6]) than adults with a high school education (7.8 per 1000 [95% CI, 6.4–9.4]) or more than a high school education (5.2 per 1000 [95% CI, 4.5–6.2]).<sup>5</sup>
- Data from a large UK primary care database of 94 870 South Asian individuals matched with 189 740 White individuals showed that South Asian individuals were at a greater risk of developing type 2 diabetes (aHR, 3.1 [95% CI, 2.97–3.23]), hypertension (1.34 [95% CI, 1.29–1.39]), IHD (1.81, [95% CI, 1.68–1.93]), and HF (1.11 [95% CI, 1.003–1.24]).<sup>13</sup>

### Secular Trends

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

- Among adults ≥18 years of age, there was a similar age-adjusted incidence of diagnosed diabetes

in 2000 (6.2 per 1000 adults) and 2019 (5.7 per 1000 adults), with a decreasing trend noted since 2008 (8.4 per 1000 adults).<sup>5</sup>

- 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>12</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>12</sup> (Chart 9-4).
- The prevalence of diagnosed diabetes in adults was higher for both males and females in the NHANES 2017 to 2020 data than in the NHANES 1988 to 1994 data. Males had a higher prevalence of both types of diagnosed diabetes than females in 2017 to 2020 (Chart 9-5).

### 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 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 ≤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 ≥65 years of age (20.7%). The prevalence of cost-related medication non-adherence 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: Risk Scores, Risk-Enhancing Factors, and Coronary Calcium

Diabetes is associated with great heterogeneity in risk of CVD, and in many individuals with diabetes, their diagnosis would not be considered a CHD risk equivalent. This emphasizes the importance of risk stratification in individuals with diabetes. Currently, the US Pooled Cohort Equation includes a diabetes factor and can be used in individuals with diabetes to predict the 10-year risk of ASCVD (for those 40–79 years of age) and lifetime risk of ASCVD (for those 20–59 years of age).<sup>28</sup> There is currently no available US-based pooled cohort risk score developed specifically in individuals with diabetes.

- Several risk prediction algorithms for type 2 diabetes have been developed.<sup>29–31</sup> From a recent systematic review of 15 observational studies reporting 7 risk models with >1 validation cohort, the Risk Equations for Complications of Type 2 Diabetes had the best calibration in primary studies with the greatest discrimination measures for all-cause mortality (C statistics, 0.75 [95% CI, 0.70–0.80]; high certainty), cardiovascular mortality (0.79 [95% CI, 0.75–0.84]; low certainty), ESKD (0.73 [95% CI, 0.52–0.94]; low certainty), MI (0.72 [95% CI, 0.69–0.74]; moderate certainty), and stroke (0.71 [95% CI, 0.68–0.74]; moderate certainty).<sup>32</sup>
- The updated version of the QDiabetes risk prediction algorithm had C statistics between 0.81 and 0.89.<sup>33</sup>
- Risk prediction algorithms for CVD among individuals with diabetes have also been developed.<sup>34–36</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>35</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>37</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>38</sup>
- The 2018 Cholesterol Clinical Practice Guideline notes the following diabetes-specific risk enhancers that are independent of other risk factors that can be used to inform the treatment decision: (1) long duration ( $\geq 10$  years for type 2 diabetes or  $\geq 20$  years for type 1 diabetes), (2) albuminuria  $\geq 30$  µg albumin/mg creatinine, and (3) eGFR  $< 60$  mL·min $^{-1}$ ·1.73 m $^{-2}$ , retinopathy, neuropathy, and an ABI  $< 0.9$  if uncertain.<sup>39</sup>
- CAC is also an effective risk stratifier for individuals with diabetes. In MESA, annual CHD event rates ranged from 0.4%/y in those with CAC scores of 0 to 4%/5 for CAC scores of  $> 400$ , and CAC provided significant improvements in the C statistic beyond risk factors.<sup>40</sup> A subsequent report noted that a duration of diabetes of at least 10 years further stratified risk, especially at higher CAC scores.<sup>41</sup> Moreover, incidence and progression of CAC and the relation of progression of CAC with subsequent CHD events also are greater for those with MetS or diabetes compared with individuals without these conditions.<sup>42</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>43,44</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>45</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>46</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>47</sup> Genetic testing can be considered if maturity-onset diabetes is suspected and can guide the management and screening of family members.
- Diabetes is most often 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 of adult populations have identified  $> 500$  genetic variants associated with diabetes,<sup>48</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>49</sup>

- A common intronic variant in the *TCF7L2* (transcription factor 7 like 2) gene is the most consistently identified diabetes variant.<sup>50–53</sup> Together, common variants account for 18% of type 2 diabetes risk.<sup>49</sup> Several of these variants have also been associated with gestational diabetes (see Chapter 11 [Adverse Pregnancy Outcomes]).<sup>54</sup>
- Few GWASs have examined type 2 diabetes in youth. Using data from n=3006 youth type 2 diabetes cases and n=6061 controls, the multiethnic ProDiGY Consortium identified 7 genome-wide significant loci, including a novel locus in *PHF2*.<sup>55</sup> *PHF2* may influence adipogenesis and fat storage through *CEBPα* and peroxisome proliferator-activated receptor γ transcriptional regulation in adipose tissue.<sup>56</sup> The 6 known loci previously identified in adult populations that generalized to youth at genome-wide significant levels were *TCF7L2*, *MC4R*, *CDC123*, *KCNQ1*, *IGF2BP2*, and *SLC16A11*.
- 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>52,57</sup> a variant in the *DNER* gene associated with diabetes in Native American individuals,<sup>58</sup> a variant in the *G6PD* gene,<sup>59</sup> and a rare variant in the *HBB* gene<sup>60</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>61</sup> A meta-analysis of  $> 77$  000 East Asian individuals with type 2 diabetes identified 61 novel loci for diabetes.<sup>62</sup>
- GWASs of quantitative glycemic traits (eg, fasting glucose, fasting insulin, and HbA1c) also have been published. These GWASs have identified  $> 600$  loci in genes and pathways related to glucose metabolism, regulation of circadian rhythms, and cell proliferation.<sup>63</sup> These loci include common and low-frequency variants, some of which may be population specific.<sup>64</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>65</sup>
- Lifestyle may modify genetic risk of diabetes. 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>66</sup> A second study in the UK Biobank assessed the interaction between diet quality and a type 2 diabetes GRS with n=5663 incident type 2 diabetes cases (N=357 419 participants of European ancestry at study baseline). The authors report an antagonistic interaction in which a simultaneous 1-SD increment in both the diet quality score and GRS was associated with a 3% lower type 2 diabetes risk, indicating that adherence to a healthy diet was associated with a reduced type 2 diabetes risk among individuals with higher genetic risk.<sup>67</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, a waist-specific polygenic score was associated with a higher risk of diabetes (OR, 1.57 [95% CI, 1.34–1.83], absolute risk increase per 1000 participant-years, 4.4 [95% CI, 2.7–6.5]; P<0.001).<sup>68</sup> Providing additional evidence are studies examining coheritability or evidence of a shared genetic architecture between type 2 diabetes and cardiometabolic diseases. For example, 1 recent study examined coheritability by estimating genetic correlation. The authors reported significant positive genetic correlation between type 2 diabetes and BMI, extreme BMI, overweight, obese, hip circumference, WC, glycemic traits, triglycerides, and CAD.<sup>69</sup> Conversely, inverse genetic correlations for type 2 diabetes were observed with HDL-C and birth weight.
- In the ACCORD trial, 2 genetic markers were identified with excess CVD mortality in the intensive treatment arm. A GRS including these genetic markers was found to be associated with the effect of intensive glycemic treatment of cardiovascular outcomes: Those with a GRS of 0 had a substantial reduction in risk in response to intensive treatment (HR, 0.24 [95% CI, 0.07–0.86]); those with a GRS of 1 experienced no difference (HR, 0.92 [95% CI, 0.54–1.56]); and those with a GRS ≥2 experienced a 3-fold increase in risk (HR, 3.08 [95% CI, 1.82–5.21]).<sup>70</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>71</sup>

### Type 1 Diabetes

- Type 1 diabetes is also heritable. Early genetic studies identified the role of the *MHC* (major histocompatibility complex) gene in this disease, with the greatest contributor being the human leukocyte

antigen region, estimated to contribute to ≈50% of the genetic risk.<sup>72</sup> Other studies have identified additional genes associated with type 1 diabetes risk, including rare variants.<sup>73</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>74</sup> In a study of 7798 high-risk children, a risk score combining type 1 diabetes genetic variants, autoantibodies, and clinical factors improved the prediction of incident type 1 diabetes (AUC ≥0.9).<sup>75</sup>

### Genetic Factors and Diabetes Complications

- 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>76</sup>
  - Genetic variants have also been identified that increase the risk of CAD or dyslipidemia in patients with diabetes<sup>77,78</sup> and that are associated with end-organ complications in diabetes (retinopathy,<sup>79</sup> nephropathy,<sup>80</sup> and neuropathy<sup>81</sup>).
  - A GRS of type 2 diabetes variants was associated with diabetes-related retinopathy (OR of the highest GRS decile compared with the 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>48</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>82</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>83</sup> and response to weight loss interventions.<sup>84</sup> Circulating glycine levels are associated with lower diabetes risk (meta-analysis RR, 0.89 [95% CI, 0.81–0.96]).<sup>85</sup> Other metabolites associated with type 2 diabetes include complex lipid species such as triacylglycerols<sup>86</sup> and alpha amino-adipic acid.<sup>87</sup>

### Prevention

- Among adults without diabetes in NHANES 2007 to 2012, 37.8% met the moderate-intensity PA goal of ≥150 min/wk, and 58.6% met the weight loss or maintenance goal for diabetes prevention. Adults with prediabetes were less likely to meet the PA and weight goals than adults with normal glucose levels.<sup>88</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>89</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>90</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>91</sup>

## Awareness, Treatment, and Control

Although lifestyle management through diet and exercise is the foundation for treatment of diabetes, metformin has for many years been recommended as first-line pharmacological treatment. However, more recently, SGLT-2 inhibitors and GLP-1Ra have been shown to reduce cardiovascular outcomes and are now currently recommended in higher-risk individuals with diabetes with preexisting CVD or multiple risk factors. In particular, SGLT-2 inhibitors have a dramatic benefit on reducing the risk of subsequent HF hospitalizations both in those with diabetes and in those with HF. Furthermore, statin therapy (including high-intensity statin for those with ASCVD or multiple risk factors) and appropriate pharmacological therapy for BP control are recommended to reduce future ASCVD risk. Control of diabetes includes a reduction of HbA1c to <7% (<8% for those with diabetes complications, including macrovascular disease), BP reduction to <130/80 mmHg, and control of LDL-C with statin therapy (and consideration of additional nonstatin use in those at greatest risk, including those with ASCVD if LDL-C is ≥70 mg/dL after maximally tolerated statin therapy). It has been estimated that aggressive control of lipids, BP, and glucose in individuals with diabetes could prevent up to 51% of CHD events in males and 61% of CHD events in females.<sup>92</sup>

### Awareness

- Of 37.1 million adults ≥18 years of age, or 14.7% of all US adults with diabetes in 2019, 8.5 million were not aware of or did not report having diabetes (undiagnosed diabetes), representing 23.0% of all US adults with diabetes.<sup>93</sup>
- A recent NHANES study of trends in awareness of prediabetes shows that the age-adjusted prevalence of prediabetes based on FPG/HbA1c

definition increased from 32.1% in 2005 to 2006 to 39.6% in 2007 to 2008 and then plateaued to 38.6% in 2017 to March 2020 without a significant trend for improvement.<sup>94</sup>

### Treatment

#### (See Chart 9-6)

- Among data from 324 706 patients with diabetes and established ASCVD studied during 2018 from within the National Patient-Centered Clinical Research Network, including 12 health systems, overall 58.6% were prescribed a statin, but only 26.8% were prescribed a high-intensity statin.<sup>95</sup> Only 3.9% were prescribed a GLP-1Ra and 2.8% an SGLT-2 inhibitor. Overall, only 4.6% were prescribed all 3 classes of therapies and 42.6% were prescribed none. Patients who were prescribed a high-intensity statin were more likely to be males or to have ASCVD.
- In a recent analysis of 2 large US health insurance databases (Clininformatics and Medicare) examining adult patients with type 2 diabetes who initiated antidiabetes treatment from 2013 through 2019, metformin was the most frequently initiated medication, used by 80.6% of Medicare beneficiaries and 83.1% of commercially insured patients, followed by sulfonylureas at 8.7% and 4.7%, respectively.<sup>96</sup> However, use of newer cardioprotective diabetes agents was low: SGLT-2 inhibitor in 0.8% (Medicare) and 1.7% (commercial) and GLP-1Ra in 1.0% (Medicare) and 3.5% (commercial), although with trends of greater use over time ( $P<0.01$ ). Those using an SGLT-2 inhibitor and GLP-1Ra were more likely to be younger or to have prevalent CVD and higher SES compared with those initiating metformin.
- From an analysis of NHANES data for 2017 to 2018, among individuals with type 2 diabetes representing 33.2 million adults nationally, 52.6% had an indication for SGLT-2 inhibitors, 32.8% for GLP-1RAs, and 26.6% for both medications.<sup>97</sup> However, only 4.5% were treated with SGLT-2 inhibitors and 1.5% with GLP-1RAs. ASCVD, HF, or CKD was associated with their use.
- Among 1 202 596 adults with type 2 diabetes in a large US administrative claims database of whom 45.2% had established ASCVD, the use of GLP-1RAs and SGLT-2 inhibitors was low overall (<12%) and even lower in the ASCVD group (<9%), and use of either was ≤5% in the subgroup ≥65 years of age, regardless of ASCVD status.<sup>98</sup>
- In a secondary analysis examining the association of race and ethnicity with the initiation of newer diabetes medications (GLP-1RAs, dipeptidyl peptidase-4 inhibitors, SGLT-2 inhibitors) in the Look AHEAD trial, initiation was lower among Black

(HR, 0.81 [95% CI, 0.70–0.94]) and American Indian/Alaska Native (HR, 0.51 [95% CI, 0.26–0.99]) participants, and yearly family income was inversely associated with initiation of newer diabetes medications (HR, 0.78 [95% CI, 0.62–0.98]) when the lowest and highest income groups were compared, findings that were influenced mostly by GLP-1Ras.<sup>99</sup>

- According to NHANES 2017 to 2020 data for adults with diabetes, 20.7% had their diabetes treated and controlled with a fasting glucose <126 mg/dL; however, 48% still had uncontrolled diabetes despite being treated and 22% were not treated and not diagnosed (unpublished NHLBI tabulation; Chart 9-6).
- 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>100</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>101</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>102</sup> It is important to note that this study showed multivariable-adjusted risk reductions of 62% for CVD events and 60% for CHD events.
- Data from the US Diabetes Collaborative Registry of 74 393 adults with diabetes show 74% at HbA1c <7%, 40% at BP <130/80 mmHg, and 49% at LDL-C <100 mg/dL (<70 mg/dL if with ASCVD) but only 15% at target for all 3 factors.<sup>103</sup>
- In a study of 1179 adults with type 2 diabetes (projected to 19.7 million in the US population) with diabetes from NHANES 2013 to 2016, 56% of adults were at target control of HbA1c (<7%, or <8% if with CVD), 51% for BP (<130/80 mmHg), and 49% for LDL-C (<100 mg/dL, or <70 mg/dL if with CVD); 84% were nonsmokers.<sup>104</sup> Only 9% had BMI <25 kg/m<sup>2</sup>. Only 17% were at all targets for HbA1c, BP, and LDL-C.
- 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), as well as decreases in mean HbA1c (7.0% and 6.7%), mean BP (130.1/77.5 and 126.0/72.1 mmHg), and mean TC (219.4 and 182.4 mg/dL). The proportion with HbA1c <7.0%, BP <140/90 mmHg, and TC <240 mg/dL improved from 31.6% to 56.2%.<sup>105</sup>

- Among HCHS/SOL study participants with diabetes, 43.0% had HbA1c <7.0%, 48.7% had BP <130/80 mmHg, and 36.6% had LDL-C <100 mg/dL; 8.4% had reached all 3 treatment targets.<sup>106</sup>
- In a national cohort of 1140 634 veterans with diabetes, in adjusted models, odds of HbA1c ≥8.0% compared with HbA1c <7% were 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>107</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>108</sup>
- Among those with type 1 diabetes in the SEARCH study, 60% reported having ≥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>109</sup>

### Mortality

(See Table 9-1)

- Diabetes was listed as the underlying cause of mortality for 102 188 people (57 532 males and 44 656 females) in the United States in 2020 (Table 9-1).<sup>110</sup>
- The 2020 overall age-adjusted death rate attributable to diabetes was 24.8 per 100 000. For males, the age-adjusted death rates per 100 000 population were 27.2 for NH White people, 57.3 for NH Black people, 37.8 for Hispanic people, 24.3 for NH Asian/Pacific Islander people, and 60.2 for NH American Indian/Alaska Native people. For females, the age-adjusted death rates per 100 000 population were 16.0 for NH White people, 39.0 for NH Black people, 25.2 for Hispanic people, 15.4 for NH Asian/Pacific Islander people, and 40.9 for NH American Indian/Alaska Native people (unpublished NHLBI tabulation using CDC WONDER<sup>111</sup>). In 2019, diabetes was the eighth leading cause of death in the United States.<sup>112</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>113</sup> In another meta-analysis of 2314 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>114</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>115</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>116</sup>
- In NIS 2017, the mortality rate for diabetic ketoacidosis was higher among males (40.5 per 10 000 admissions) compared with females (35.3 per 10 000 admissions) and NH Black people (39.1 per 10 000 admissions) compared with NH White people (36.2 per 10 000 admissions) and Hispanic people (36.3 per 10 000 admissions).<sup>117</sup>

## Complications

### **Peripheral Artery Disease**

(See Chart 9-7)

- 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>118</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>118</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>119</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>120</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>121</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>122</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>123</sup>

### **Retinopathy**

- Among those ≤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>124</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>125</sup>
- Among adults ≥18 years of age with diagnosed diabetes in 2019, the prevalence of a severe vision disability or blindness was 11.8% (95% CI, 11.1%–12.4%).<sup>5</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>126</sup>
- According to NHIS 2016 and 2017, among individuals with young-onset diabetes (diagnosed <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>127</sup>

### **Chronic Kidney Disease**

- 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>128</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 change significantly 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>129</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>105</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>130</sup>

### **Neuropathy**

- In the T1D Exchange Clinic Registry, from 2016 to 2018, the prevalence of self-reported diabetic peripheral neuropathy was 11%.<sup>131</sup>

### **CVD Complications**

#### (Chart 9-7)

- From the UK Clinical Practice Research Datalink for 734543 adults with and without type 2 diabetes diagnosed in 2000 to 2006 with follow-up for first CVD events over 11 years, type 2 diabetes was associated with a small increase in CVD events (aHR, 1.06 [95% CI, 1.02–1.09]) in White individuals, but a greater increase was seen in individuals of South Asian ethnicity (1.28 [95% CI, 1.09–1.51]), attributable primarily to an increased risk of MI (1.53 [95% CI, 1.08–2.18]).<sup>132</sup>
- Data from a large clinical trial of youth with early-onset type 2 diabetes followed up for >13 years since diagnosis of diabetes showed a cumulative incidence of 67.5% for hypertension, 51.6% for dyslipidemia, 54.8% for diabetic kidney disease, and 32.4% for nerve disease.<sup>133</sup> At least 1 complication occurred in 60.1% of the participants, and at least 2 complications occurred in 28.4%. Risk factors for the development of complications included underrepresented racial or ethnic group, hyperglycemia, hypertension, and dyslipidemia.

- Data among 1.9 million individuals with diabetes from the CALIBER UK cohort show the most common initial CVD complications for those with diabetes to be PAD (16.2%) and HF (14.1%), followed by stable angina (11.9%), nonfatal MI (11.5%), and stroke (10.3%).<sup>134</sup>
- In a study of 4095 participants with type 2 diabetes, microvascular disease in adults with type 2 diabetes free of HF in the Look AHEAD study was associated with a 2.5-fold higher risk of incident HF than no microvascular disease (HR, 2.54 [95% CI, 1.73–3.75]).<sup>135</sup> The HRs for HF by type of microvascular disease were 2.22 (95% CI, 1.51–3.27), 1.30 (95% CI, 0.72–2.36), and 1.33 (95% CI, 0.86–2.07) for nephropathy, retinopathy, and neuropathy, respectively.
- A systematic review and meta-analysis of 26 observational studies among 1325 493 individuals across 30 countries showed age at diabetes diagnosis to be inversely associated with all-cause mortality and macrovascular and microvascular disease risk (all  $P<0.001$ ).<sup>136</sup> Each 1-year increase in age at diabetes diagnosis was associated with a 4%, 3%, and 5% decreased risk of all-cause mortality, macrovascular disease, and microvascular disease, respectively, adjusted for age.
- A systematic review and meta-analysis of 5 eligible prospective studies of 22 591 participants with an average follow-up of 9.8 years showed reduced cardiovascular outcomes from replacement analyses of saturated fat with polyunsaturated fat (RR for 2% energy replacement, 0.87 [95% CI, 0.77–0.99]) or carbohydrate (RR for 5% energy replacement, 0.82 [95% CI, 0.67–1.00]).<sup>137</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>138</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>139</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>140</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>120</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>141</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>142</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>143</sup>
- In MESA, 63% of participants with diabetes had a CAC score >0 compared with 48% of those without diabetes.<sup>144</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>145</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>146</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>147</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>148</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>149</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>150</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>151</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 an aHR of 1.3 (95% CI, 1.2–1.5).<sup>152</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>153</sup>

### Coronavirus Disease 2019

- 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>154–157</sup>
  - From an internet survey that included 760 adults with diabetes during February to March 2021, younger adults (18–29 years of age) with diabetes were more likely to report having missed medical care during the past 3 months (87%) than were those 30 to 59 years of age (63%) or ≥60 years of age (26%), with 44% of younger adults reporting difficulty accessing diabetes medications and a lower intention to receive COVID-19 vaccination (66%) compared with adults ≥60 years of age.<sup>158</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>159</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>160</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>161</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>162</sup>

## Health Care Use

### (See Table 9-1)

- According to the 2016 US Nationwide Emergency Department Sample, 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 the US Nationwide Emergency Department Sample 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>163</sup>
- In 2019, there were 702 000 principal diagnosis discharges for diabetes (HCUP,<sup>164</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>165</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>166</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>167</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>168</sup> From 2007 to 2018, list prices of branded insulins increased by 262% and for branded noninsulin antidiabetic agents by 165%.<sup>169</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>170</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>171</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>172</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 \$16752 per year for people with diabetes, of which \$9601 was attributed to diabetes.<sup>172</sup>
- Informal care is estimated to cost \$1192 to \$1321 annually per person with diabetes.<sup>173</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>174</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>175</sup> The diabetes-related preventable hospitalization rate has decreased slightly<sup>175</sup> or stayed stable.<sup>176</sup>

- A systematic review estimated that CVD costs account for 20% to 49% of the total direct costs of diabetes care.<sup>177</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, 1.64 (95% UI, 1.50–1.75) million deaths were 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 International Diabetes Federation 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>178</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>179</sup> The International Diabetes Federation 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>180</sup>

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

Population group	Prevalence of diagnosed diabetes, 2017–2020: ≥20 y of age	Prevalence of undiagnosed diabetes, 2017–2020: ≥20 y of age	Prevalence of prediabetes, 2017–2020: ≥20 y of age	Incidence of diagnosed diabetes, 2019: ≥18 y of age	Mortality, 2020: all ages*	Hospital discharges, 2019: all ages	Cost, 2017
Both sexes	29 300 000 (10.6%)	9 700 000 (3.5%)	115 900 000 (46.4%)	1 398 000	102 188	702 000	\$327 Billion
Males	16 400 000 (12.2%)	4 600 000 (3.5%)	63 500 000 (52.9%)	723 000	57 532 (56.3%)†	...	...
Females	12 900 000 (9.1%)	5 100 000 (3.5%)	52 400 000 (40.0%)	675 000	44 656 (44.7%)†	...	...
NH White males	11.5%	2.6%	57.2%	...	37 120	...	...
NH White females	7.7%	2.8%	38.8%	...	26 978	...	...
NH Black males	11.8%	5.6%	35.3%	...	10 080	...	...
NH Black females	13.3%	3.2%	35.7%	...	9 415	...	...
Hispanic males	14.5%	5.3%	50.7%	...	7 136	...	...
Hispanic females	12.3%	4.5%	41.3%	...	5 696	...	...
NH Asian males	14.4%	5.4%	51.6%	...	2 257	...	...
NH Asian females	9.9%	5.2%	40.2%	...	1 866	...	...
NH American Indian or Alaska Native	...	...	...	...	1 356	...	...

Undiagnosed diabetes is defined as those whose fasting glucose is ≥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. In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019–2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>181</sup>

COVID-19 indicates coronavirus disease 2019; ellipses (...), data not available; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

\*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 versus females.

Sources: Prevalence: Prevalence of diagnosed and undiagnosed diabetes: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES.<sup>8</sup> Percentages for sex and racial and ethnic groups are age adjusted for Americans ≥20 years of age. Incidence: Centers for Disease Control and Prevention, National Diabetes Statistics Report.<sup>5</sup> Mortality (for underlying cause of diabetes): Unpublished NHLBI tabulation using National Vital Statistics System.<sup>110</sup> These data represent diabetes as the underlying cause of death only. Mortality for NH Asian people includes Pacific Islander people. Hospital discharges (with a principal diagnosis of diabetes): Healthcare Cost and Utilization Project.<sup>164</sup> Cost: American Diabetes Association.<sup>172</sup>

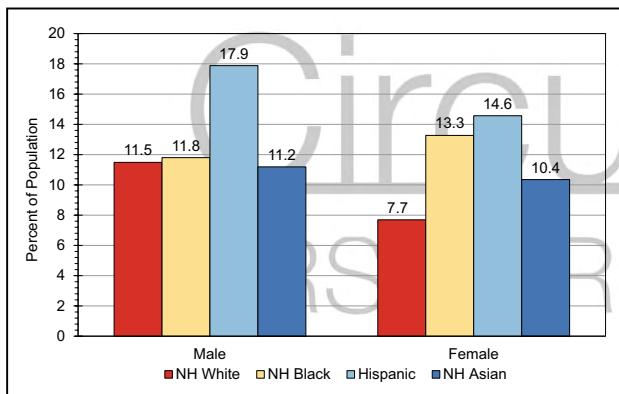
**Table 9-2. Global Prevalence and Mortality of Diabetes, 2020**

	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)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and UI, uncertainty interval.

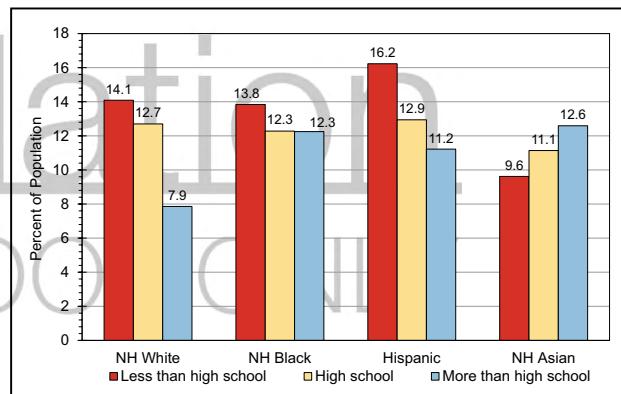
Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>182</sup>



**Chart 9-1. Age-adjusted prevalence of diagnosed diabetes in US adults ≥20 years of age by race and ethnicity and sex (NHANES 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>181</sup>

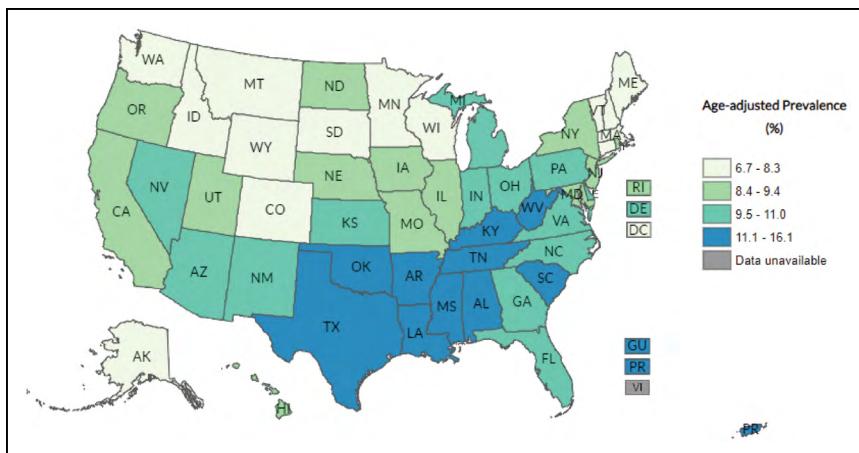
COVID-19 indicates coronavirus disease 2019; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>8</sup>



**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 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>181</sup>

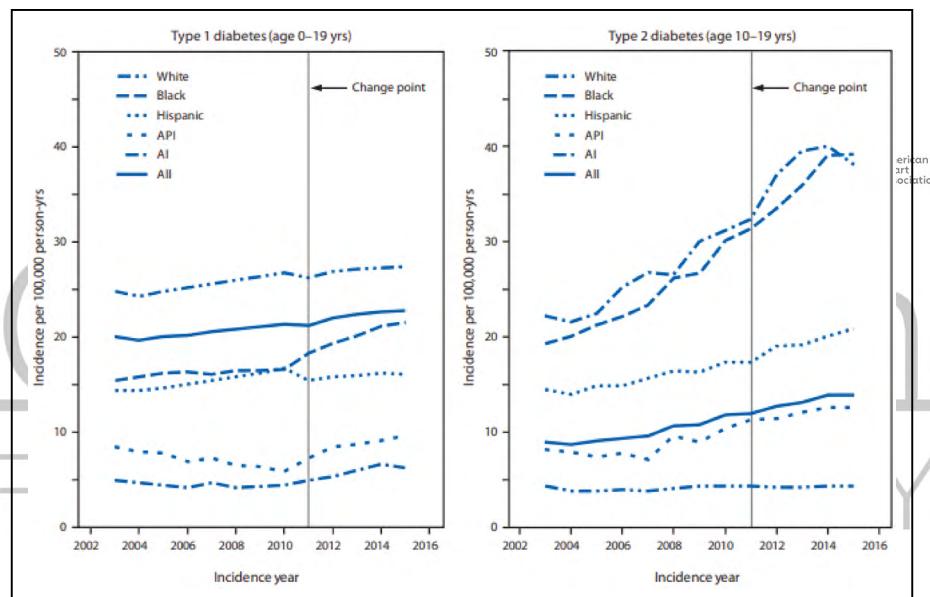
COVID-19 indicates coronavirus disease 2019; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>8</sup>



**Chart 9-3. Age-adjusted percentage of adults with diagnosed diabetes, US states and territories, 2020.**

Reprinted image has been altered to remove background colors, white space, and page headers and footers.

Source: Reprinted from Behavioral Risk Factor Surveillance System prevalence and trends data.<sup>11</sup>

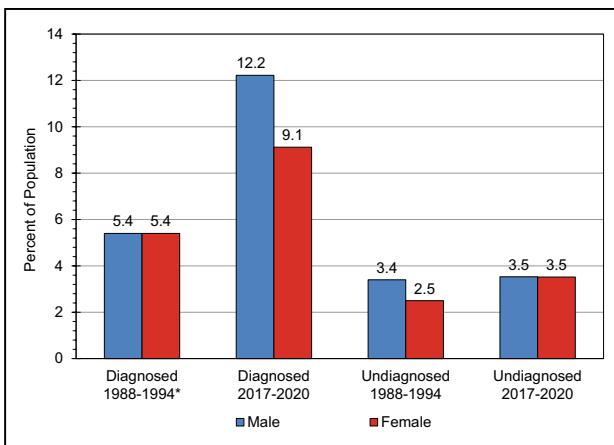


**Chart 9-4. Incidence of type 1 and type 2 diabetes overall and by race and ethnicity among US youths ≤19 years of age (SEARCH study, 2002–2015).**

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.

AI indicates American Indian; API, Asian/Pacific Islander; and SEARCH, Search for Diabetes in Youth.

Source: Reprinted from Divers et al.<sup>12</sup>

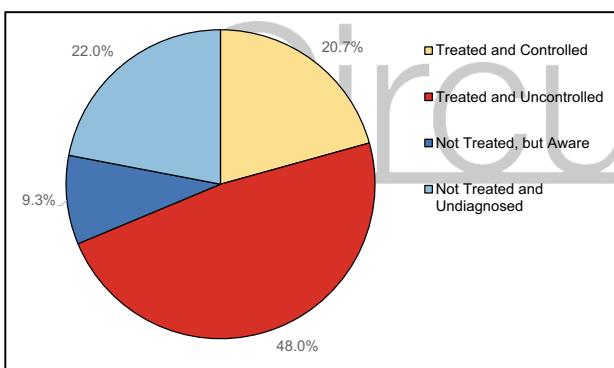


**Chart 9-5. Prevalence of diagnosed and undiagnosed diabetes in US adults  $\geq 20$  years of age by sex (NHANES 1988–1994 and 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>181</sup> The definition of diabetes changed in 1997 (from glucose  $\geq 140$  to  $\geq 126$  mg/dL).

COVID-19 indicates coronavirus disease 2019; and NHANES, National Health and Nutrition Examination Survey.

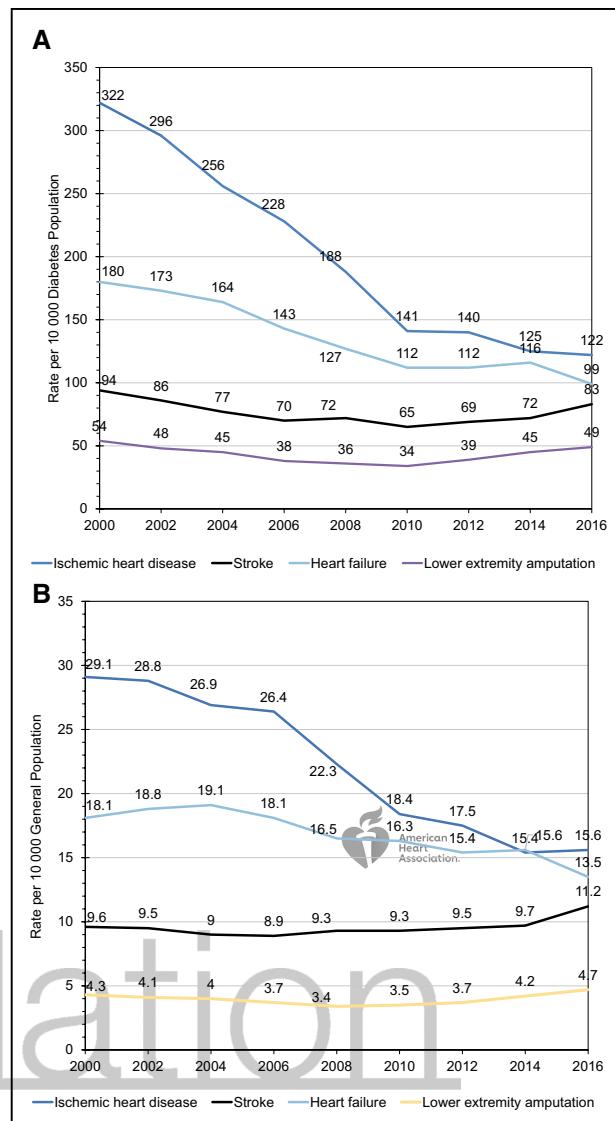
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>8</sup>



**Chart 9-6. Awareness, treatment, and control of diabetes in US adults  $\geq 20$  years of age (NHANES 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>181</sup> 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  $\geq 126$  mg/dL. COVID-19 indicates coronavirus disease 2019; and NHANES, National Health and Nutrition Examination Survey.

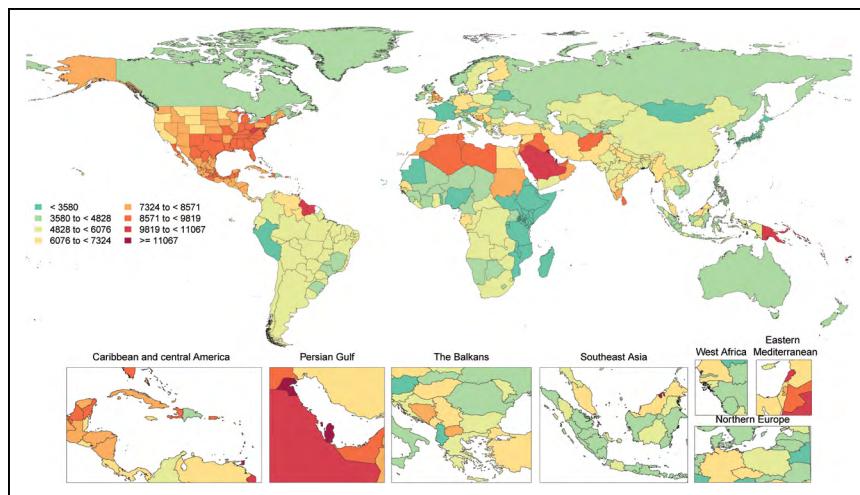
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>8</sup>



**Chart 9-7. Trends in age-standardized hospitalization rates for diabetes-related complications among US adults  $\geq 18$  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  $\geq 75$  years of age.

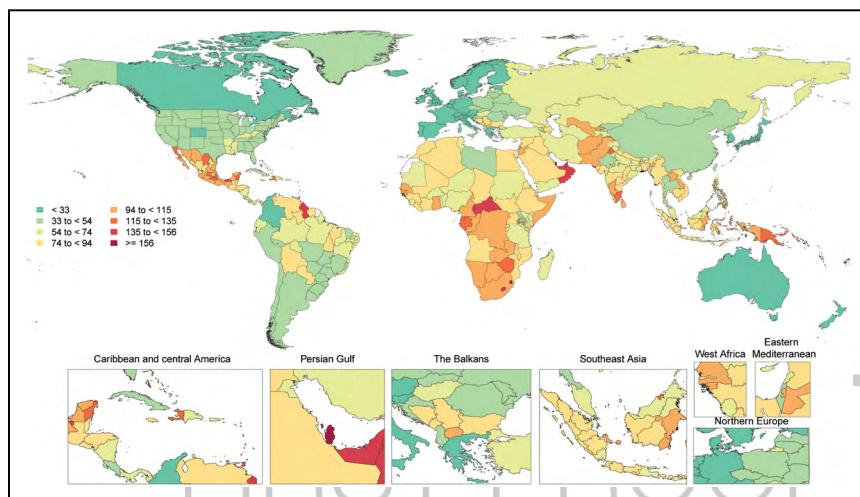
Source: Centers for Disease Control and Prevention Diabetes Atlas<sup>120</sup> using data from Healthcare Cost and Utilization Project<sup>164</sup> and National Health Interview Survey.<sup>183</sup>



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

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease. Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>182</sup>

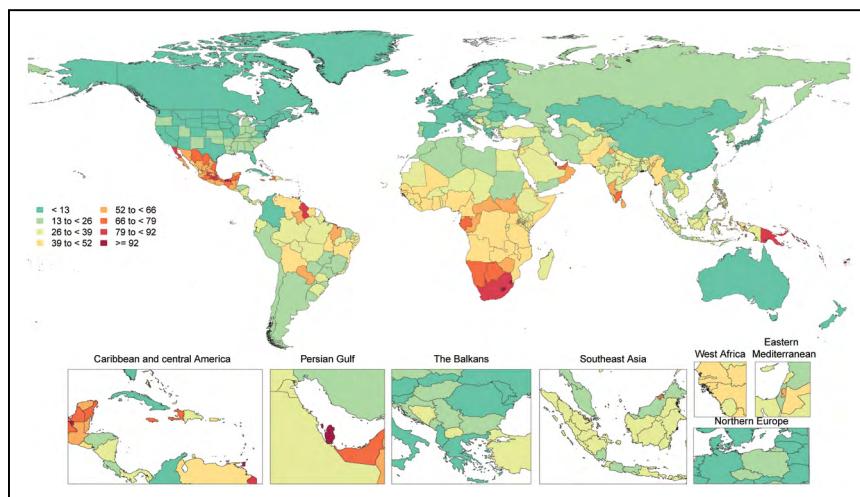


**Chart 9-9. Age-standardized global mortality rates attributable to high FPG per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. High FPG is defined as serum fasting plasma glucose of >4.8 to 5.4 mmol/L.

FPG indicates fasting plasma glucose; and GBD, Global Burden of Disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>182</sup>



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

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>182</sup>

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# Circulation

## 10. METABOLIC SYNDROME

**See Charts 10-1 through 10-8**

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### Definition

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

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

and possibly osteoarthritis, as well as a general proinflammatory 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, or 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). According to data from NHANES 2011 to 2016, the prevalence of MetS according to the International Diabetes Federation in adolescents 12 to 19 years of age was estimated to be 4.24% (95% CI, 2.49%–5.99%) overall, 6.04% (95% CI, 2.92%–9.16%) in adolescent males, and 2.28% (95% CI, 2.08%–3.48%) in adolescent females.<sup>4</sup>
- According to data from NHANES 1999 to 2018, the prevalence of MetS among youths 12 to 19 years of age was 4.34% (95% CI, 3.33%–5.65%) for NH White, 3.66% (95% CI, 2.67%–4.99%) for NH Black, 7.70% (95% CI, 6.32%–9.36%) for Mexican American, 4.84% (95% CI, 2.89%–7.99%) for other Hispanic, and 1.84% (95% CI, 0.89%–3.76%) for others.<sup>5</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>6</sup>
- Uncertainty remains concerning the definition of the obesity component of MetS in the pediatric population because it is age dependent. Therefore, the use of BMI percentiles<sup>7</sup> and waist-height ratio<sup>8</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>7</sup>

### Adults

**(See Chart 10-2)**

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

- According to data from NHANES 1999 to 2018, the overall MetS prevalence increased from 36.2% (95% CI, 33.2%–39.1%) to 47.3% (95% CI, 45.3%–49.3%;  $P_{trend} < 0.001$ ).<sup>9</sup>
- On the basis of NHANES 2011 to 2016, the overall prevalence of MetS was 34.7% (95% CI,

33.1%–36.3%) and was similar for males (35.1% [95% CI, 32.9%–37.3%]) and females (34.3% [95% CI, 32.7%–36.0%]).<sup>10</sup> The prevalence of MetS increased with age, from 19.5% (95% CI, 17.8%–21.4%) among people 20 to 39 years of age to 39.4% (95% CI, 37.2%–41.7%) for people 40 to 59 years of age and 48.6% (95% CI, 46.0%–51.2%) among people ≥60 years of age.

- In 2017 to 2018, Mexican American adults generally had the highest prevalence of MetS at 52.2% (95% CI, 47.0%–54.2%), whereas NH White adults had 46.6% (95% CI, 42.9%–50.2%), NH Black adults had 47.6% (95% CI, 44.7%–50.5%), other Hispanic adults had 45.9% (95% CI, 41.9%–50.0%), and Asian/other adults had 46.7% (95% CI, 41.9%–51.4%).<sup>9</sup>
- 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>11</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>12</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>13</sup>
- The prevalence of MetS has been noted to be high in individuals with certain conditions, including schizophrenia spectrum disorders<sup>14</sup> and bipolar disorder<sup>15</sup>; prior solid organ transplantations<sup>16</sup>; prior hematopoietic cell transplantation<sup>17,18</sup>; HIV infection<sup>19</sup>; COPD<sup>20</sup>; prior treatment for blood cancers<sup>18,21</sup>; systemic inflammatory disorders such as psoriasis,<sup>22,23</sup> systemic lupus erythematosus,<sup>24</sup> ankylosing spondylitis,<sup>25</sup> and rheumatoid arthritis<sup>26,27</sup>; multiple sclerosis<sup>28</sup>; type 1 diabetes<sup>29,30</sup>; latent autoimmune diabetes in adults<sup>30</sup>; prior gestational diabetes<sup>31</sup>; prior pregnancy-induced hypertension<sup>32</sup>; acne keloidalis nuchae<sup>33</sup>; periodontitis<sup>34,35</sup>; gallstones<sup>36</sup>; cerebral palsy<sup>37</sup>; war-related bilateral lower-limb amputation<sup>38</sup> or spinal cord injury<sup>39</sup> in veterans; and chronic opiate dependence,<sup>40</sup> as well as in individuals in select professions, including law enforcement,<sup>41</sup> commercial truck driving,<sup>42</sup> and firefighting.<sup>43</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>44</sup> A recent study updated the NHANES analysis from 1999 to 2018 for the trend in prevalence of MetS among youth 12 to 19 years of age

and reported that the prevalence of MetS remained stable at 4.36% (95% CI, 3.65%–5.20%) over the study period.<sup>5</sup>

### Adults

(See Charts 10-4 through 10-6)

- Secular trends in MetS differ according to the definition used.<sup>45–47</sup> Chart 10-4 demonstrates trends using the harmonized MetS criteria in NHANES 2009 to 2010 to 2017 to 2018; Chart 10-5 demonstrates trends using ATP III criteria in NHANES 2007 to 2014.
- In the ARIC study (1987–1998), the 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>48</sup>

## Risk Factors

### Youth

- In the PREMA study, independent predictors of MetS from childhood to adolescence were LBW, small head circumference, and a parent with overweight or obesity.<sup>49</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 males who received longer breastfeeding (OR, 1.49 [95% CI, 1.01–2.22]) but not females who received longer breastfeeding (OR, 0.94 [95% CI, 0.63–1.42]) compared with control groups.<sup>50</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>51</sup>
- A recent review has summarized the evidence identifying obesity and weight gain among obese children as important risk factors for MetS among youth.<sup>52</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>53</sup>
- Among 9897 children and adolescents 10 to 18 years of age in China, long-term exposure to ambient air pollution (eg, PM2.5, fine particulate matter <10-μm diameter, and NO<sub>2</sub>) was positively

associated with the prevalence of MetS. For every 10– $\mu\text{g}/\text{m}^3$  increase in PM2.5, fine particulate matter <10- $\mu\text{m}$  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>54</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>55</sup> Higher consumption of ultraprocessed foods was associated with prevalent MetS. A study using data from NHANES 2009 to 2014 reported that a 10% increase in dietary contribution of ultraprocessed foods was associated with a 4% prevalence of MetS increase (PR, 1.04 [95% CI, 1.02–1.07]).<sup>56</sup> Furthermore, compared with ultraprocessed food contribution <40%, the dietary contribution of ultraprocessed foods >71% was associated with a 28% higher prevalence of MetS (PR, 1.28 [95% CI, 1.09–1.50]).
- 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 International Diabetes Federation definition.<sup>57</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, 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>58</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 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>59</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>60</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>61</sup>

### Adults

#### Incident MetS

##### Diet

- Dietary habits are directly associated with incident MetS, including a Western diet,<sup>62</sup> high inflammatory diet pattern,<sup>63–65</sup> and consumption or intake of soft drinks,<sup>66</sup> energy-dense beverages,<sup>67</sup> SSBs,<sup>68</sup> fructose,<sup>69</sup> carbohydrates,<sup>70</sup> total fat,<sup>71</sup> meats (total, red, and processed but not white meat),<sup>72,73</sup> and fried foods.<sup>74</sup>
- Subjects in the highest versus lowest quintile of an unhealthy plant-based diet index, a composite measure of a diet with a higher intake of refined grains, potatoes, SSBs, sweets, and salty food and lower intake of whole grains, fruits, vegetables, nuts, legumes, tea, and coffee, had a 50% higher risk of developing incident MetS.<sup>75</sup>
- Restrained and emotional eating behaviors<sup>76</sup> and a problematic relationship with eating and food<sup>77</sup> are risk factors for incident MetS.
- Dietary habits are also inversely associated with incident MetS, including alcohol use,<sup>78</sup> fiber intake,<sup>79</sup> Mediterranean diet,<sup>80–82</sup> fruit consumption ( $\geq 4$  servings/d versus <1 serving/d),<sup>83</sup> dairy consumption (particularly yogurt and low-fat dairy products),<sup>84,85</sup> consumption of animal or fat protein,<sup>86</sup> coffee consumption,<sup>63,64,87,88</sup> vitamin D intake,<sup>89</sup> intake of tree nuts,<sup>90</sup> walnut intake,<sup>91</sup> and intake of long-chain omega-3 PUFAs.<sup>92</sup>

### Physical Activity

- 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 the development of MetS.<sup>93</sup> For every increase of 10 MET-h/wk (equal to  $\approx 150$  minutes of moderate PA per week), the 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>94</sup> aerobic or resistance training,<sup>95</sup> and cardiorespiratory fitness (eg, maximal oxygen uptake).<sup>96</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>97</sup> The long-term meeting of step-based guidelines or an increase in daily steps was associated with reduced risk of MetS from 39% to 12% over 7 years of follow-up among older European females.<sup>98</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>99</sup>
- Blood biomarkers that are inversely associated with incident MetS include insulin sensitivity,<sup>100</sup> adiponectin,<sup>101</sup> total testosterone,<sup>100,102</sup> serum 25-hydroxyvitamin D,<sup>103–107</sup> total and indirect bilirubin,<sup>108</sup> follicle-stimulating hormone in postmenopausal females,<sup>109</sup> and sex hormone-binding globulin.<sup>100,102</sup>

## Other

- Risk factors for incident MetS include age,<sup>110</sup> smoking,<sup>111,112</sup> childhood MetS,<sup>113</sup> childhood cancer,<sup>114</sup> obesity or high BMI,<sup>115</sup> weight gain,<sup>116</sup> and weight fluctuation.<sup>117</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>118</sup> Furthermore, depressed subjects in America were at higher odds of MetS than those in Europe (OR, 1.46 [95% CI, 1.16–1.84]).<sup>119</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>120</sup>
- In a meta-analysis, incident MetS was associated with perinatal factors, including LBW (pooled OR, 1.79 [95% CI, 1.39–2.31]) and PTB (pooled OR, 1.72 [95% CI, 1.12–2.65]).<sup>121</sup>
- Among perimenopausal females (mean age, 55±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>122</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), γ-glutamyltransferase (RR, 1.98 [95% CI, 1.89–2.07] for highest versus lowest quartile or quintile), or ultrasonography (RR, 3.22 [95% CI, 3.05–3.41]) was used to assess NAFLD.<sup>123</sup>

## Prevalent MetS

### Diet

- In cross-sectional studies, prevalent MetS was directly associated with a high-salt diet,<sup>124</sup> white

rice consumption,<sup>125</sup> a high DII,<sup>126,127</sup> high dietary acid load,<sup>128</sup> high insulin load or insulin index diet,<sup>129</sup> a long-chain food supply (compared with a short-chain food supply),<sup>130</sup> excessive dietary calcium (>1200 mg/d) in males,<sup>131</sup> and inadequate energy intake among patients undergoing dialysis.<sup>132</sup>

- Prevalent MetS is inversely associated with total antioxidant capacity from diet and dietary supplements,<sup>133</sup> animal-based oils such as butter and ghee,<sup>134</sup> organic food consumption,<sup>135</sup> and Mediterranean-DASH Intervention for Neurodegenerative Delay diet, identified as a new dietary pattern of the combination of Mediterranean and DASH diets.<sup>136</sup>

## Physical Activity

- In cross-sectional studies, prevalent MetS is directly associated with low cardiorespiratory fitness<sup>104,137</sup> and low levels of PA<sup>138,139</sup> and is inversely associated with “weekend warrior” and regular PA patterns,<sup>140</sup> any length of moderate- to vigorous-intensity PA,<sup>139</sup> and handgrip strength.<sup>141–143</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 females.<sup>144</sup>

## Blood Biomarkers

- Blood biomarkers directly associated with prevalent MetS include proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-α<sup>145</sup>; retinol binding protein 4<sup>146</sup>; cancer antigen 19-9<sup>137,147</sup>; serum liver chemistries, including alanine transaminase,<sup>148</sup> aspartate transaminase, alanine transaminase/aspartate transaminase ratio, alkaline phosphatase, and γ-glutamyl transferase<sup>149</sup>; serum vitamin levels,<sup>150</sup> including retinol and α-tocopherol; serum thyrotropin in individuals with euthyroidism<sup>151</sup>; and erythrocyte parameters<sup>152</sup> such as hemoglobin level and red blood cell distribution width. For example, participants with elevated serum CA 19-9 ( $\geq 37$  U/mL) had an increased risk of prevalent MetS compared with those with serum CA 19-9 <37 U/mL (multivariable aOR, 2.10 [95% CI, 1.21–3.65]).<sup>147</sup>
- In cross-sectional studies, prevalent MetS is inversely associated with anti-inflammatory cytokines (interleukin-10),<sup>145</sup> ghrelin,<sup>145</sup> adiponectin,<sup>145</sup> and antioxidant factors (paraoxonase-1).<sup>145</sup>

## Other

- Prevalent MetS is also directly associated with elevated urine sodium<sup>153</sup> and high heavy metal exposure.<sup>154</sup>
- In cross-sectional studies, prevalent MetS is inversely associated with the ratio of muscle mass to visceral fat in college students,<sup>155</sup> vacation frequency,<sup>156</sup> and marijuana use.<sup>157</sup>
- A systematic review and meta-analysis found that adults in psychological high-stress groups had a higher chance of having MetS than those in the low-stress group (OR, 1.45 [95% CI, 1.21–1.74]).<sup>158</sup> Occupational stress showed the strongest association with MetS (OR, 1.69 [95% CI, 1.18–2.42]), whereas perceived general stress showed the weakest effect (OR, 1.22 [95% CI, 1.02–1.46]).
- 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>159</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>160</sup>

## Social Determinants of Health

- In NHANES 2003 to 2008, high neighborhood racial and ethnic diversity<sup>161</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.
- Prior studies have reported higher MetS incidence among individuals with lower educational attainment, lower SES,<sup>162</sup> more experiences of everyday discrimination,<sup>163</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>164</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>165</sup>
- In the HELENA study among 1037 European adolescents 12.5 to 17.5 years of age, those with mothers with low education showed a higher MetS

risk ( $\beta$  estimate, 0.54 [95% CI, 0.09–0.98]) 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 [95% CI, 0.08–1.31]).<sup>166</sup>

- Using data from the Korean National Health and Nutrition Examination Survey (2016–2018), 1 study reported that high SES was inversely associated with the prevalence of MetS after adjustment for covariates (OR, 0.67 [95% CI, 0.50–0.89]).<sup>167</sup>
- Similar findings were reported around the world on the association of socioeconomic inequalities with MetS.<sup>168–170</sup> In a Spanish working population, the prevalence of MetS by ATP III criteria among males was 8.01% for social class I, 8.72% for social class II, and 9.82% for social class III ( $P=0.004$ ); the values among females were 1.35%, 3.85%, and 4.6%, respectively. Subjects with no education or primary school education in the French West Indies had higher risk of MetS (OR, 2.4 [95% CI, 1.3–4.4]) compared with those participants having equivalent to high school or higher than high school education.<sup>169</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>48</sup>
- Isolated MetS, which could be considered an early 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 compared with healthy control subjects had a higher incidence of hypertension (34% versus 14%;  $P<0.001$ ) and diabetes (12% versus 1%;  $P<0.001$ ).<sup>171</sup>

## Genetics and Family History

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

- The combined genetic heritability in self-identified Black individuals and White individuals for ATP III–defined MetS is estimated to be  $\approx 25\%$ .<sup>172</sup>
- 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>173</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>174–178</sup> A recent multiethnic GWAS for MetS components has identified ethnicity-specific genetic associations (6 loci in African American individuals, 3 loci in European American individuals, 3 loci in Japanese American individuals, 2 loci in Mexican American individuals) with substantial interethnic heterogeneity.<sup>179</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>180</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>181</sup>
- SNPs of inflammatory genes (encoding interleukin-6, interleukin-1 $\beta$ , and interleukin-10) and plasma fatty acids, as well as interactions among these SNPs, are differentially associated with odds of MetS.<sup>182</sup>
- A UK Biobank study of 291107 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>183</sup>
- Recently, 90 novel loci (cumulative 94 loci) have been identified for NAFLD.<sup>184</sup> A total of 8 common genetic loci (*MTARC1*, *ADH1B*, *TRIB1*, *GPAM*, *MAST3*, *TM6SF2*, *APOE*, *PNPLA3*) have also been identified for association with hepatic steatosis, a leading risk factor for cardiometabolic diseases.<sup>185</sup>

## Prevention and Awareness of MetS

- Identification of MetS represents a call to action for a multidisciplinary team of health care professionals and patients to address underlying lifestyle-related risk factors.<sup>186</sup>
- Despite the high prevalence of MetS, the public's recognition of MetS is limited, and a study showed that the average MetS Knowledge Scale was  $36.7 \pm 18.8$  (range, 0–100).<sup>187</sup> Communicating with patients about MetS and its clinical assessment

may increase risk perception and motivation toward a healthier behavior.<sup>188</sup>

## Morbidity and Mortality

### Adults

#### CVD Morbidity and Mortality

- MetS is associated with CVD morbidity and mortality. A meta-analysis of 87 studies comprising 951083 subjects showed that MetS increased the risk of CVD (summary RR, 2.35 [95% CI, 2.02–2.73]), with significantly 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>189</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>190</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 BP, and hyperglycemia conferred the greatest risk for CVD (HR, 2.36 [95% CI, 1.54–3.61]) and mortality (HR, 3.09 [95% CI, 1.93–4.94]) in the Framingham Offspring Study.<sup>115</sup>
- In the INTERHEART case-control study of 26903 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 International Diabetes Federation (OR, 2.20 [95% CI, 2.03–2.38]) definitions, with a PAR of 14.5% (95% CI, 12.7%–16.3%) and 16.8% (95% CI, 14.8%–18.8%), respectively, and associations were similar across all regions and ethnic groups. In addition, the presence of  $\geq 3$  versus  $< 3$  elevated risk factors was associated with an increased risk of MI (OR, 1.50 [95% CI, 1.24–1.81]). Similar results were observed when the International Diabetes Federation definition was used.<sup>191</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>192</sup>
- Among 3414 patients with stable CVD and atherosgenic 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>193</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>194</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>195</sup>
- MetS is associated with risk of stroke.<sup>196</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]). The risk was higher for ischemic stroke (RR, 2.12 [95% CI, 1.46–3.08]) than hemorrhagic stroke (RR, 1.48 [95% CI, 0.98–2.24]). In a combined analysis from the ARIC and JHS studies, 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>197</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>198</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.
- In a recent meta-analysis of 13 cohort studies comprising 59 919 participants  $>60$  years of age, MetS was significantly associated with stroke recurrence (RR, 1.46 [95% CI, 1.07–1.97]).<sup>199</sup>

### 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>200</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>201</sup> There was significant heterogeneity across the studies

(all-cause mortality,  $P=55.9\%$ ,  $P=0.001$ ; CVD mortality,  $P=58.1\%$ ,  $P=0.008$ ). 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.

- In a recent meta-analysis of 13 cohort studies comprising 59 919 participants  $>60$  years of age, MetS was significantly associated with all-cause mortality (RR, 1.27 [95% CI, 1.18–1.36]).<sup>199</sup>
- The impact of MetS on mortality has been shown to be modified by objective sleep duration.<sup>202</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>203</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>204</sup> MetS severity score was also strongly associated with early onset of diabetes.<sup>205</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>113</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>206</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>207</sup> An analysis of 5803 participants in 4 cohort studies (Cardiovascular Risk in Young Finns, Bogalusa Heart Study, Princeton Lipid Research Study, Insulin Study) showed that childhood MetS predicted high carotid IMT in adults from 11 years of age onward and type 2 diabetes in adults from 14 years of age onward.<sup>113</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>208</sup>

## Adults

### MetS and Subclinical CVD

- MetS has also been associated with incident AF,<sup>209,210</sup> HF,<sup>211</sup> and PAD.<sup>212</sup> The adjusted HR for incident AF was 1.38 (95% CI, 1.36–1.39). The aRR for incidence PAD was 1.76 (95% CI, 1.05–2.92).
- 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>213,214</sup> There appears to be a synergistic relationship among MetS, NAFLD, and prevalence of CAC,<sup>215</sup> as well as a synergistic relationship with smoking.<sup>216</sup>
- Individuals with MetS have a higher degree of endothelial dysfunction than individuals with a similar burden of traditional cardiovascular risk factors.<sup>217</sup> The aOR for the association of MetS with peripheral endothelial dysfunction was 2.06 ( $P=0.009$ ). Furthermore, individuals with both MetS and diabetes have demonstrated increased microvascular and macrovascular dysfunction.<sup>218</sup> MetS is associated with increased thrombosis, including increased resistance to aspirin<sup>219</sup> and clopidogrel loading.<sup>220</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,  $0.28\pm0.06$  [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>221</sup>
- In modern imaging studies using echocardiography, MRI, cardiac CT, and positron emission tomography, MetS is closely related to increased epicardial adipose tissues<sup>222</sup>; increased visceral fat<sup>223</sup>; increased ascending aortic diameter<sup>224</sup>; high-risk coronary plaque features, including increased necrotic core<sup>225</sup>; impaired coronary flow reserve<sup>226</sup>; abnormal indices of LV strain<sup>227</sup>; LV diastolic dysfunction<sup>228</sup>; LV dyssynchrony<sup>229</sup>; and subclinical RV dysfunction.<sup>230</sup> For example, the epicardial adipose thickness was higher in patients with MetS than in those without MetS (difference in means, 1.15 mm [95% CI, 0.78–1.53]).<sup>222</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 MetS.<sup>231</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. Among White men and women, compared with the <25th percentile of a MetS severity score, the risk of incident diabetes was 0.97 (95% CI, 0.62–1.53) for the 25th to 50th percentile, 1.29 (95% CI, 0.76–2.19) for the 50th to 75th percentile, and 2.24 (95% CI, 1.21–4.15) for above the 75th percentile. Among Black men and women, compared with below the 25th percentile of a MetS severity score, the risk of incident diabetes was 2.15 (95% CI, 1.28–3.62) for the 25th to 50th percentile, 4.00 (95% CI, 2.22–7.18) for the 50th to 75th percentile, and 5.30 (95% CI, 2.73–10.29) for above the 75th percentile.
- 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>232</sup> Similar findings were also reported in the Korean nationwide cohort study.<sup>233</sup> By setting

the reference group as subjects having 4 to 5 components of MetS, subjects having  $\leq 1$  component of MetS had the lowest risk of incident type 2 diabetes (aHR, 0.27 [95% CI, 0.266–0.271]), and the risk increased as components of MetS increased during baseline and the second visit.

## 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 cancer),<sup>236–238</sup> as well as with gastroenteropancreatic neuroendocrine tumors.<sup>239</sup> A nationwide cohort study conducted among Korean individuals studied the changes in MetS status and breast cancer risk and found that compared with the sustained non-MetS group, the adjusted HR for breast cancer was 1.11 (95% CI, 1.04–1.19) in the transition to MetS group, 1.05 (95% CI, 0.96–1.14) in the transition to non-MetS group, and 1.18 (95% CI, 1.12–1.25) in the sustained MetS group.<sup>240</sup>
- MetS is linked to poorer cancer outcomes, including increased risk of recurrence and overall mortality.<sup>241,242</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>243</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>244</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>245</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 1.22 [95% CI, 1.09–1.37] for breast and prostate cancer, respectively).<sup>246</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>247</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. According to data from NHANES 2011 to 2014, the overall prevalence of NAFLD among US adults is 21.9%.<sup>248</sup> The global prevalence of NAFLD is estimated to be 25.2%.<sup>249</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>250</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>248,251</sup>
- MetS has been associated with cirrhosis,<sup>252</sup> colorectal adenomas,<sup>253</sup> acute pancreatitis,<sup>254</sup> and Barrett esophagus.<sup>255</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>256</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>257</sup>
- MetS is associated with dementia<sup>258</sup> (particularly Alzheimer dementia<sup>259</sup>), cognitive decline,<sup>260</sup> and lower cognitive performance in older adults at risk for cognitive decline.<sup>261</sup> For example, during the mean follow-up of 4.9 years, the adjusted HRs in a non-MetS group that progressed to MetS compared with the sustained normal group were 1.11 (95% CI, 1.08–1.13) for total dementia, 1.08 (95% CI, 1.05–1.11) for AD, and 1.20 (95% CI, 1.13–1.28) for vascular dementia.<sup>258</sup> The adjusted HRs in the improved group (MetS to normal) compared with the sustained normal group were 1.12 (95% CI, 1.10–1.15) for total dementia, 1.10 (95% CI, 1.07–1.13) for AD, and 1.19 (95% CI, 1.12–1.27) for vascular dementia. The adjusted HRs in the sustained group (MetS to MetS) compared with the sustained normal group were 1.18 (95% CI, 1.16–1.20) for total dementia, 1.13 (95% CI, 1.11–1.15) for AD, and 1.38 (1.32–1.44) for vascular dementia.
  - 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>262,263</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>264</sup>
  - MetS and its components are associated with more severe infection with SARS-CoV-2 and high risk for poor outcomes in COVID-19 illness.<sup>265–268</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 ≈24% for each additional MetS component present.<sup>269</sup>
- The presence of MetS increases the risk for postoperative complications, including prolonged hospital stay and risk for postsurgical complications (OR, 1.20 [95% CI, 1.03–1.09] and 1.22 [95% CI, 1.09–1.37] for patients with breast and prostate cancer with MetS undergoing tumor removal, respectively), blood transfusion, surgical site infection, and respiratory failure, across various surgical populations.<sup>246,270–274</sup>

## Global Burden of MetS

- MetS is becoming hyperendemic around the world. Published evidence has described the prevalence

of MetS in Canada,<sup>275</sup> Latin America,<sup>276</sup> Aruba,<sup>277</sup> India,<sup>278–281</sup> Bangladesh,<sup>282</sup> Iran,<sup>283–285</sup> Ghana,<sup>286</sup> the Gaza Strip,<sup>287</sup> Jordan,<sup>288</sup> Ethiopia,<sup>289,290</sup> Nigeria,<sup>291,292</sup> South Africa,<sup>293</sup> Ecuador,<sup>294</sup> and Vietnam,<sup>295</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>296</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% (International Diabetes Federation), 6.7% (ATP III), and 8.9% (de Ferranti).<sup>297</sup> Among obese or overweight children and adolescents, pooled prevalence was estimated at 24.1%, 36.5%, and 56.3% with the International Diabetes Federation, ATP III, and de Ferranti criteria, respectively.
- A recent systematic review has synthesized the prevalence of MetS according to different definitions in the pediatric population across the world.<sup>298</sup> According to the International Diabetes Federation, the prevalence of MetS was 3.1% to 5.4% in the United States, 2.1% in Canada, 0.3% to 0.9% in Colombia, 1.5% in Venezuela,<sup>299</sup> 2.1% to 2.6% in Brazil, 9.5% in Chile, 0.4% to 2.7% in Europe, 3.8% in Spain, 1.9% in South Africa, 1.1% to 7.6% in China, 1.0 to 2.1% in Korea, 2.6% in Malaysia, 2.0% in Saudi Arabia, 8.4% in Iran, and 2.7% in Australia.

## Latin America

- In a systematic review of 10 Brazilian studies, the weighted mean prevalence of MetS in Brazil was 29.6%.<sup>299</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>300</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>301</sup> Among older Mexican adults ( $\geq 65$  years of age), the prevalence was 72.9% (75.7% in males, 70.4% in females).<sup>302</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>299,301</sup> 33.0% in Australian Aboriginal individuals, and 50.3% in Torres Strait Islander individuals.<sup>303</sup>

**Europe**

(See Chart 10-7)

- 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>304</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>305</sup>

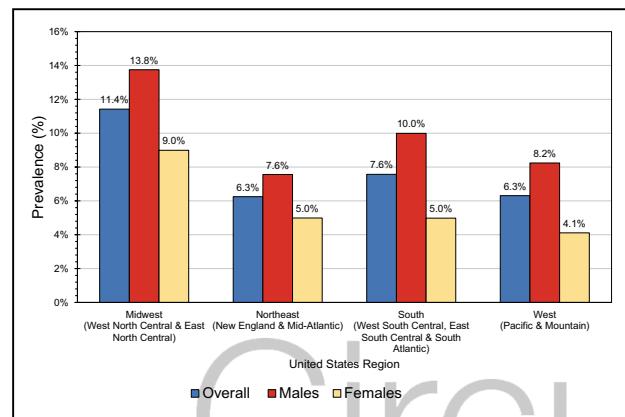
**Asia and Middle East**

(See Chart 10-8)

- On the basis of data from NIPPON DATA (1990–2005), the age-adjusted prevalence of MetS in a

Japanese population was 19.3%.<sup>195</sup> In a partially representative Chinese population, the 2009 age-adjusted prevalence of MetS in China was 21.3%,<sup>306</sup> whereas in northwest China, the prevalence for 2010 was 15.1%,<sup>307</sup> and in 2018, the prevalence in Chinese adults in Hong Kong was 14.1%.<sup>308</sup>

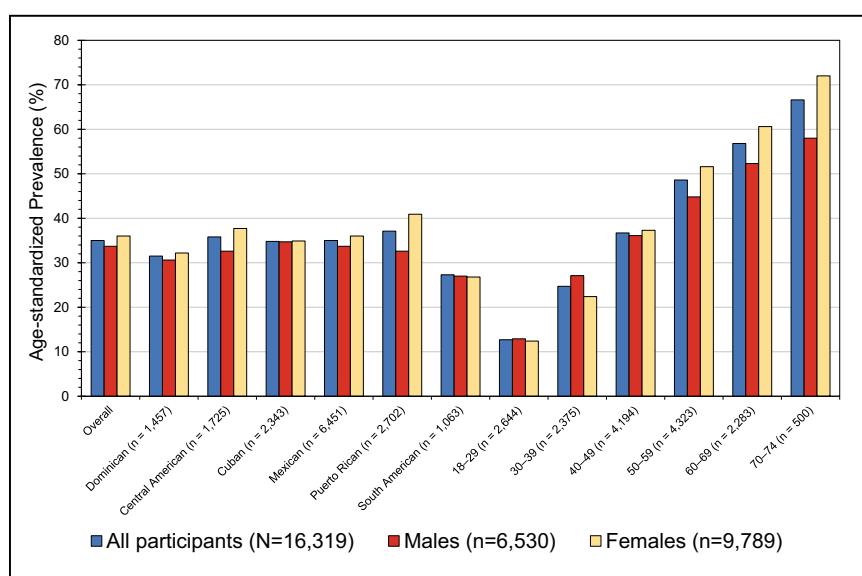
- In a meta-analysis of cross-sectional studies that assessed the prevalence of MetS in 15 Middle Eastern countries, the pooled prevalence estimate for MetS was 31.2% (95% CI, 28.4%–33.9%). Pooled prevalence estimates ranged from a low of 23.6% in Kuwait to 40.1% in the United Arab Emirates, depending on the time frame, country studied, and definition of MetS used (Chart 10-8). There was high heterogeneity among the 61 included studies.<sup>309</sup>



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

MetS indicates metabolic syndrome; and NHANES, National Health and Nutrition Examination Survey.

Source: Data derived from DeBoer et al.<sup>310</sup>

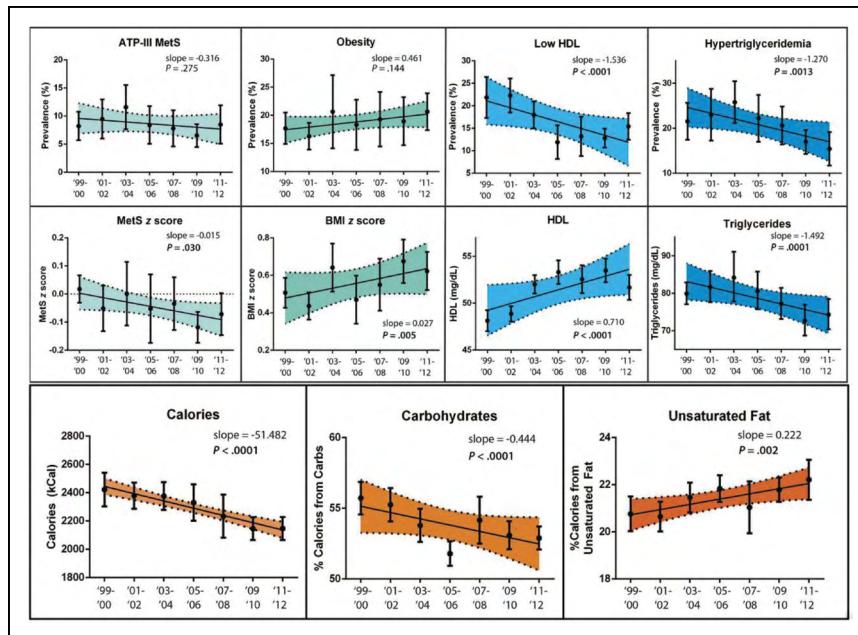


**Chart 10-2. Age-standardized prevalence of MetS by age and sex in Hispanic/Latino people in HCHS/SOL, United States, 2008 to 2011.**

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.

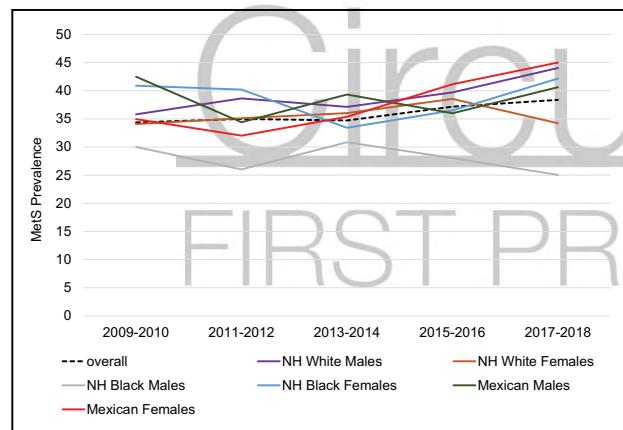
Source: Data derived from Heiss et al.<sup>12</sup>



**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, high-density lipoprotein; MetS, metabolic syndrome; and NHANES, National Health and Nutrition Examination Survey.

Source: Reproduced with permission from Lee et al.<sup>44</sup> Copyright © 2016 American Academy of Pediatrics.

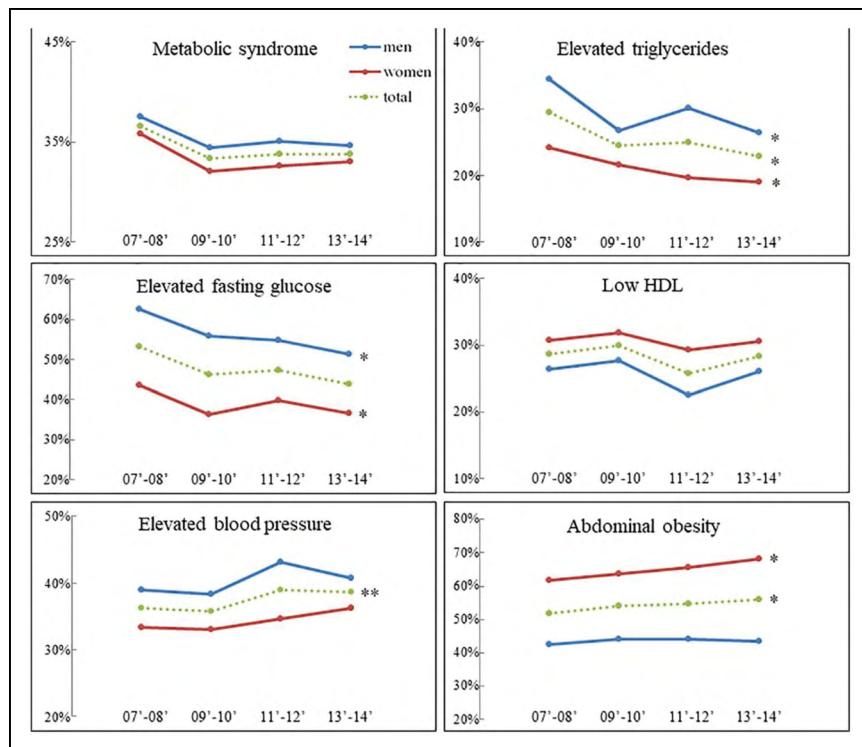


**Chart 10-4. Prevalence of MetS among US adults using the harmonized MetS criteria (NHANES, 2009–2018).**

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.

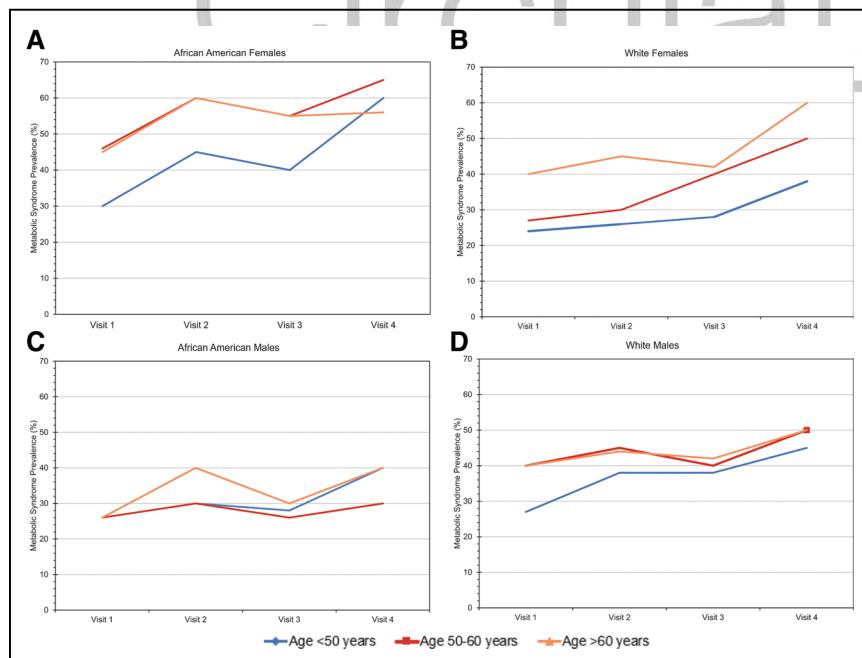
Source: Data courtesy of Junxiu Liu using NHANES.<sup>311</sup>



**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.  $P_{\text{trend}} < 0.05$ .  $**P_{\text{trend}} = 0.05$  after adjustment for age, sex, and race, as appropriate.

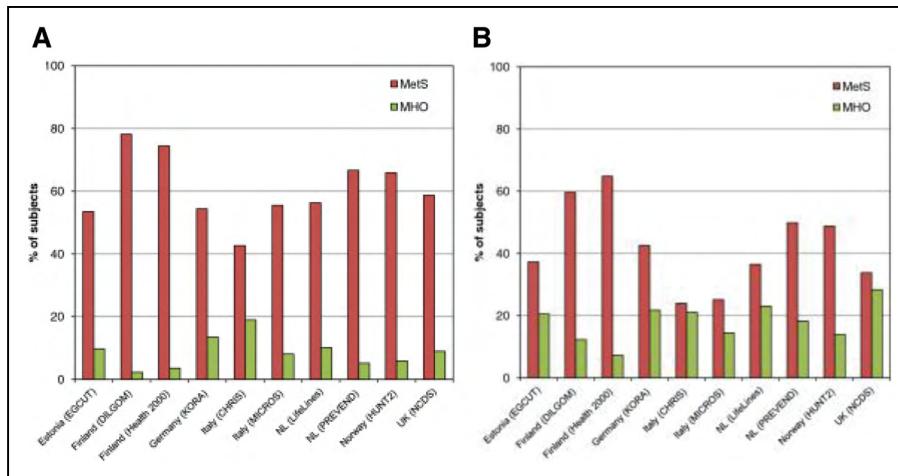
Source: Reprinted from Shin et al<sup>45</sup> with permission from Elsevier. Copyright © 2018 Elsevier.



**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. **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>48</sup>

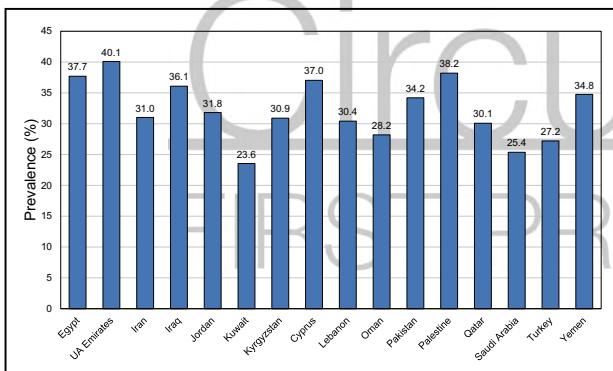


**Chart 10-7. Age-standardized prevalence of MetS and MHO among obese (body mass index  $\geq 30 \text{ kg/m}^2$ ) people in different European cohorts, 1995 to 2012 (global data).**

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

CHRIS indicates Collaborative Health Research in South Tyrol Study; DILGOM, Dietary, Lifestyle, and Genetics Determinants of Obesity and Metabolic Syndrome; EGCUT, Estonian Genome Center of the University of Tartu; HUNT2, Nord-Trøndelag Health Study; KORA, Cooperative Health Research in the Region of Augsburg; MetS, metabolic syndrome; MHO, metabolically healthy obesity; MICROS, Microisolates in South Tyrol Study; NCDS, National Child Development Study; NL, the Netherlands; and PREVEND, Prevention of Renal and Vascular End-Stage Disease.

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

MetS indicates metabolic syndrome; and UA, United Arab.

\*Pooled prevalence estimates obtained with the random-effects model.

Source: Data derived from Ansari-Moghaddam et al.<sup>309</sup>

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# Circulation

## 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, delivery of an infant who is SGA, pregnancy loss (eg, miscarriage or stillbirth), and placental abruption. 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 in infancy or accumulation of cardiometabolic risk factors later in life) 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

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

- 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. Gestational diabetes often resolves after delivery.
- PTB: PTB includes spontaneous or indicated delivery before 37 weeks' gestation American Heart Association.
- 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
- Placental abruption: Premature separation of a normally implanted placenta from the uterus before delivery.

### 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 gestational weight gain, with an aOR of 2.51 (95% CI, 2.31–2.74) for females with prepregnancy obesity and high ( $\geq 1.0$  SD) gestational weight gain (Chart 11-1).<sup>5</sup>

- 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>
- A meta-analysis of 17 403 participants from 30 cross-sectional or case-control studies examined risk factors for PTB in Ethiopia (PTB prevalence is 11% in Ethiopia).<sup>7</sup> This study showed that pregnancy-induced hypertension (aOR, 5.11 [95% CI, 3.73–7.01]), living with HIV (aOR, 4.74 [95% CI, 2.79–8.05]), rural residence (aOR, 2.35 [95% CI, 1.56–3.55]), premature rupture of membrane, history of abortion, multiple pregnancies, and anemia during pregnancy were associated with PTB.
- In 24 369 females from 12 studies (case-controls, cohort, and cross-sectional) in sub-Saharan Africa, chronic hypertension (OR from 5 studies ranged from 2.2–10.5), overweight (OR from 3 studies ranged from 1.4–7.0), obesity (OR from 5 studies ranged from 1.8–3.9), diabetes (OR from 1 study was 5.4 [95% CI, 1.1–27.0]), and alcohol use (OR from 1 study was 4.0 [95% CI, 1.8–8.8]) were significantly associated with a high risk of preeclampsia.<sup>8</sup>

### Pregnancy-Related Complications: Mortality and CVD

#### Mortality

- The pregnancy-related mortality rate was 17.4 per 100 000 live births in 2018.<sup>9</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 being 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 maternal deaths (eg, from cardiomyopathy, arrhythmia, and congenital HD) are the most

common cause of maternal or pregnancy-related mortality in high-income countries. In the United States, these accounted for 26.5% of maternal deaths according to an observational study using 2011 to 2013 data from the CDC Pregnancy Mortality Surveillance System.<sup>10,11</sup> In low- to middle-income countries, the second leading cause of death is hypertension, accounting for 14% of maternal deaths.<sup>12</sup>

### Associations With 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>13</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>14</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).
- In a study of 10 292 females in the WHI with APO data and adjudicated HF outcomes, only HDP was significantly associated with HF (aOR, 1.75 [95% CI, 1.22–2.50]) and HFpEF (aOR, 2.06 [95% CI, 1.29–3.27]).<sup>15</sup> In mediation analyses, hypertension explained 24% (95% CI, 12%–73%), CHD explained 23% (95% CI, 11%–68%), and BMI explained 20% (95% CI, 10%–64%) of the association between HDP and HF.

### 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>16</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 at 116 per 1000 live births.
- Rates of chronic hypertension before pregnancy increased significantly between 2007 and 2018.<sup>17</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 ≥1 intermediate, 1 poor, or ≥2 poor (versus all ideal) CVH metrics during pregnancy, respectively.<sup>18</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]).
- Among 7633 pregnant females recruited between 12 and 20 weeks of gestation in the Ottawa and Kingston Birth Cohort from 2002 to 2009, risk factors for gestational hypertension and preeclampsia were studied and compared. Risk factors for gestational hypertension and preeclampsia were largely similar; aRRs for gestational hypertension and preeclampsia for overweight were 1.80 (95% CI, 1.35–2.41) and 1.93 (95% CI, 1.37–2.70), respectively; for obesity, 2.81 (95% CI, 2.07–3.81) and 3.38 (95% CI, 2.40–4.76); for nulliparity, 2.59 (95% CI, 1.90–3.52) and 2.78 (95% CI, 2.00–3.86); for preeclampsia in previous pregnancy, 14.09 (95% CI, 9.28–21.40) and 6.35 (95% CI, 3.69–10.94); for diabetes, 3.24 (95% CI, 1.17–8.97) and 3.76 (95% CI, 1.62–8.71); and for twin birth, 4.82 (95% CI, 1.47–15.83) and 10.25 (95% CI, 5.48–19.15).<sup>19</sup>
- In a meta-analysis of 25 356 688 pregnancies from 92 studies published between 2000 and 2015, the following factors at ≤16 weeks' gestation were associated with significantly elevated risks for preeclampsia (reported as pooled unadjusted RR): age >35 years (versus <35 years; 1.2 [95% CI, 1.1–1.3]); prior preeclampsia (8.4 [95% CI, 7.1–9.9]); chronic hypertension (5.1 [95% CI, 4.0–6.5]); prepregnancy diabetes (3.7 [95% CI, 3.1–4.3]); prepregnancy obesity ( $\text{BMI} >30 \text{ kg/m}^2$  versus <30  $\text{kg/m}^2$ ; 2.8 [95% CI, 2.6–3.1]); prior stillbirth (2.4 [95% CI, 1.7–3.4]); multifetal pregnancy (2.9 [95%

CI, 2.6–3.1]); nulliparity (2.1 [95% CI, 1.9–2.4]); CKD (1.8 [95% CI, 1.5–2.1]); systemic lupus erythematosus (2.5 [95% CI, 1.0–6.3]); antiphospholipid antibody syndrome (2.8 [95% CI, 1.8–4.3]); and conception by assisted reproductive techniques (1.8 [95% CI, 1.6–2.1]). PAF was highest for nulliparity (32.3% [95% CI, 27.4%–37.0%]), followed by prepregnancy  $\text{BMI} >25 \text{ kg/m}^2$  (23.8% [95% CI, 22.0%–25.6%]) and prior preeclampsia (22.8% [95% CI, 19.6%–26.3%]).<sup>20</sup>

### Weight Gain

- In a meta-analysis of 13 studies including 156 170 singleton pregnancies in females who delivered at term, higher-than-recommended gestational weight gain per the 2009 National Academy of Medicine (Institute of Medicine) guidelines (12.5–18 kg for underweight [ $\text{BMI} <18.5 \text{ kg/m}^2$ ], 11.5–16 kg for normal weight [ $\text{BMI}, 18.5\text{--}24.9 \text{ kg/m}^2$ ], 7.0–11.5 kg for overweight [ $\text{BMI}, 25.0\text{--}29.9 \text{ kg/m}^2$ ], and 5.0–9.0 kg for obese [ $\text{BMI} >30.0 \text{ kg/m}^2$ ]) was associated with higher risks for overall HDP (OR, 1.79 [95% CI, 1.61–1.99]), gestational hypertension (OR, 1.67 [95% CI, 1.43–1.95]), and preeclampsia (OR, 1.92 [95% CI, 1.36–2.72]).<sup>21</sup>
- Among 8296 nulliparous females in the nuMoM2b American study, higher HDP risks were observed for excess weight gain in midpregnancy (from 5–13 to 16–21 weeks' gestation; aIRR, 1.16 [95% CI, 1.01–1.35]) and late pregnancy (from 16–21 to 22–29 weeks' gestation; aIRR, 1.19 [95% CI, 1.02–1.40]) but not in early pregnancy (from prepregnancy to 5–13 weeks' gestation; aIRR, 0.95 [95% CI, 0.83–1.08]).<sup>22</sup>
- In a meta-analysis of 12 studies, interpregnancy weight gain was associated with increased HDP risk; each 1- $\text{kg/m}^2$  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>23</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>24</sup>

**Diet and Exercise**

- In a meta-analysis of 23 trials (7236 participants), the joint effects of exercise and diet interventions on the development of preeclampsia were studied.<sup>25</sup> In females randomized to diet with or without exercise, compared with expectant management, there was no significant difference in the risk of preeclampsia (RR, 1.01 [95% CI, 0.80–1.27]) or HDP (RR, 0.87 [95% CI, 0.70–1.06]). In the intervention group, compared with expectant management, gestational weight gain was significantly lower (−1.47 kg, [95% CI, −1.97 to −0.97]). Meta-regression weighted by the size of the studies showed no significant association between gestational weight gain and the risk of PE or HDP ( $P=0.314$  and  $P=0.124$ , respectively).
- Among 8507 women in the multiethnic Boston Birth Cohort, a greater adherence to a Mediterranean-style diet was associated with a 22% lower odds of preeclampsia (aOR, 0.78 [95% CI, 0.64–0.96] for the highest compared with lowest adherence of diet score).<sup>26</sup>
- 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 HDP; 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>27</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>28</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>29</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 HDP (RR, 0.74 [95% CI, 0.67–0.82]).<sup>30</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>31</sup>

**Other**

- In a meta-analysis of 10 studies, air pollution (particulate matter [PM2.5]) exposure during pregnancy was associated with higher risk for HDP (OR, 1.52 [95% CI, 1.24–1.87] per 10  $\mu\text{g}/\text{m}^3$ ).<sup>32</sup>
- In an observational study, 12 715 Chinese females who had a singleton birth and underwent routine serum lipid screenings in early (9–13 weeks) and late (28–42 weeks) pregnancy were followed up for the development of APOs.<sup>33</sup> Elevated serum triglyceride levels during early pregnancy were associated with increased risks of preeclampsia (OR, 1.75 [95% CI, 1.29–2.36]). Persistently high triglyceride levels increased the risks of preeclampsia (OR, 2.53 [95% CI, 1.66–3.84]).
- In a study of 2148 pregnant females, the association between COVID-19 and APOs was studied.<sup>34</sup> Participants were enrolled in 43 institutions across 18 countries, and 725 (33.2%) had COVID-19. Pregnant females with COVID-19 were more likely to develop preeclampsia (8.1 versus 4.4 percent; aRR, 1.77 [95% CI, 1.25–2.52]) compared with pregnant females without COVID-19.

**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>22,35</sup>
- Maternal, paternal, and fetal genomes may influence preeclampsia. Using the population-based Swedish Birth and Multi-Generation Registries of 244 564 sibling pairs, 1 study reported that ≈50% of the variance in preeclampsia was attributed to genetic factors and that maternal genomes contributed more to preeclampsia liability than fetal or paternal genomes.<sup>36</sup> Specifically, 35% of the variance in liability of preeclampsia was attributable to maternal genetic effects, 20% to fetal genetic effects (maternal and paternal genetic effects), 13% to the couple effect, and <1% to shared sibling environment.
- Many genetic risk factors for HDP may overlap with traditional CVD risk factors, most notably BP

and anthropometry phenotypes. According to data from the UK Biobank, GRSs for SBP (aOR per 1 SD, 1.22 [95% CI, 1.17–1.27]), DBP (aOR per 1 SD, 1.22 [95% CI, 1.17–1.26]), and BMI (aOR per 1 SD, 1.06 [95% CI, 1.02–1.10]) were significantly associated with HDP risk, whereas GRSs for heart rate, type 2 diabetes, smoking, and LDL-C were not associated.<sup>37</sup>

- 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 PRS for systolic BP; aOR, 0.65 per 5-mmHg lowering of SBP;  $P_{\text{heterogeneity}}=0.037$ ).<sup>37</sup>

#### Genetic Variants

- A limited number of preeclampsia GWASs have been published; available GWASs have examined both the maternal and fetal genomes. One GWAS of preeclampsia analyzed 4380 offspring of females with preeclampsia and 310238 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>38</sup> *FLT1* encodes a transmembrane tyrosine kinase receptor that mediates angiogenesis by binding placental growth factor.
- A second GWAS meta-analysis of 7219 European mothers with preeclampsia and 155 660 controls and 2296 Central Asian mothers with preeclampsia and 2059 controls identified the *FLT1* locus and variants at *ZNF831* and *FTO*.<sup>39</sup> *ZNF831* and *FTO* were previously associated with BP, among other cardiometabolic traits.<sup>40</sup> Furthermore, a GRS for hypertension was associated with preeclampsia ( $P=1.2\times10^{-12}$ , effect [log OR]=0.18 [95% CI, 0.13–0.23], with effect corresponding to the increase in the risk of preeclampsia per 1 SD in GRS).<sup>39</sup>
- The role of variants associated with preeclampsia risk factors (eg, hypertension and BMI) in preeclampsia is supported by a study of 498 preeclampsia cases. Specifically, both a hypertension GRS and a BMI GRS were associated with increased odds of preeclampsia.<sup>41</sup>
- *TTN* variants, present in DCM and PPCM, are enriched in patients with preeclampsia, suggesting a shared genetic architecture. 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 (see Chapter 22 [Cardiomyopathy and Heart Failure]).<sup>42</sup>

#### Prevention

##### Lifestyle Modifications

- PA is recommended for pregnant females without obstetric or medical complications.<sup>43–46</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>47</sup>
- Aerobic exercise for ≈30 to 60 minutes 2 to 7 times/wk 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>48</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 pre-eclampsia (based on medical history or ultrasonographic indicators), low-dose aspirin started at ≤16 weeks' gestation reduced the risks for pre-eclampsia (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>49</sup>
- Specific aspirin dosage and preeclampsia prevention was studied in 23 randomized trials (32 370 females). Females assigned at random to 150 mg experienced a 62% reduction in risk of preterm pre-eclampsia (RR, 0.38 [95% CI, 0.20–0.72]).<sup>50</sup> Aspirin doses <150 mg produced no significant reductions. The number needed to treat with 150 mg aspirin was 39 (95% CI, 23–100). There was a maximum 30% reduction in risk of all gestational age pre-eclampsia at all aspirin doses.

##### Chronic Hypertension Treatment

- In a randomized clinical trial of 2408 pregnant females who had chronic hypertension before 23 weeks, a more intensive antihypertensive strategy targeting a BP of <140/90 mmHg versus a strategy of no treatment unless BP was severely elevated (≥160/105 mmHg) demonstrated an 18% reduction in the composite outcome of preeclampsia with severe features, PTB before 35 weeks, placental abruption, or fetal/neonatal death (aRR, 0.82 [95% CI, 0.74–0.92]).<sup>51</sup> In this same trial, targeting a BP of <140/90 mmHg was also associated with reduced risk of developing any preeclampsia (RR,

0.79 [95% CI, 0.69–0.89]), with no increased risk in an SGA infant.

### 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>52</sup>
- In an analysis of 65 286 425 females from the NIS from January 1, 1998, through December 31, 2014, females with HDP had a higher risk of stroke compared with those without HDP (34.5% versus 6.9%;  $P<0.0001$ ).<sup>53</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>54</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>55</sup>
- In an analysis from the Nurses' Health Study including >60 000 parous participants, history of HDP was associated with a 63% increased risk of incident CVD (HR, 1.63 [95% CI, 1.37–1.94]) with a greater risk for preeclampsia (HR, 1.72 [95% CI, 1.42–2.10]) than for gestational hypertension (HR, 1.41 [95% CI, 1.03–1.93]).<sup>56</sup> There was also a dose relationship, with HRs of 1.48 (95% CI, 1.23–1.78) and 2.28 (95% CI, 1.70–3.07) for history of 1 and ≥2 HDP, respectively, compared with parous individuals without a history of HDP. Mediation analysis suggested that 64% (95% CI, 39%–83%) of the increased risk of CVD conferred by HDP was explained by traditional CVD risk factors such as the subsequent development of chronic hypertension, hypercholesterolemia, diabetes, and changes in BMI.

### Complications: Offspring Morbidity and Mortality

- Among 6410 individuals born from 1934 to 1944 in the Helsinki Birth Cohort Study, in utero exposure to HDP 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>57</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>58</sup> No significant pooled associations were found for offspring lipids, glucose, or insulin.
- A meta-analysis of 40 studies showed that offspring (at <10 years of age) of mothers with preeclampsia had increased SBP (mean difference, 2.2 mm Hg [95% CI, 1.28–3.12]) and DBP (mean difference, 1.41 mm Hg [95% CI, 0.3–2.52]) compared with control subjects.<sup>59</sup>

## Gestational Diabetes

### Incidence, Prevalence, and Secular Trends

(See Table 11-1 and Chart 11-4)

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- 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>60</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.
  - 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).
  - Temporal trends in gestational diabetes rates were estimated from a serial cross-sectional analysis of NCHS data for 12 610 235 females 15 to 44 years of age with singleton first live births from 2011 to 2019 in the United States (mean age, 26.3 years [SD, 5.8 years]).<sup>61</sup> Gestational diabetes rates increased across all races and ethnicities from 47.6 to 63.5 per 1000 live births from 2011 to 2019, a mean annual percent change of 3.7% (95% CI, 2.8%–4.6%) per year.
    - Of the participants, the following were race-specific gestational diabetes rates: Hispanic/Latina, 66.6 per 1000 live births (95% CI, 65.6–67.7; RR, 1.15 [95% CI, 1.13–1.18]), NH Asian/

Pacific Islander, 102.7 per 1000 live births (95% CI, 100.7–104.7; RR, 1.78 [95% CI, 1.74–1.82]), NH Black, 55.7 per 1000 live births (95% CI, 54.5–57.0; RR, 0.97 [95% CI, 0.94–0.99]), and NH White, 57.7 per 1000 live births (95% CI, 57.2–58.3; referent group).

- Gestational diabetes rates were highest in Asian Indian participants, 129.1 per 1000 live births (95% CI, 100.7–104.7; RR, 2.24 [95% CI, 2.15–2.33]). Among Hispanic/Latina participants, gestational diabetes rates were highest among Puerto Rican individuals, 75.8 per 1000 live births (95% CI, 71.8–79.9; RR, 1.31 [95% CI, 1.24–1.39]).

### 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 gestational weight gain (OR per 1-SD higher gestational weight gain, 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 h/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>62</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>63</sup>
- A systematic review of 17 studies demonstrated that individuals with gestational diabetes had statistically significant differences in alfa and beta diversity of gut microbes.<sup>64</sup> Six prospective studies found that microbiota change during pregnancy is associated with risk of gestational diabetes.

- Among 8 574 264 females 15 to 44 years of age at first live singleton birth in the United States, 1 747 066 were born outside the United States.<sup>65</sup> In females born outside the United States, gestational diabetes rates were higher (70.3 versus 53.2 per 1000 live births; rate ratio, 1.32 [95% CI, 1.31–1.33]). These findings were consistent in most racial and ethnic groups.

### Genetics/Family History

- Although gestational diabetes is thought to be heritable, heritability 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>66</sup>
- Reflecting the hypothesis that gestational diabetes and diabetes have a shared genetic architecture, many gestational diabetes genetic studies have examined variants previously mapped for type 2 diabetes. For example, a meta-analysis of 23 studies examined the relevance of 100 type 2 diabetes variants that were reported by a minimum of 2 studies for gestational diabetes. This meta-analysis identified significant associations for gestational diabetes with 16 variants in 8 loci (in or near *IGF2BP2*, *CDKAL1*, *GLIS3*, *CDKN2A/2B*, *HHEX*/*IDE*, *TCF7L2*, *MTNR1B*, and *HNF1A*).<sup>67</sup>
- GRSs composed of diabetes loci predict gestational diabetes. In a case-control study of 2636 females with gestational diabetes and 6086 females without gestational diabetes from the Nurses' Health Study 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>68</sup>
- Association of diabetes GRSs 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];  $P=1.75\times10^{-8}$ ; and OR, 2.66 [95% CI, 1.51–4.63];  $P=0.0006$ , respectively, for the top 25% of GRSs compared with the bottom 75%).<sup>69</sup>
- Few GWASs of gestational diabetes have been published, and available GWASs have identified known diabetes genetic variants only. For example, the largest published gestational diabetes GWAS included 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. This GWAS identified 2 loci at genome-wide significance levels.<sup>70</sup> Both loci,

*CDKAL1* and *MTNR1B*, were previously identified by type 2 diabetes and fasting glucose GWASs.<sup>71,72</sup> It is interesting to note that lead variants at both loci also were associated with lower fasting insulin levels during pregnancy.

- A GWAS of diverse ancestry in 5485 females with gestational diabetes and 347 856 without gestational diabetes identified 5 loci with genome-wide significant association with gestational diabetes, mapping to/near *MTNR1B*, *TCF7L2*, *CDKAL1*, *CDKN2A* to *CDKN2B*, and *HKDC1*.<sup>73</sup> All loci except *HKDC1* have been previously reported at genome-wide significance for type 2 diabetes. Mendelian randomization analyses demonstrated significant causal association of higher BMI on increased gestational diabetes risk.

### Prevention

- In a community-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>74</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>75</sup> and adverse cardiac structure and function were higher in >20 years of follow-up.<sup>76</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>77</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>78</sup>
- In a systematic review that pooled 8 cohort studies, the odds of CVD in females with gestational diabetes were 68% higher (95% CI, 1.11–2.52) compared with females without gestational diabetes.<sup>52</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>79</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>80</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>81</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>82,83</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>83</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 5 396 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>84</sup>

### Risk Factors

- 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>85</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>86</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>87</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>28</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>88</sup>
- In a study of 8026 births during the first wave of the COVID-19 pandemic in New York, no racial and ethnic differences were found in either preterm or very PTB between Black and White females.<sup>89</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 PM2.5 exposure per IQR higher exposure, and risk was greater among NH Black females compared with NH White females.<sup>90</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>90</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>91</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: the 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>92</sup>

### Social Determinants and Health Equity in PTB

- 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>93</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>94</sup>
- In a study from data from the California Office of Statewide Health Planning and Development, 2794 females with unstable housing were exactly propensity score matched with 2318 control subjects.<sup>95</sup> Females with unstable housing had higher odds of PTB (OR, 1.2 [95% CI, 1.0–1.4];  $P<0.05$ ) and preterm labor (OR, 1.4 [95% CI, 1.2–1.6];  $P<0.001$ ).

### Genetics/Family History

- There is evidence of intergenerational transmission of PTB risk.<sup>96</sup> For example, heritability estimates for maternal genetic effects on PTB have ranged from 15% to 40%, although these estimates also may include effects of the fetal genome. Fetal genetic factors were estimated to account for 0 to 13% of the variation in gestational age at delivery; similarly negligible to small genetic effects were estimated for the paternal contribution.<sup>97</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>98</sup> These genes have previously established roles in uterine development, maternal nutrition, and vascular control. Another GWAS in 84 689 infants found a locus on chromosome 2q13, which includes several interleukin-1 family member genes, that was associated with gestational duration.<sup>99</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 10734 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];  $P=2.2\times10^{-12}$ ), lower PTB risk (OR, 0.7/cm [95% CI, 0.96–0.98];  $P=2.2\times10^{-9}$ ), and higher birth weight (15 g/cm [95% CI, 13.7–16.3];  $P=1.5\times10^{-11}$ ).<sup>100</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];  $P=1.0\times10^{-47}$ ) but not gestational duration or PTB risk.

### 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>29</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]). 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>101</sup>
- Black race–White race disparities in PTB are also present among females of high SES; among 2170686 singleton live births in the United States from 2015 to 2017 to college-educated females with private insurance who were not receiving WIC 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>102</sup>

### Complications: Maternal CVD and Mortality

- Among 57904 females in the Nurses' Health Study 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>103</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>104</sup>
- In a separate study from the Swedish national birth registry among 2189190 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>105</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>52</sup>
- Among 2189477 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>106</sup>

### Complications: Offspring Morbidity and Mortality

- In a meta-analysis of 4 cohort studies, having been born preterm was associated with increased risk for MetS in children and adults (pooled OR, 1.72 [95% CI, 1.12–2.65]).<sup>107</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 those born term.
  - In sibling 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>108–110</sup>

### Offspring Cardiac Remodeling and HF

- In a 2020 meta-analysis of 32 studies, individuals born preterm had higher LV mass (increase versus control subjects, 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>111</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>112</sup>
- Among 2613 030 individuals without congenital malformations born in Sweden from 1987 to 2012 with a median follow-up of 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 (aIRR, 1.54 [95% CI, 1.11–2.12]), 4.71 for 28 to 31 weeks (aIRR, 2.60 [95% CI, 1.33–5.08]), and 20.1 for <28 weeks (aIRR, 12.9 [95% CI, 7.06–23.7]).<sup>113</sup>

### Offspring 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>114</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>115</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>116</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]).

### LBW or 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%).<sup>117</sup> Prevalence of LBW by race is shown in Chart 11-6.

#### 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>87</sup>
- In an individual participant data meta-analysis of 265 270 births from 39 cohorts in Europe, North America, and Australia, prepregnancy underweight BMI (BMI <18.5 kg/m<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 gestational weight gain had the highest odds for SGA delivery (3.12 [95% CI, 2.75–3.54]), but risks were elevated when gestational weight gain 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>28</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>118</sup>
- In a study of 156 278 nulliparous females in Ontario, Canada, with singleton pregnancies between January 2011 and December 2018, the associations between prepregnancy HbA1c, glucose, lipids, and alanine aminotransferase and SGA were studied.<sup>119</sup> There were 19 367 with SGA. Females with SGA had lower pregravid fasting glucose, random glucose, and triglyceride levels than those without SGA. Therefore, prepregnancy cardiometabolic biomarkers were not associated with the development of SGA.

#### **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>90</sup>
- The median risk was 10.8% higher (range, 2.0%–36.0%) for whole-pregnancy PM2.5 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>90</sup>
- In a systematic review examining heat, 3 of 3 studies (2.7 million births) demonstrated that 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>90</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: the normalized difference vegetation index) within a 100- to 500-m buffer were associated with lower risk for LBW or SGA (pooled standardized OR, 0.94 [95% CI, 0.92–0.97]).<sup>92</sup>

#### **Social Determinants and Health Equity**

- 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>93</sup>
- 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>29</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 females, Hispanic females, and females of other race and ethnicity, respectively, compared with White females.<sup>120</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>101</sup>

#### **Genetics/Family History**

- Birth weight shows evidence of intergenerational transmission, which may extend across 3 generations.<sup>121</sup> For example, a study using population-based Swedish Multi-Generation and Medical Birth Registers that included 2 193 142 births reported that females whose full sisters had a child born SGA had an elevated risk of having a child born SGA (OR, 1.8 [95% CI, 1.7–1.9]). For brothers, the corresponding risk of SGA was 1.3 (95% CI, 1.2–1.4). This study also reported that 37% of the liability in

SGA was explained by fetal genetic effects, whereas maternal genetic effects explained only 9% of SGA liability.<sup>122</sup>

- Few SGA GWASs have been published. However, genetic risk factors for SGA share similarities in the genetic architecture of birth weight and maternal SBP.<sup>123</sup> In a study of N=11 951 infants and N=5182 mothers of European ancestry, each decile increase in the fetal PRS for higher birth weight was associated with a lower odds of SGA (OR, 0.75 [95% CI, 0.71–0.80]). This effect was similar in magnitude to the association for maternal PRS and SGA (OR, 0.81 [95% CI, 0.75–0.88]). Last, an SBP maternal PRS also was associated with increased SGA odds (OR, 1.15 [95% CI, 1.04–1.27]).

#### **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>52</sup>
- In data from 11 110 females in the prospectively collected Västerbotten 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>124</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>107</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>108</sup>
- A 2018 meta-analysis examined associations between birth weight and adult cardiometabolic outcomes.<sup>125</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>126</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>127</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>128</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>129</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 ≥10 weeks) in a meta-analysis of 212 184 females (including 770 with antiphospholipid syndrome) from 8 studies.<sup>130</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 PM2.5 exposure per IQR greater exposure, and risk was higher by 42% (95% CI, 6%–91%) with high third-trimester PM2.5 exposure.<sup>90</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>90</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>91</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>131</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>132</sup>

### Genetics/Family History

- The heritability of any pregnancy loss has been reported at 29% (95% CI, 20%–38%) for any miscarriage.<sup>133</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 ≥35 years of age with recurrent pregnancy loss versus 70% in females with nonrecurrent pregnancy loss).<sup>134</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>135</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 the presence of rare variants in 13% of the females with recurrent pregnancy loss.<sup>136</sup>
- In a GWAS of 69 054 females with sporadic pregnancy loss, 750 females with recurrent pregnancy loss, and 359 469 control subjects, 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 *HMGCF9*, *TLE1*, *TLE4*, *E2F8*, and *SIK1*.<sup>133</sup>

### Complications: Maternal CVD

- Among >95 000 ever-gravid females in the Nurses' Health Study II followed up for a mean of 23 years, a history of pregnancy loss was independently associated with a 21% greater risk for developing incident CVD (HR, 1.21 [95% CI, 1.10–1.33]), with similar associations for incident CHD (HR, 1.20 [95% CI, 1.07–1.35]) and stroke (HR, 1.23 [95% CI, 1.04–1.44]), compared with no pregnancy loss.<sup>137</sup> The risk was greater for females with ≥2 pregnancy losses (HR, 1.34 [95% CI, 1.21–1.62]) versus 1 pregnancy loss (HR, 1.18 [95% CI, 1.04–1.44]). Mediation analysis suggested that traditional risk factors such as hypertension, hyperlipidemia, and type 2 diabetes explained only <2% of the association between pregnancy loss and CVD.
- Data from the Nurses' Health Study 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>138</sup>

- In 79 121 postmenopausal females from the WHI, ≈35% experienced a history of pregnancy loss. This was associated with higher adjusted risk of incident CVD (HR, 1.11 [95% CI, 1.06–1.16]) over a mean follow-up of 16 years.<sup>139</sup>
- A systematic review of 84 studies (28993 438 patients) with a median follow-up of 7.5 years postpartum evaluated the associations between APOs and CVD.<sup>52</sup> The risk of CVD was higher among females with stillbirth (OR, 1.5 [95% CI, 1.1–2.1]). In this meta-analysis, miscarriage was not associated with CVD.

## Placental Abruptio

### Incidence, Prevalence, and Secular Trends

- The incidence of placental abruption is between 0.5% and 5.1%, with the majority of studies reporting an incidence of 0.5% to 1%.<sup>140</sup> In the nuMoM2b study, placental abruption was identified in 62 (0.66%) of 9450 nulliparous females: 35 (56%) were antepartum and 27 (44%) were intrapartum.<sup>141</sup>

### Risk Factors (Including Social Determinants)

- In the nuMoM2b study, risk factors for placental abruption were studied in 9450 females.<sup>141</sup> For females with abruption, the mean gestational age at delivery was  $35.6 \pm 4.4$ ; it was  $38.8 \pm 2.2$  weeks for females without abruption. Gravidity was associated with abruption (OR, 3.1 [95% CI, 1.6–6.0]).
- Several risk factors for placental abruption were identified in a case crossover study in Finland, Malta, and Aberdeen.<sup>142</sup> Preeclampsia (194 [6.5%] versus 115 [3.8%]; aOR, 1.69 [95% CI, 1.23–2.33]), idiopathic antepartum hemorrhage (556 [18.6%] versus 69 [2.3%]; aOR, 27.05 [95% CI, 16.61–44.03]), placenta previa (80 [2.7%] versus 21 [0.7%]; aOR, 3.05 [95% CI, 1.74–5.36]), maternal age of 35 to 39 years compared with 20 to 25 years (365 [12.2%] versus 323 [10.8%]; aOR, 1.32 [95% CI, 1.01–1.73]), and single marital status (aOR, 1.36 [95% CI, 1.04–1.76]) were independently associated with placental abruption.

### Genetics/Family History

- A study from the medical birth register of Norway estimated the heritability of placental abruption between sisters of placental abruption to be 16% (95% CI, 8%–23%).<sup>143</sup>
- A GWAS in the PAGE study (507 placental abruption cases and 1090 controls) and a GWAS meta-analysis in 2512 participants (959 placental abruption cases and 1553 controls) that included PAGE and the previously reported PAPE study

were undertaken.<sup>143</sup> Independent loci suggestively associated with placental abruption included rs4148646 and rs2074311 in *ABCC8*; rs7249210, rs7250184, rs7249100, and rs10401828 in *ZNF28*; rs11133659 in *CTNNB2*; and rs2074314 and rs35271178 near *KCNJ11*. Independent loci suggestively associated with placental abruption in the GWAS meta-analysis included rs76258369 near *IRX1* and rs7094759 and rs12264492 in *ADAM12*. Functional analyses of these genes showed trophoblast-like cell interaction, endocrine system disorders, CVDs, and cellular function.<sup>143</sup>

### Maternal CVD

- A meta-analysis of 11 cohort studies of 6 325 152 pregnancies analyzed the association between placental abruption and CVD.<sup>143b</sup> Risks of CVD morbidity/mortality among the abruption and nonabruption groups were 16.7 and 9.3 per 1000 births, respectively (RR, 1.76 [95% CI, 1.24–2.50];  $P=94\%$ ).
- Among >1.5 million pregnancies from the HCUP in California, placental abruption occurred in 14 881 females (1%).<sup>144</sup> Median follow-up time from delivery to event or censoring was 4.87 years (IQR, 3.54–5.96 years). Placental abruption was associated with HF (aHR, 1.44 [95% CI, 1.09–1.90]). HDP and PTB modified and mediated, respectively, the association between placental abruption and HF.

### 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>145</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>146</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>147</sup>
- Data from the WHO Global Survey on Maternal and Perinatal Health (23 countries) and 22 birth cohort studies were used to estimate the 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>148</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]; aOR 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]; aOR among multiparous females, 3.45 [95% CI, 2.79–4.25]).<sup>149</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]; aOR among 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 HDP.
- 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>150</sup>
- Based on data from 204 countries in the GBD Study 2020, 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 million (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 GBD Study 2020, 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 million (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).
- Rates of placental abruption varied across 7 countries.<sup>151</sup> Compared with births in 2000, births after 2000 in European countries had lower abruption rates. In the United States, there was an increase in placental abruption rates up to 2000 and a plateau thereafter. Changes in smoking prevalence may have partially explained the period effect in the United States ( $P=0.01$ ).

**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	1 148 057	0.7	5.1
30–34	1 110 010	1.0	7.0
35–39	546 995	1.4	9.6
≥40	122 052	2.1	12.8
Race and Hispanic origin‡			
NH White	2 054 437	0.7	5.3
NH Black	558 044	1.2	4.8
NH Asian	254 326	0.9	11.1
Hispanic	917 822	1.0	6.6
American Indian/Alaska Native	31 375	2.1	9.2
Native Hawaiian/Pacific Islander	9337	1.8	8.4
>1 Race	80 836	0.9	5.8
Prepregnancy BMI§			
Underweight	134 392	0.3	2.9
Normal weight	1 699 751	0.4	3.6
Overweight	997 977	0.8	6.1
Obesity class 1	548 092	1.3	8.8
Obesity class 2	266 105	2.0	11.2
Obesity class 3	187 689	3.2	13.9

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

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

†The number of 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 &gt;1 race were categorized as &gt;1 race.

§Prepregnancy BMI was classified as underweight (BMI  $<18.5 \text{ kg/m}^2$ ), normal weight (BMI, 18.5–24.9  $\text{kg/m}^2$ ), overweight (BMI, 25.0–29.9  $\text{kg/m}^2$ ), obesity class 1 (BMI, 30.0–34.9  $\text{kg/m}^2$ ), obesity class 2 (BMI, 35.0–39.9  $\text{kg/m}^2$ ), and obesity class 3 (BMI  $\geq 40.0 \text{ kg/m}^2$ ).Source: Data derived from Table 1 of Deputy et al.<sup>60</sup>

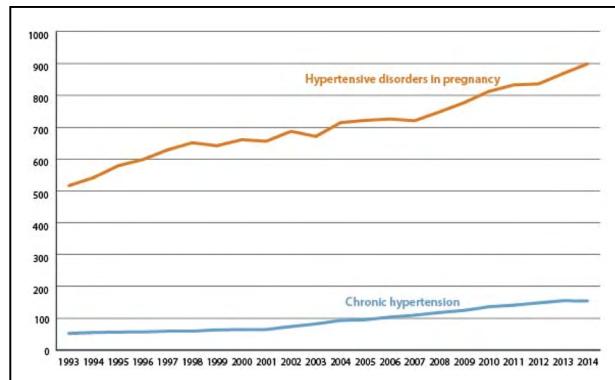
	Gestational Weight Gain Category		
Pre-Pregnancy Body Mass Index Category	Low ( $\leq 1.1$ SD)	Medium (-1.0 to 0.9 SD)	High ( $\geq 1.0$ SD)
Underweight	1.09 (0.94 – 1.26)	1.04 (0.96 – 1.12)	1.13 (0.98 – 1.30)
Normal weight	1.04 (1.01 – 1.08)	Referent	1.10 (1.06 – 1.14)
Overweight	1.23 (1.16 – 1.32)	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 gestational weight gain 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 HDP (gestational hypertension or preeclampsia), gestational diabetes, PTB (<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>. Gestational weight gain values corresponding to the SD cutoffs were not provided by the source, but the median gestational weight gain was 14.0 kg (95% CI, 3.9–27.0).

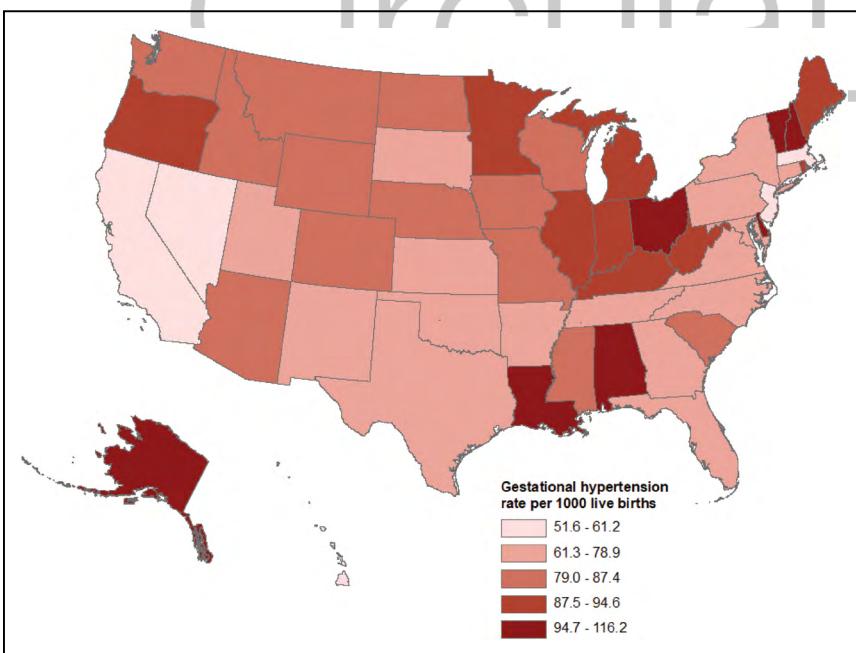
APO indicates adverse pregnancy outcome; BMI, body mass index; HDP, hypertensive disorders of pregnancy; and PTB, preterm birth.

Source: Data derived from Santos et al.<sup>5</sup>



**Chart 11-2. Trends in the rates of hypertensive disorders per 10 000 delivery hospitalizations, United States, 1993 to 2014.**

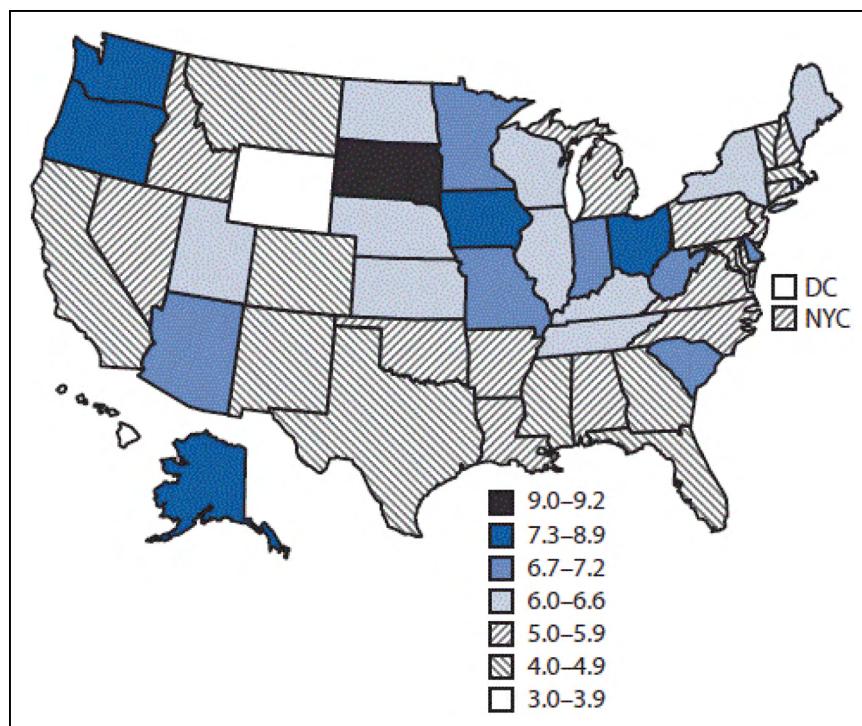
Source: Reprinted from Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion.<sup>16</sup>



**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 3 736 144 females 15 to 44 years of age with a live birth.

Source: Unpublished map using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research.<sup>152</sup>

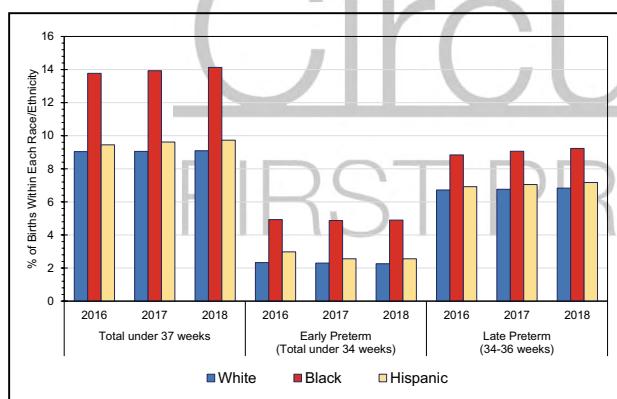


**Chart 11-4. Standardized\* prevalence of gestational diabetes among females who had a live birth by state, United States, 2016.**

NYC indicates New York City.

\*Standardized to age and race and ethnicity distribution of US resident females with a live birth in 2012.

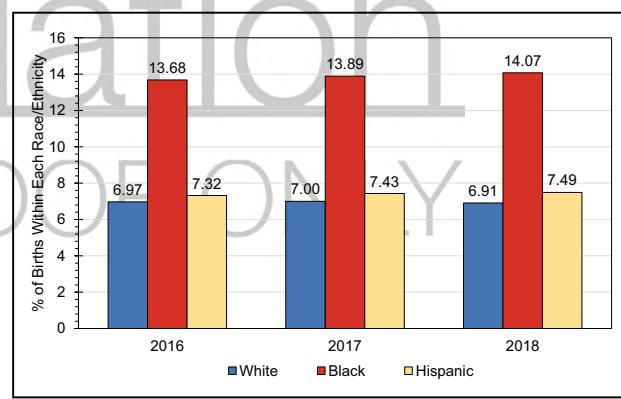
Source: Reprinted from Deputy et al.<sup>60</sup>



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

PTB indicates preterm birth.

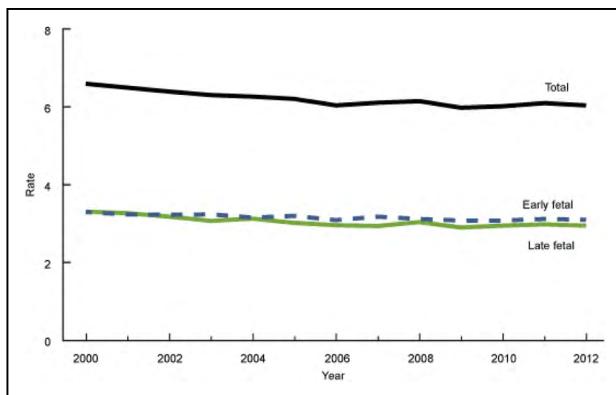
Source: Data derived from Martin et al.<sup>117</sup>



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

LBW indicates low birth weight.

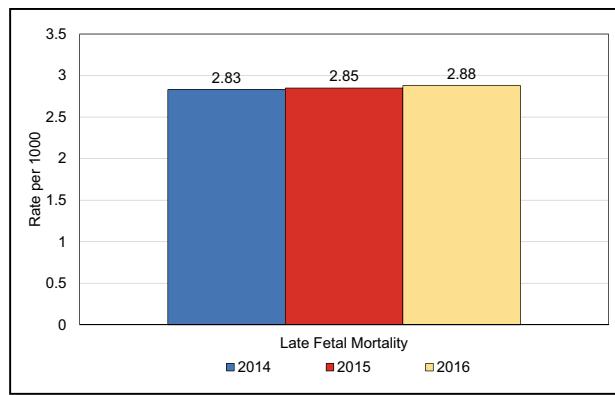
Source: Data derived from Martin et al.<sup>117</sup>



**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.

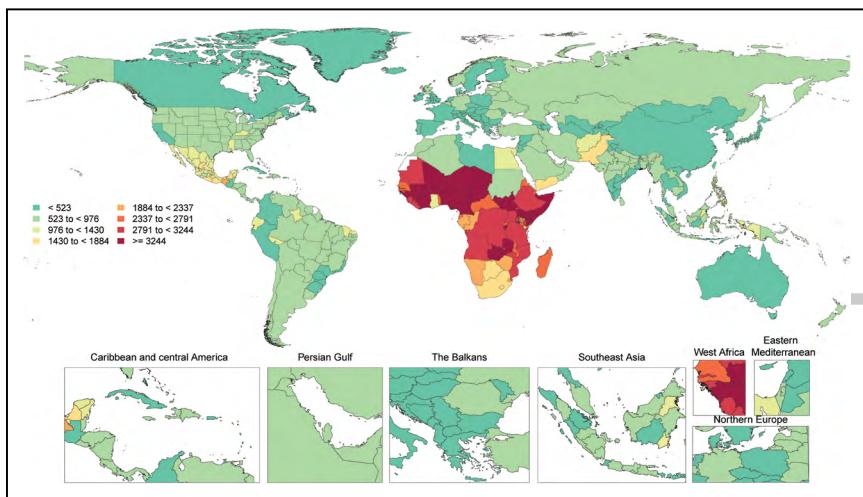
Source: Reprinted from Gregory et al.<sup>153</sup>



**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>128</sup>

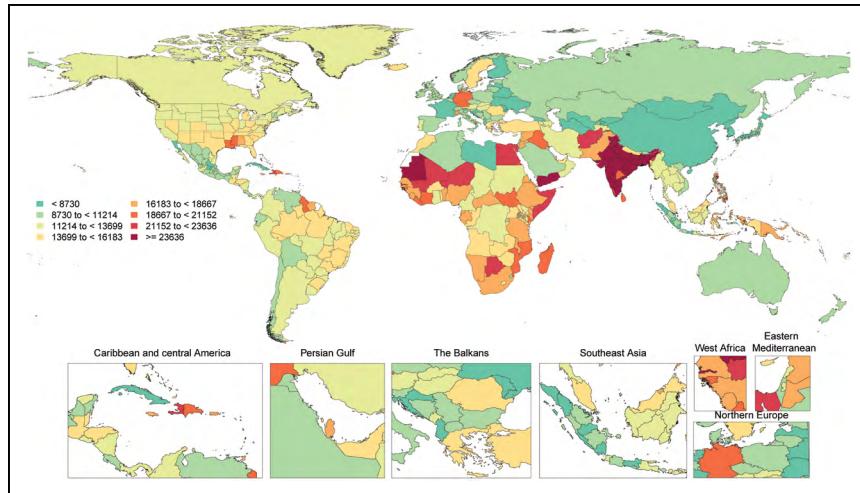


**Chart 11-9. Global incidence rates of maternal hypertensive disorders per 100 000 females, 15 to 49 years of age, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>154</sup>



### Chart 11-10. Global incidence rates of neonatal PTB per 100 000, both sexes, at birth, 2020.

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and PTB, preterm birth.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>154</sup>

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## 12. KIDNEY DISEASE

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

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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, a task force from the American Society of Nephrology and the National Kidney Foundation recommended using the eGFR equation without the race variable and to facilitate increased and timely use of cystatin C, which is a filtration marker not affected by race.<sup>2–5</sup> Newer versions of the eGFR equations, which do not incorporate race, have been developed and validated since, and efforts are underway to consider their implementation and their impact on CKD identification and outcomes.<sup>6</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>7,8</sup>
- ESRD is defined as severe CKD requiring long-term kidney replacement therapy such as hemodialysis, peritoneal dialysis, or kidney transplantation.<sup>8</sup> Individuals with ESRD are an extremely high-risk population for CVD morbidity and mortality.

### Prevalence

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

- Using from NHANES 2015 to 2018, the USRDS has estimated the prevalence of CKD by eGFR and

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

albuminuria categories as shown in Chart 12-1. The overall prevalence of CKD ( $e\text{GFR} < 60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$  or  $\text{ACR} \geq 30 \text{ mg/g}$ ; 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  $\text{ACR} \geq 30 \text{ mg/g}$  was 12.4% for NH Black adults, 10.2% for Hispanic adults, and 9.4% for NH White adults. In contrast, the prevalence of  $e\text{GFR} < 60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$  was lowest among Hispanic adults (3.0%), followed by NH Black adults (6.4%) and NH White adults (8.4%).<sup>1</sup>
- In the Framingham Offspring Study, the prevalence of mildly reduced eGFR ( $60–89 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ) was reported in 62% of participants, higher than reported in the NHANES data, possibly related to the higher age of the cohort.<sup>9</sup>
- In 2019, the age-, race-, and sex-adjusted prevalence of ESRD in the United States was 2302 per million people, an increase of 1.4% over 2018.<sup>10</sup>
- ESRD prevalence varied by race and ethnicity (Chart 12-2). In 2019, ESRD prevalence was highest in Black adults, followed by Native American 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 (92.2%) and lowest among those  $<18$  years of age (42.0%).<sup>10</sup> In contrast, peritoneal dialysis was highest among those  $<18$  years of age (47.1%) and lowest among those  $\geq 75$  years of age (7.1%).  
  - In 2019, 13.1% of all patients on dialysis used home dialysis, although this varied geographically (Chart 12-3). Peritoneal dialysis was the modality for home dialysis for 11.2%, an annual increase of 8.5% from 2018; home hemodialysis was the modality for home dialysis in 1.9%, representing an annual growth of 20.1% from 2018.

### 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 NHANES 1999 to 2010 data.<sup>11</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>12</sup> In 2019, the age-, race-, and sex-adjusted incidence of ESRD was 386 per million, an increase of 0.4% from the previous year.<sup>10</sup> The incidence of ESRD was highest among Black individuals and lowest among White individuals (Chart 12-4).

## 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 2019 primarily because of improved survival (Chart 12-2), whereas the incidence rate appeared to stabilize or decrease (Chart 12-4).
  - 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>13</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 ( $BMI \geq 30 \text{ kg/m}^2$ ).<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>14</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>15</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>16</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>17</sup>
- In the CRIC study, with the use of unsupervised consensus clustering, a higher rate of progression of kidney function was reported in patients with less favorable levels of bone mineral density, poor cardiac and kidney function markers, and inflammation (HR, 1.63 [95% CI, 1.27–2.09]), followed by patients with a higher prevalence of diabetes and obesity and who used more medications (HR, 1.3 [95% CI, 1.05–1.67]), compared with the referent cluster.<sup>18</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>19</sup>

## Social Determinants of CKDs

- 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.  

- 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>20</sup>
- In the CKID study, Black children with CKD were more likely than White children to have public insurance, lower household income, and greater food insecurity (41% versus 14%;  $P < 0.001$ ).<sup>21</sup>
- A meta-analysis of 43 studies reported that lower SES, particularly income, was associated with a higher prevalence of CKD (OR, 1.34 [95% CI, 1.18–1.53];  $P < 0.001$ ) and faster progression to ESRD (RR, 1.24, [95% CI, 1.12–1.37];  $P < 0.001$ ).<sup>22</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; OR, 1.29 [95% CI, 1.03–1.63]); however, among those with CKD, acculturation measures were not associated with hypertension or diabetes control.<sup>23</sup>

## Genetics/Family History

- It is estimated that ~30% of early-onset CKD is caused by single-gene variants, and several hundred loci have been implicated in monogenic CKD.<sup>24,25</sup>

- GWASs in >1 million individuals revealed >260 candidate loci for CKD phenotypes, including eGFR and serum urate.<sup>26–29</sup> Recently, GWAS meta-analysis in individuals of European ancestry identified 424 genetic loci (201 novel loci) associated with eGFR (estimated with creatinine). Among these, 348 loci were validated in association with eGFR estimation with the use of cystatin or blood urea nitrogen.<sup>30</sup>
- Whole-genome sequencing-based GWASs, which provided a more granular understanding of the genetic architecture, in >23 000 multiethnic populations identified 3 novel loci associated with eGFR that are more commonly observed in individuals from non-European ancestry.<sup>31</sup> Rare and low-frequency genetic variants are likely to be population specific, and greater inclusion of individuals of non-European ancestry in future genomic discovery efforts may aid in understanding the comprehensive genetic architecture of renal function and CKD.<sup>31</sup>
- Refinement in discovery and validation efforts combining multiomics data has identified 182 likely causal genes for kidney function.<sup>32</sup> These data may be leveraged for drug repurposing, therapeutic pathway prioritization, and identification of potential drug interactions.
- A transcriptome-wide association study combined with functional validation has identified *DACH1* as a CKD risk gene that contributes to tubular damage and kidney fibrosis.<sup>33</sup> Racial differences in CKD prevalence might be attributable partially 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>34</sup> Specific SNPs in *APOL1* are present in individuals of African ancestry but absent in other racial groups. This 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>35</sup>
- Although certain variants of *APOL1* increase risk, this explains only a portion of the racial disparity in ESRD risk.<sup>34</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>36</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>37</sup>
- Use of PRSs 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>38</sup>

## Awareness, Treatment, and Control

- Despite improvements in CKD awareness from 7.2% in NHANES 2003 to 2006 to 12.1% in 2015 to 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, an intensive SBP treatment goal of <130 mm Hg versus a standard goal of <140 mm Hg decreased the risk of all-cause mortality (HR, 0.79 [95% CI, 0.63–1.00]) in a pooled analysis of 4 randomized clinical trials.<sup>39</sup>

## Complications

- DALYs for CKD were 457.25 per 100 000 in 2002 versus 536.85 per 100 000 in 2019.<sup>40</sup>

## Cost

- In 2019, Medicare spent >\$87.2 billion caring for people with CKD and \$51.0 billion caring for people with ESRD.<sup>1</sup>
- Medicare spending per person per year for beneficiaries with ESRD increased from \$86 923 to \$94 608 for hemodialysis (from 2009 to 2019), from \$67 184 to \$81 097 for peritoneal dialysis (from 2009 to 2019), and from \$33 514 to \$38 863 for kidney transplantation (from 2009 to 2019).<sup>10</sup>
- After adjustment for inflation, total spending among Medicare fee-for-service beneficiaries with CKD increased 62% in the decade between 2009 and 2019, and cardiovascular causes accounted for 24.4% inpatient-related expenditures in 2019.<sup>10</sup>
- Total hospitalization expenditure in Medicare fee-for-service beneficiaries with ESRD was \$12.2 billion in 2019, and outpatient spending was \$13.1 billion in 2019.<sup>10</sup>

## Global Burden of Kidney Disease

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

- The GBD Study 2020 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 million (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 million (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>41</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>42</sup>
- The addition of eGFR or albuminuria improves CVD prediction beyond traditional risk factors used in risk equations.<sup>42</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>43</sup> In the CRIC study of 2399 participants without a history of CVD at baseline, a composite inflammation score (interleukin-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>44</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>45</sup>
- In a post hoc analysis of patients with hypertension 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>46</sup>
- In Framingham Offspring Study participants without CVD, participants with even mildly reduced kidney function (eGFR, 60–69 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>) experienced higher incidence of CVD (HR, 1.40 [95% CI, 1.02–1.93]).<sup>9</sup>

### Prevalence of CVD Among People With CKD

(See Charts 12-9 through 12-11)

- 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 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 77.3% of patients with ESRD on hemodialysis have any CVD, whereas 66.4% of patients on peritoneal dialysis and 54.8% 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>47</sup> Albuminuria was associated with higher prevalence of AF and percent time in AF and nonsustained VT.
- Between 2009 and 2019, the adjusted rate of hospitalizations for cardiovascular causes among older Medicare fee-for-service beneficiaries decreased by ≈33% among individuals with CKD and by ≈29% among individuals without CKD.<sup>10</sup>
- The 2-year adjusted survival probability after a first hospitalization for CAD in 2017 to 2019 among older Medicare fee-for-service beneficiaries was 0.77 for an individual without CKD, 0.63 for an individual with stage 3 CKD, and only 0.50 for an individual with stage 4 or 5 CKD (Chart 12-11).



### 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>48</sup>
- Both eGFR and albuminuria appear to predict HF events more strongly than CHD or stroke events.<sup>42</sup>
- In CRIC study participants with CKD, increases in NT-proBNP (the top quartile of NT-proBNP change) were significantly associated with greater risk of incident HF (HR, 1.79 [95% CI, 1.06–3.04]) and AF (HR, 2.32 [95% CI, 1.37–3.93]), and increases in soluble ST2 (the top quartile of soluble ST2 change) were associated with HF (HR, 1.89 [95% CI, 1.13–3.16]).<sup>49</sup>
- In a meta-analysis of patients with CKD, the prevalence of pulmonary hypertension 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>50</sup>
- Among Medicare beneficiaries with CKD, presence of pulmonary hypertension was associated with an increased risk of mortality after 1 (HR, 2.87 [95% CI, 2.79–2.95]), 2 to 3 (HR, 1.56 [95% CI, 1.51–1.61]), and 4 to 5 (HR, 1.47 [95% CI, 1.40–1.53]) years of follow-up and a higher risk of all-cause, cardiovascular, and noncardiovascular hospitalization during the same period.
- A patient-level pooled analysis of randomized trials explored the relationship between CKD and

prognosis in females who undergo PCI.<sup>51</sup> Creatinine clearance <45 mL/min was an independent risk factor for 3-year MACEs (aHR, 1.56 [95% CI, 1.23–1.98];  $P<0.01$ ) and all-cause mortality (aHR, 2.67 [95% CI, 1.85–3.85];  $P<0.01$ ).

- Despite having 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>52</sup> However, the risk of HF associated with CKD might be greater for Black people and Hispanic people than for White people.<sup>48</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>53</sup>
- In a prospective study of 7916 patients on hemodialysis and peritoneal dialysis, risk for ischemic stroke/systemic embolism (subdistribution HR, 0.87 [95% CI, 0.79–0.96]) and major bleeding (subdistribution HR, 0.79 [95% CI, 0.64–0.97]) was lower in those undergoing peritoneal dialysis compared with those undergoing hemodialysis.<sup>54</sup>
- In the German diabetes dialysis (4D) study, patients in the highest oxalate quartile had an increased risk of cardiovascular events (HR, 1.40 [95% CI, 1.08–1.81]) and SCD (HR, 1.62 [95% CI, 1.03–2.56]).<sup>55</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>56</sup>
- Among veterans with diabetes and CKD, the proportion receiving an ACE inhibitor/angiotensin receptor blocker was 66% (95% CI, 62%–69%) in 2013 to 2014.<sup>57,58</sup>
- In NHANES 1999 to 2014, 34.9% of adults with CKD used an ACE inhibitor/angiotensin receptor blocker. The use of ACE inhibitors/angiotensin receptor blockers increased in the early 2000s among adults with CKD but plateaued subsequently.<sup>57</sup>
- Among Medicare beneficiaries with CKD, in 2019, 54.4% of patients with CKD were on  $\beta$ -blockers and 64.3% were on lipid-powering 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>59</sup>
- A secondary analysis of the ASPREE clinical trial comparing 100 mg enteric-coated aspirin daily with matching placebo did not demonstrate

cardiovascular benefit but showed increased risk of bleeding in those with CKD.<sup>60</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>61</sup>
- In the Valkyrie study, among patients on hemodialysis with AF ( $n=132$ ), a reduced dose of rivaroxaban significantly decreased the composite outcome of fatal and nonfatal cardiovascular events (HR, 0.41 [95% CI, 0.25–0.68]).<sup>62</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>63</sup>
- Among patients who underwent TAVR in the PARTNER trial, CKD stage either improved or was unchanged after the procedure.<sup>64</sup>
- In intermediate-risk patients with aortic stenosis and CKD, SAPIEN 3 TAVR and SAVR were associated with similar risk of reaching the composite primary outcome of death, stroke, rehospitalization, and new hemodialysis after a 5-year follow-up.<sup>65</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>66</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>67</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>68</sup>
- In a pooled analysis of data from the ARIC, MESA, and CHS studies, healthy lifestyle behaviors (no smoking, moderate to vigorous PA, no alcohol

intake, adherence to healthy diet using diet score, and BMI <30 kg/m<sup>2</sup>) were associated with lower all-cause mortality, major coronary events, ischemic stroke, and HF.<sup>69</sup>

- SGLT-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>70</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).
- In an RCT of 7437 individuals with stage 3/4 CKD and type 2 diabetes, a novel mineralocorticoid receptor antagonist (finnerenone) reduced the incidence of composite outcome of death resulting from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for HF (HR, 0.87 [95% CI, 0.76–0.98]).<sup>71</sup>
- In a secondary analysis of the FIDELIO-DKD trial enrolling patients with CKD and type 2 diabetes, finnerenone use was associated with lower incidence of new-onset AF (HR, 0.71 [95% CI, 0.53–0.94]).<sup>72</sup>

## Cardiovascular Hospitalization and Mortality Attributable to CVD Among People With CKD

### (See Chart 12-12)

- CVD is a leading cause of death for people with CKD. Mortality risk depends not only on eGFR but also on the 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>73</sup>
- Data from the prospective CRIC study 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 12-12).<sup>74</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>75</sup>
  - Cystatin C-based eGFR was a stronger predictor of HF than creatinine-based eGFR among patients with CKD in the CRIC study.<sup>76</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>77</sup>

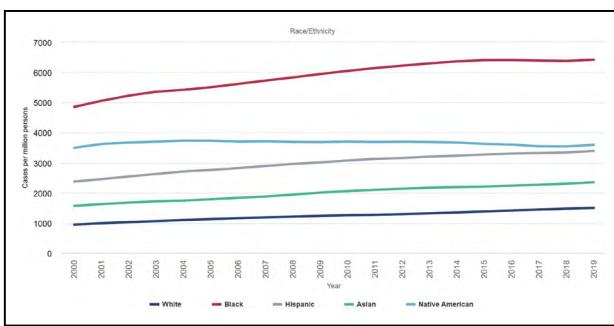
### Footnote

A portion of the data reported here have been supplied by the USRDS.<sup>10</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
G1: Normal or high (eGFR ≥90 mL/min/1.73m <sup>2</sup> )	53.5	4.1	0.58	58.3
G2: Mildly decreased (eGFR 60–89 mL/min/1.73m <sup>2</sup> )	31.5	2.9	0.43	34.8
G3a: Mildly to moderately decreased (eGFR 45–59 mL/min/1.73m <sup>2</sup> )	3.9	0.84	0.27	5.0
G3b: Moderately to severely decreased (eGFR 30–44 mL/min/1.73m <sup>2</sup> )	0.88	0.40	0.17	1.5
G4: Severely decreased (eGFR 15–29 mL/min/1.73m <sup>2</sup> )	0.11	0.09	0.17	0.37
G5: Kidney failure (eGFR <15 mL/min/1.73m <sup>2</sup> )	0.01	0.01	0.09	0.11
Total	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 2021 United States Renal Data System Annual Data Report, volume 1, Table 1.1,<sup>10</sup> using NHANES 2015 to 2018.<sup>78</sup>

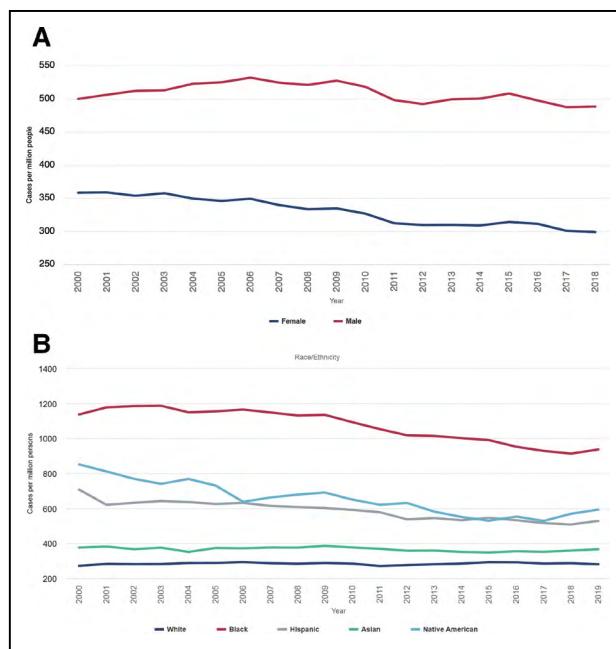


**Chart 12-2. Temporal trends in ESRD prevalence by race and ethnicity, United States, 2000 to 2019.**

Prevalence estimates are presented as cases per million people and are adjusted for age, sex, race, and ethnicity.

ESRD indicates end-stage renal disease.

Source: Reprinted from 2021 United States Renal Data System Annual Data Report, volume 2, Figure 1.8.<sup>10</sup>

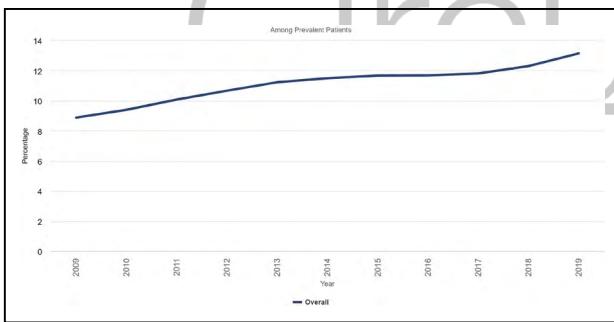


**Chart 12-4. Temporal trends in ESRD incidence, United States, 2000 to 2019.**

**A.** Incidence by sex. **B.** Incidence by race and ethnicity. Incidence estimates are presented as cases per million people and are adjusted for age, sex, race, and ethnicity.

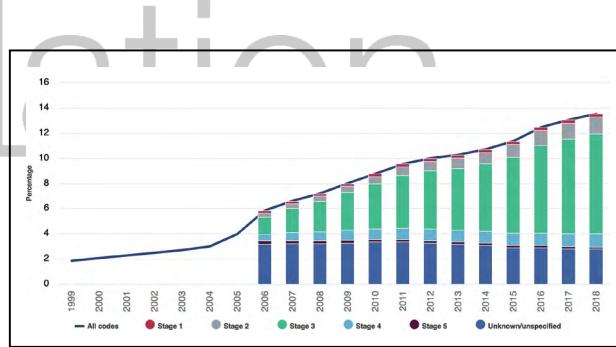
ESRD indicates end-stage renal disease.

Source: Reprinted from 2021 United States Renal Data System Annual Data Report, volume 2, Figure 1.4.<sup>10</sup> American Heart Association.



**Chart 12-3. Use of home dialysis among prevalent cases, 2009 to 2019.**

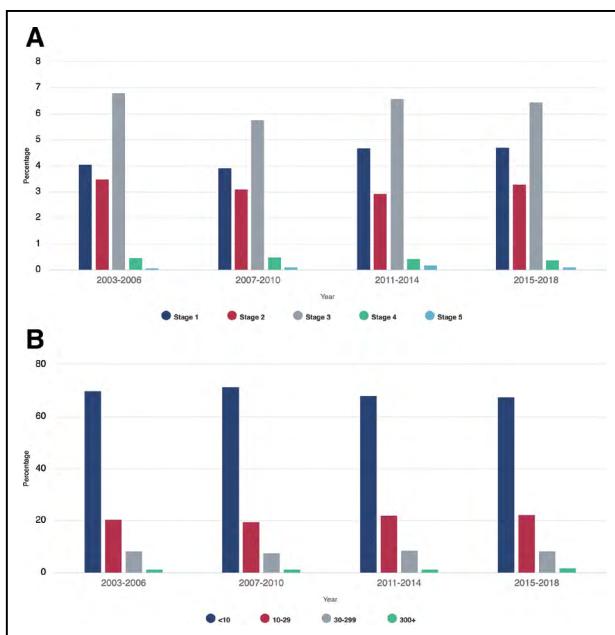
Source: Reprinted from 2021 United States Renal Data System Annual Data Report, volume 2, Figure 2.1a.<sup>10</sup>



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

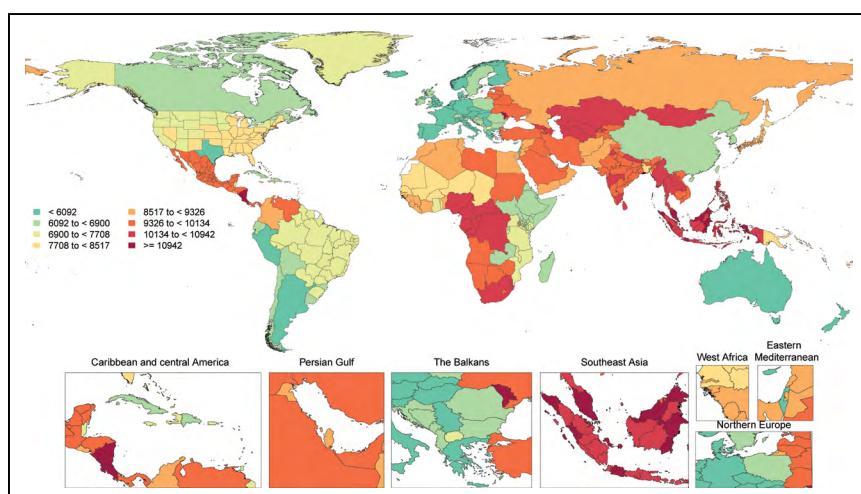
CKD indicates chronic kidney disease.

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 ration; 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>78</sup> data 2003 to 2006, 2007 to 2010, 2011 to 2014, and 2015 to 2018.<sup>00</sup>

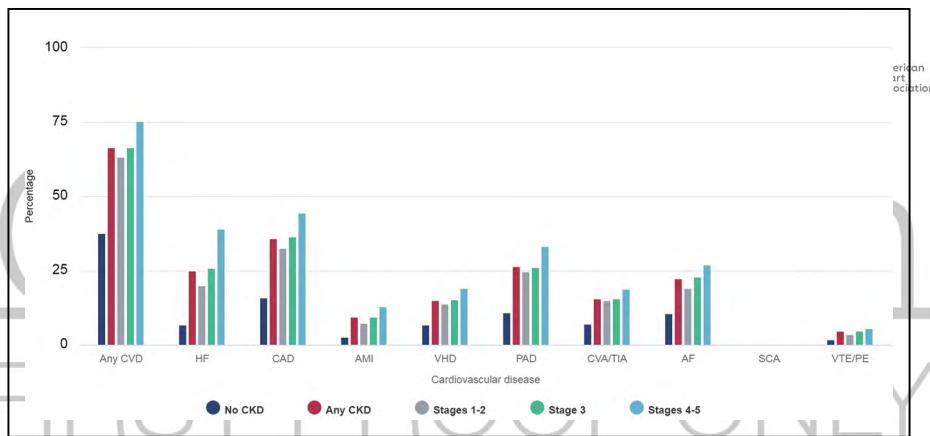
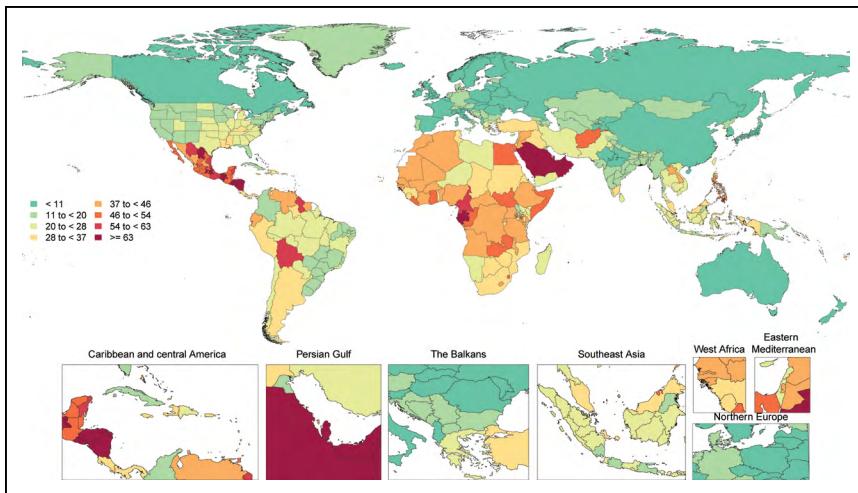


**Chart 12-7. Age-standardized global prevalence rates for CKD per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

CKD indicates chronic kidney disease; and GBD, Global Burden of Disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>40</sup>

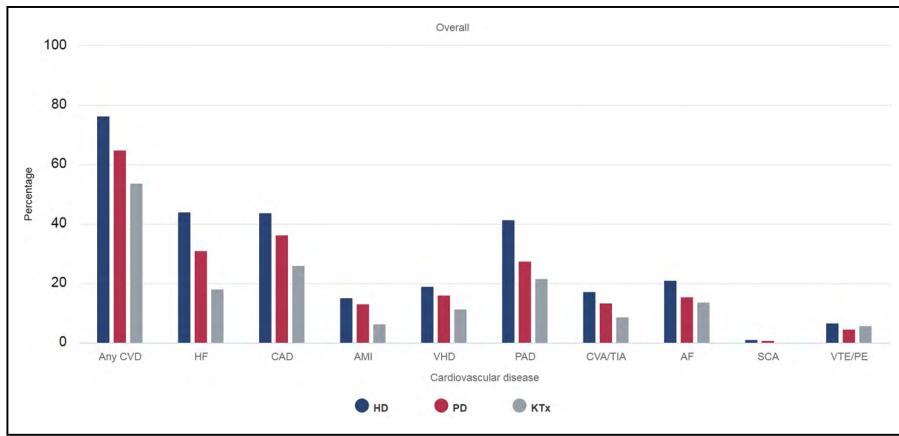


**Chart 12-9. Adjusted prevalence of common CVDs in Medicare beneficiaries ≥66 years of age, by CKD status and stage, United States, 2018.**

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 artery disease; PE, pulmonary embolism; SCA, sudden cardiac arrest; TIA, transient ischemic attack; VHD, valvular heart disease; and VTE, venous thromboembolism.

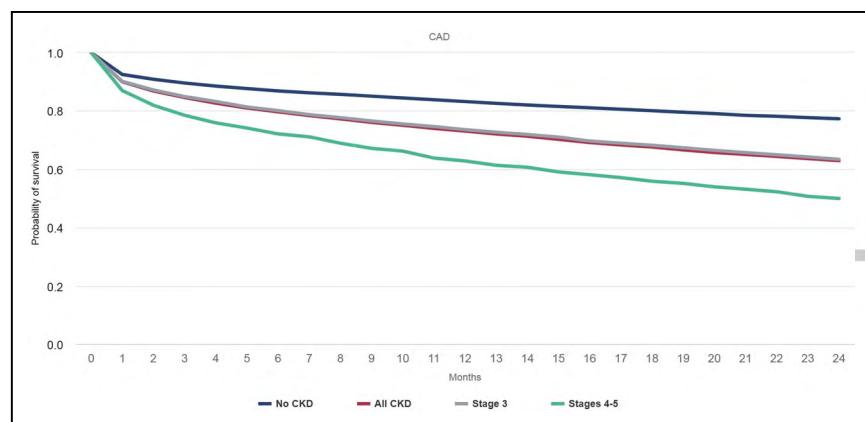
Source: Reprinted from 2020 United States Renal Data System Annual Data Report, volume 1, Figure 4.2.<sup>1</sup>



**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 artery disease; PD, peritoneal dialysis; PE, pulmonary embolism; SCA, sudden cardiac arrest; TIA, transient ischemic attack; VHD, valvular heart disease; and VTE, venous thromboembolism.

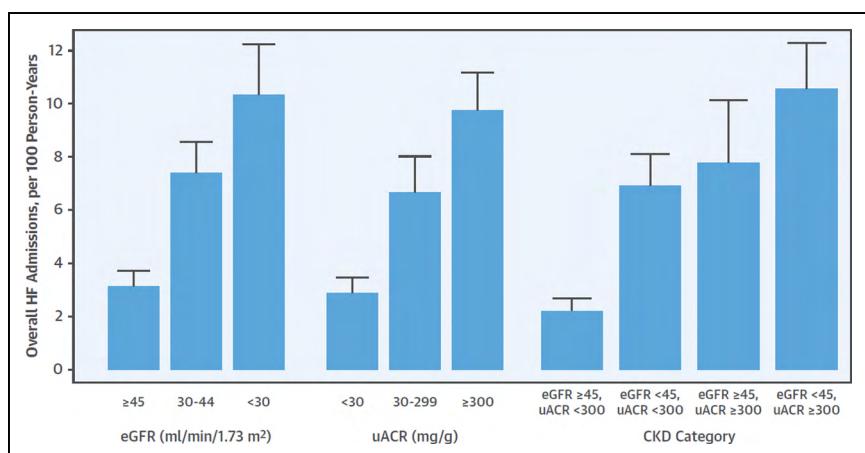
Source: Reprinted from 2020 United States Renal Data System Annual Data Report, volume 2, Figure 8.1.<sup>1</sup>



**Chart 12-11. Survival probability in older adults after hospital admission for CAD, by CKD status and stage, United States, 2017 to 2019.**

Older adults: age ≥66 years.  
CAD indicates coronary artery disease; and CKD indicates chronic kidney disease.

Source: Reprinted from 2021 United States Renal Data System Annual Data Report, volume 2, Figure 3.7.<sup>10</sup>



**Chart 12-12. 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>74</sup> Central Illustration, with permission from the American College of Cardiology Foundation. Copyright © 2019 American College of Cardiology Foundation.

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# Circulation

## 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. Sleep health is a construct that includes various parameters related to regularity, satisfaction, alertness, timing, efficiency, and duration of sleep.<sup>1</sup> Sleep quality is frequently assessed subjectively with the Pittsburgh Sleep Quality Index, for which a score of >5 is considered poor sleep quality.<sup>1,2</sup> Good sleep quality is also characterized by length of time taken to fall asleep (<20 minutes) and percent of time in bed spent asleep (sleep efficiency; at least 85%).

The American Academy of Sleep Medicine and the Sleep Research Society recommend that adults obtain ≥7 hours of sleep per night to promote optimal health.<sup>3</sup> 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 risks. These societies have also 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>4</sup>

OSA and insomnia are the 2 most frequently encountered sleep disorders. OSA is categorized by the frequency of complete and incomplete occlusion of airways during sleep (apneas and hypopneas, respectively) that result in reduced oxygen saturation and arousals or awakenings at night. An AHI is calculated as the number of breathing interruptions per hour of sleep. OSA is characterized as mild (AHI 5–<15 events per hour), moderate (AHI 15–30 events per hour), and severe (AHI >30 events per hour). Insomnia is a disorder characterized by 3 symptoms assessed by questionnaire: difficulty initiating sleep, difficulty maintaining sleep, and early morning awakening. Patients with insomnia are dissat-

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

fied with their sleep, and difficulties occur despite having adequate opportunity for sleep. Acute insomnia may occur over a short period of time and resolve on its own. Chronic insomnia is the persistence of insomnia symptoms that occur at least 3 times per week and last for ≥3 months. Insomnia may or may not be accompanied by short sleep duration. Patients with insomnia feel unrefreshed on awakening.

### Prevalence

(See Charts 13-1 through 13-3)

- Differences in sleep duration across sex and age groups were noted in a meta-analysis assembling 34 population studies with >200000 adults in the Netherlands.<sup>5</sup> Sex differences were observed from adulthood, with females reporting longer sleep duration ( $b=0.14$  h [95% CI, 0.13–0.21]) but lower sleep efficiency ( $b=-0.02$ % [95% CI, -0.03 to -0.02]) than males.
- Analysis of BRFSS 2020 data indicates that the proportion of adults reporting insufficient sleep (<7 hours) was 32.8% (females, 32.2%; males, 33.4%). Prevalence of reporting insufficient sleep was lowest among older adults (>65 years of age) with 27.3% of females and 24.7% of males in this older group reporting <7 hours of sleep per night (Chart 13-1).<sup>6</sup>
- The prevalence of insufficient sleep differs by disability status. In BRFSS 2016 data, 43.8% of adults with at least 1 disability reported insufficient sleep (<7 hours) compared with 31.6% of adults with no disability. Having an increasing number of disabilities was associated with a higher likelihood of reporting insufficient sleep compared with having no disability in the fully adjusted model: adjusted PR, 1.20 (95% CI, 1.17–1.23) for 1 type; 1.34 (95% CI, 1.30–1.38) for 2 types; 1.41 (95% CI, 1.35–1.47) for 3 types; and 1.55 (95% CI, 1.49–1.62) for ≥4 types. The functional disability types included serious difficulty in hearing, vision, cognition, or mobility or any difficulty in self-care and independent living.<sup>7</sup>
- The NHIS 2020 asked respondents, “During the past 30 days, how often did you wake up feeling well rested?” Results showed that 43.7% responded never or some of the days, with females reporting this more frequently than males (46.9% versus 40.4%; unpublished tabulation using NHIS<sup>6</sup>; Chart 13-2).
- In adulthood, insomnia symptoms were least frequent in adults 26 to 40 years of age and most frequent in adults >65 years of age. The prevalence of insomnia symptoms was 1.5 to 2.9 times more frequent in the United States across all adults >25 years of age compared with those in the Netherlands. Females had higher odds of reporting

difficulty initiating sleep (OR, 2.26 [95% CI, 2.16–2.36]), difficulty maintaining sleep (OR, 2.05 [95% CI, 1.91–2.19]), and early morning awakening (OR, 1.49 [95% CI, 1.37–1.62]) than males after adjustment for demographics.<sup>5</sup>

- The NHIS 2020 asked respondents, “During the past 30 days, how often did you have trouble falling asleep?” and “During the past 30 days, how often did you have trouble staying asleep?” Results showed that 32.1% responded never, 43.6% responded some of the days, and 24.3% responded most or all days to either one of those questions. Females more often reported having any sleep problem on most or all days than males (27.8% versus 20.6%; unpublished tabulation using NHIS<sup>6</sup>; Chart 13-3).
- A systematic review estimated the prevalence of OSA in cerebrovascular disease in 3242 patients with cerebral infarction, TIA, ischemic stroke, or hemorrhagic stroke. Researchers 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>8</sup>

### **Children/Adolescents**

- According to parental report in the 2016 to 2018 National Survey of Children’s Health, 34.9% of children 4 months to 17 years of age slept less than recommended for their age. Prevalence of short sleep duration was 40.3% (95% CI, 35.9%–44.7%) in infants 4 to 11 months of age, 33.3% (95% CI, 31.2%–35.4%) for children 1 to 2 years of age, 34.8% (95% CI, 33.1%–36.7%) for children 3 to 5 years of age, 37.4% (95% CI%, 36.3–38.6%) for children 6 to 12 years of age, and 31.2% (95% CI, 30.1%–32.4%) for adolescents 13 to 17 years of age.<sup>9</sup>
- In a meta-analysis of population studies in the Netherlands, insomnia symptoms were higher from childhood into adolescence: 4% of children 3 to 5 years of age reported difficulty initiating sleep and 6% reported difficulty maintaining sleep compared with 13% and 9%, respectively, for children 6 to 13 years of age. Sex differences in insomnia symptoms become evident at puberty and remain throughout adulthood.<sup>5</sup>

### **Adults: Young, Middle-Aged, and Old**

- Older adults are more likely to report adequate sleep than younger adults. 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%) for adults 45 to 64

years of age, and 73.7% (95% CI, 73.2%–74.2%) for adults  $\geq 65$  years of age.<sup>10</sup>

### **Risk Factors**

- Predictors of short sleep duration in adults  $\geq 50$  years of age surveyed in NHANES 2005 to 2008 included smoking (OR, 0.63 [95% CI, 0.51–0.79] for previous smoking compared with current smoking; OR, 0.68 [95% CI, 0.53–0.85] for never smoking compared with current smoking), physical inactivity (OR, 1.48 [95% CI, 1.15–1.86] for no PA versus PA), diet (OR, 0.93 [95% CI, 0.91–0.95] for higher nutrient adequacy, calculated as the sum of meeting versus not meeting nutrient requirements according to age/sex-specific recommended intakes for 22 nutrient components), 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>11</sup>
- According to NHANES data from 2005 to 2008, characteristics associated with trouble sleeping in adults  $\geq 50$  years of age include not being married (OR, 1.16 [95% CI, 1.01–1.36] versus being married), alcohol consumption (OR, 0.39 [95% CI, 0.36–0.43] compared with no 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 health), and depressive symptoms (OR, 4.71 [95% CI, 3.60–6.17] for  $\geq 10$  versus <10 on the Patient Health Questionnaire).<sup>11</sup>
- Among a sample of 852 Black adults, predictors of moderate to severe OSA (AHI  $\geq 15$  events per hour) included 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>12</sup>
- Data from the Taiwan National Health Interview Survey indicate that the following characteristics are associated with a higher 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, 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>13</sup> With the use of the Charlson Comorbidity Index, which predicts 10-year mortality

for a patient on the basis of comorbid conditions, a greater burden of comorbidities was associated with a higher risk of incident insomnia (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  $\geq 3$ ). The following were 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.

- NHANES data from 2005 to 2014 in 22 471 adults showed that the prevalence of sleep disorders increased from 7.5% in 2005 to 2006 to 10.41% in 2013 to 2014 ( $F=5.4848$ ,  $P<0.001$ ). Having a higher HEI score, indicative of a higher diet quality, was associated with reduced risk of reporting a sleep disorder (optimal HEI score versus inadequate: OR, 0.913 [95% CI, 0.912–0.915]) in the fully adjusted model. Greens and beans, added sugars, saturated fats, total vegetables, and total protein foods were the top 5 most important components, accounting for 85% of the weights for sleep disorders.<sup>14</sup>
- In MESA, participants with a high alternative Mediterranean diet score were less likely to report insomnia symptoms (OR, 0.81 [95% CI, 0.62–0.98]) after adjustment for sociodemographic variables.<sup>15</sup>

## Social Determinants

### Race and Ethnicity and Sleep

(See Chart 13-4)

- In 2014, the prevalence of healthy sleep duration was lower among Native Hawaiian/Pacific Islander people (52.5%), NH Black people (50.4%), and NH multiracial people (49.6%) compared with White people (62.6%). There was no difference between White people and Hispanic people (61.1%) and Asian people (64.2%). All racial and ethnic groups other than Asian people were more likely to report short sleep than White people (RR for Native Hawaiian/Pacific Islander people, 1.61 [95% CI, 1.40–1.85]; Black people, 1.64 [95% CI, 1.48–1.82]; Hispanic people, 1.11 [95% CI, 1.00–1.23]; and NH multiracial people, 1.73 [95% CI, 1.18–2.55]). Long sleep was more likely in Black people than White people (RR reduction, 1.21 [95% CI, 1.02–1.43]) and less likely in Asian people than White people (RR reduction, 0.72 [95% CI, 0.55–0.94]).<sup>16</sup>
- In BRFSS 2020, NH Black adults had the highest percentage of respondents reporting sleeping  $<7$  h/night (43.5%), whereas NH Asian (30.5%) and NH White (30.7%) adults had the lowest percentage of respondents reporting sleeping  $<7$  hours (Chart 13-4).
- In the NHIS 2020, Asian adults reported the lowest prevalence of never being well rested or being well

rested some of the time (36.1% versus 43.9%–47.0% for other racial and ethnic groups). White and NH American Indian/Alaska Native adults reported the lowest prevalence of never having difficulty falling asleep or maintaining sleep (27.8% and 30.2%, respectively, versus 37.4%–32.3% for other racial and ethnic groups).

- In a sample of Black adults from the JHS, average sleep duration was  $6.7\pm 1.1$  hours, 61.5% had short sleep duration, and the prevalence of moderate to severe OSA (AHI  $\geq 15$  events per hour) was 23.6%.<sup>12</sup>

### Other Social Determinants of Sleep

- In addition to race and ethnicity, social characteristics associated with short sleep duration in adults  $\geq 50$  years of age include education (OR, 0.68 [95% CI, 0.56–0.84] for greater than high school versus less than high school), not being married (OR, 1.43 [95% CI, 1.25–1.67] versus married), and poverty/income ratio (OR, 0.65 [95% CI, 0.54–0.79] for poverty/income ratio  $\geq 2$  versus  $<1$ ).<sup>11</sup>
- In the combined BRFSS 2014 and 2016 surveys, bisexual males had higher rates of very short ( $\leq 4$  h/night; 6.5% versus 4.0%) and long ( $\geq 9$  h/night; 10.4% versus 6.5%) sleep durations compared with heterosexual males. Lesbian and bisexual females had higher rates of very short (6.8% and 7.6%, respectively) and short (5–6 h/night; 36.5% and 37.1%, respectively) sleep durations compared with heterosexual females (very short sleep, 3.7%; short sleep, 30.5%). Among males, gay Black people (OR, 6.07 [95% CI, 2.34–15.73]) and gay Latino people (OR, 4.61 [95% CI, 1.54–13.76]) had higher adjusted odds of very short sleep compared with gay White people. Asian and Pacific Islander gay people had lower odds of very short (OR, 0.14 [95% CI, 0.02–0.93]) and long (OR, 0.16 [95% CI, 0.03–0.74]) sleep but higher odds of short sleep (OR, 3.04 [95% CI, 1.25–7.41]) compared with gay White people.<sup>17</sup>
- Among Native Hawaiian and Pacific Islander adults 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 with feeling well rested.<sup>18</sup>
- In a cross-sectional survey of 3284 adults, sleep health was better with successively higher age groups. In all age groups, higher frequency of fast food consumption, daily minutes of TV watching, social media use, internet use, and lower regularity of lifestyle behaviors were associated with lower sleep health. In young adults 18 to 34 years of age, number of pets and daily reading minutes were also

inversely related to sleep health, whereas in middle-aged adults 35 to 54 years of age, higher daily minutes of reading and lower moderate to vigorous PA were associated with poorer sleep health. In older adults  $\geq 55$  years of age, less time in moderate to vigorous PA and higher percent of sedentary time were associated with poorer sleep health.<sup>19</sup>

## Family History and Genetics

- Heritability estimates for sleep disorders, including OSA, are  $\approx 40\%$ .<sup>20</sup>
- A UK Biobank study ( $n=85\,670$ ) using accelerometer-derived measures of sleep and rest-activity patterns identified 47 loci across 8 sleep traits encompassing sleep duration, quality, and timing.<sup>21</sup> Ten novel variants for sleep duration and 26 novel variants for sleep quality that were not detected in much larger studies of self-reported sleep traits were identified, including a missense variant (p.Tyr727Cys) in *PDE11A*. The cumulative variance explained by these loci ranged from 0.04% for sleep midpoint timing to 0.8% for number of nocturnal sleep episodes. These cumulative variance-explained estimates are considerably smaller than the expected proportion of phenotypic variance explained by commonly occurring SNPs, which ranged from 2.8% (variation in sleep duration) to 22.3% (number of nocturnal sleep episodes).
- Several variants have been found to be associated with self-reported 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>22–24</sup>
- A GWAS of self-reported daytime napping in the UK Biobank ( $N=452\,633$ ) and the 23andMe research cohort ( $N=541\,333$ ) identified 61 replicated loci, including missense variants in established drug targets for sleep disorders (*HCRT1*, *HCRT2*). Many of the loci colocalized with loci for other sleep phenotypes and cardiometabolic outcomes. For example, mendelian randomization suggested a causal link between more frequent daytime napping and higher BP and WC.<sup>25</sup>
- 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, gene-sleep interactions were identified for some lipid loci, including *LPL* and *PCSK9*, and 4.25% of the variance in triglycerides could be explained from gene–short sleep interactions.<sup>26</sup>
- Data from 404 044 participants in the UK Biobank were used to derive a GRS for sleep duration. Mendelian randomization analyses showed

increased odds of CVD with genetically predicted short sleep duration  $\leq 6$  hours: PE (OR, 1.30 [95% CI, 1.11–1.53]), arterial hypertension (OR, 1.15 [95% CI, 1.09–1.20]), AF (OR, 1.13 [95% CI, 1.03–1.24]), chronic IHD (OR, 1.15 [95% CI, 1.06–1.25]), CAD (OR, 1.24 [95% CI, 1.12–1.37]), and MI (OR, 1.21 [95% CI, 1.09–1.34]). There was no association with genetically predicted long sleep duration  $\geq 9$  hours.<sup>27</sup>

- Data from the FinnGen study (217 955 individuals) estimated the heritability of OSA at 0.08 (95% CI, 0.06–0.11) and identified 5 loci associated with OSA located near *GAPVD1*, *RMST/NEDD1*, *CXCR4*, *CAMK1D*, and *FTO*. Genetic correlations were found between OSA and BMI ( $r_g=0.72$  [95% CI, 0.62–0.83]), hypertension ( $r_g=0.35$  [95% CI, 0.23–0.48]), type 2 diabetes ( $r_g=0.52$  [95% CI, 0.37–0.66]), CHD ( $r_g=0.38$  [95% CI, 0.17–0.58]), and stroke ( $r_g=0.33$  [95% CI, 0.03–0.63]).<sup>28</sup>

## Awareness, Treatment, and Control

- 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>29</sup>
- A meta-analysis of 7 RCTs with patients with moderate to severe OSA randomized to either CPAP therapy or control for a mean follow-up of 37 months did not reveal any reduction in the risk of major cardiovascular events (RR, 0.74 [95% CI, 0.47–1.17]). All-cause mortality (RR, 0.95 [95% CI, 0.53–1.73]), MI (RR, 0.99 [95% CI, 0.57–1.72]), stroke (RR, 0.95 [95% CI, 0.72–1.24]), cardiovascular mortality (RR, 0.70 [95% CI, 0.27–1.80]), and noncardiovascular mortality (RR, 1.53 [95% CI, 0.61–3.82]) were not influenced by CPAP treatment. However, in sensitivity analyses using prespecified CPAP adherence of  $\geq 4$  h/night for the SAVE trial, CPAP treatment reduced the risk of major cardiovascular events (RR, 0.70 [95% CI, 0.50–0.98]) and stroke (RR, 0.56 [95% CI, 0.37–0.84]).<sup>30</sup>

## Mortality

- A meta-analysis of 43 studies indicated that both short sleep ( $<7$  h/night; RR, 1.13 [95% CI,

1.10–1.17]) and long sleep (>8 h/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. Among adults <65 years of age, both short sleep duration ( $\leq 5$  h/night) and long sleep duration ( $\geq 8$  h/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.<sup>32</sup>
- Data from adults  $\geq 50$  years of age participating in NHANES 2005 to 2008 indicated that long sleep duration ( $>8$  h/night) was associated with an increased risk of all-cause mortality overall (partially aHR, 1.90 [95% CI, 1.38–2.60]) and among males (partially aHR, 1.48 [95% CI, 1.05–2.09]), females (partially aHR, 2.32 [95% CI, 1.48–3.61]), and those  $\geq 65$  years of age (partially aHR, 1.80 [95% CI, 1.30–2.50]) but not among those  $<65$  years of age (partially aHR, 1.92 [95% CI, 0.78–4.69]). Partially adjusted models accounted for demographics (sex, age, race and ethnicity) and SES. Additionally adjusting for other lifestyle behaviors, including smoking, diet, PA, and health factors, abolished these associations. No statistically significant associations were observed between short sleep ( $<7$  h/night) and all-cause mortality.<sup>11</sup>
- A meta-analysis of 137 prospective cohort studies with a total of 5134036 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 a higher risk of all-cause mortality in a dose-response fashion. Only severe OSA was associated with a higher risk of cardiovascular mortality (HR, 2.73 [95% CI, 1.94–3.85]).<sup>34</sup>
- A meta-analysis of 19 cohort studies reported an increased risk of all-cause mortality in those reporting difficulty initiating sleep (HR, 1.13 [95% CI, 1.03–1.23]) that was more pronounced in adults  $<65$  years of age (HR, 1.33 [95% CI, 1.16–1.53]). Difficulty initiating sleep also was associated with an increased risk of cardiovascular mortality (HR, 1.20 [95% CI, 1.01–1.43]). From 13 studies, there was no added risk of all-cause mortality (HR, 1.05 [95% CI, 0.96–1.14]) or cardiovascular mortality (HR, 1.03 [95% CI, 0.82–1.31]) in those reporting difficulty maintaining sleep. From 6 studies, there was no added risk of all-cause mortality (HR, 0.97

[95% CI, 0.91–1.04]) or cardiovascular mortality (HR, 0.93 [95% CI, 0.76–1.13]) in those reporting difficulty maintaining sleep.<sup>35</sup>

## Complications

### Sleep Duration

- A meta-analysis examined sleep duration and total CVD (26 articles), CHD (22 articles), and stroke (16 articles). Relative to sleep of 7 to 8 h/night, every 1-hour reduction in sleep was associated with increased risk of total CVD (RR, 1.06 [95% CI, 1.03–1.08]), CHD (RR, 1.07 [95% CI, 1.03–1.12]), and stroke (RR, 1.05 [95% CI, 1.01–1.09]). Every 1-hour increase in sleep was associated with increased risk of total CVD (RR, 1.12 [95% CI, 1.08–1.16]), CHD (RR, 1.05 [95% CI, 1.00–1.10]), and stroke (RR, 1.18 [95% CI, 1.14–1.21]).<sup>31</sup>
- A study in Spain estimated sleep duration with wrist actigraphy and measured atherosclerotic plaque burden with 3-dimensional vascular ultrasound in 3804 adults between 40 and 54 years of age without a history of CVD or OSA.<sup>36</sup> In fully adjusted models, sleeping <6 h/night was significantly associated with a higher noncoronary plaque burden compared with sleeping 7 to 8 h/night (OR, 1.27 [95% CI, 1.06–1.52]), whereas those sleeping 6 to 7 h/night (OR, 1.10 [95% CI, 0.94–1.30]) or >8 h/night (OR, 1.31 [95% CI, 0.92–1.85]) did not differ from those sleeping 7 to 8 h/night.
- A cross-sectional study in Greece (N=1752) reported associations between self-reported sleep duration and carotid IMT from a carotid duplex ultrasonography examination. Compared with adequate sleep duration (7–8 hours), 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]) were associated with larger mean carotid IMT. There was no difference between those reporting sleeping 7 to 8 hours and those reporting sleeping 6 to <7 hours ( $b=0.012$  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 adequate 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.<sup>37</sup>
- 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 adequate sleepers (7–9 h/d). 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.<sup>38</sup>
- 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. They identified 4 sleep patterns: adequate stable (mean range, 7.4–7.5 hours), adequate decreasing (mean decrease, 7.0 to 5.5 hours), short increasing (mean increase, 4.9 to 6.9 hours), and short stable (mean range, 4.2–4.9 hours). Compared with the adequate stable group, increased risk of incident cardiovascular events was observed for the short increasing group (HR, 1.22 [95% CI, 1.04–1.43]) and the short stable group (HR, 1.47 [95% CI, 1.05–2.05]) but not the adequate decreasing group (HR, 1.13 [95% CI, 0.97–1.32]). Risk of all-cause mortality was higher for the adequate decreasing group (HR, 1.34 [95% CI, 1.15–1.57]) and the short stable group (HR, 1.50 [95% CI, 1.07–2.10]) but not the short increasing group (HR, 0.95 [95% CI, 0.80–1.13]).<sup>39</sup>
  - The association between daytime napping and stroke was evaluated in a meta-analysis of 7 prospective studies. After adjustment for total sleep duration, the pooled RR of stroke was 1.38 (95% CI, 1.19–1.60).<sup>40</sup>
  - In the Rush Memory and Aging Project, daytime napping in older adults (81.4±7.5 years of age) was associated with higher risk of HF (per 1-SD increase in square root-transformed nap duration: HR, 1.38 [95% CI, 1.12–1.69]; frequency >1.7 times per day: HR, 2.20 [95% CI, 1.41–3.46]).<sup>41</sup>

### **Restful Sleep and Sleepiness**

- Medical records from patients in Japan (N=1 980 476) were examined to determine whether restful sleep was associated with incident CVD over an average of 1122 days (≈3 years). Restful sleep was assessed with the question, “Do you have a good rest with sleep?” Restful sleep, defined by answering “yes,” 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]) compared with nonrestful sleep (answering “no”).<sup>42</sup>
- In the UK Biobank, a 1-point increase in healthy sleep score, including chronotype (morning), sleep duration (7–8 h/d), insomnia (never/rarely or sometimes), snoring (no), and excessive daytime sleepiness (never/rarely or sometimes), was associated with reduced incidence of HF (HR, 0.85 [95% CI, 0.83–0.87]).<sup>43</sup>
- A meta-analysis combined data from 17 prospective cohort studies with a total of 153 909 participants

to examine excessive daytime sleepiness and risk of CVD events. Mean follow-up time was 5.4 years (range, 2–13.8 years). Excessive daytime sleepiness was associated with a higher 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]) compared with no excessive daytime sleepiness.<sup>44</sup>

- Data from the MIDUS study examined the association of a composite sleep health measure (sleep regularity, satisfaction, alertness, timing, efficiency, and duration) with risk of HD (yes/no to question on diagnosis of HD). Sleep was assessed by questionnaire and actigraphy. Each 1-unit increase in the self-reported sleep health composite was associated with 54% higher risk of HD ( $b=0.43$  [95% CI, 0.26–0.60]); the actigraphy sleep health composite was associated with 141% higher risk ( $b=0.88$  [95% CI, 0.44–1.32]).<sup>45</sup>

### **Obstructive Sleep Apnea**

- In the Jackson Heart Sleep Study, the associations between OSA and BP control or resistant hypertension were examined among 664 Black adults with hypertension (average, 65 years of age). 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>46</sup>
- A prospective study examined 744 adults without hypertension or severe OSA at baseline and found that mild to moderate OSA was significantly associated with incident hypertension over an average of 9.2 years of follow-up (aHR, 2.94 [95% CI, 1.96–4.41]). 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>47</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 h/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>48</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>49</sup>
  - In a meta-analysis of 3350 patients with ACS (7 studies) or AMI (3 studies) and OSA, OSA was associated with an increased risk of major cardiovascular and cerebrovascular events (RR, 2.18 [95% CI, 1.45–3.26]). OSA was associated with an increased risk of revascularization in 8 studies (3036 patients; RR, 1.93 [95% CI, 1.23–3.02]) and increased the risk of hospitalization for HF (RR, 2.06 [95% CI, 1.20–3.54]). Recurrent MI (RR, 1.44 [95% CI, 0.83–2.51]), all-cause death (RR, 1.22 [95% CI, 0.58–2.54]), and stroke (RR, 1.37 [95% CI, 0.53–3.52]) were not different between patients with and those without OSA.<sup>50</sup>
  - In a cohort of 297 243 veterans with a diagnosed sleep disorder between 2006 and 2012, 6002 were diagnosed with central sleep apnea. Prevalences of hypertension (72.4 % versus 60.8%), HF (23.6% versus 8.3%), IHD (33.4% versus 18.9%), cerebrovascular disease (9.2% versus 3.9%), COPD (22.0% versus 15.2%), diabetes (37.7% versus 29.0%), pulmonary hypertension (4.4% versus 1.3%), arrhythmia (19.2% versus 7.3%), and AF (14.6% versus 4.6%) were higher in patients with central sleep apnea compared with those with other sleep disorders. Patients with central sleep apnea were more likely to have pulmonary hypertension (RR, 2.06 [95% CI, 1.20–3.54]), AF (RR, 2.06 [95% CI, 1.20–3.54]), and HF (RR, 2.06 [95% CI, 1.20–3.54]) than those with other sleep disorders. Central sleep apnea was associated with higher risk of cardiac disease-related hospitalization (IRR, 1.50 [95% CI, 1.16–1.95]).<sup>51</sup>

### Insomnia

- In 14 cohort studies with a mean follow-up of 10.8 years, risk of hypertension was increased in those with insomnia (RR, 1.21 [95% CI, 1.10–1.33]) with high heterogeneity.<sup>52</sup>
- A meta-analysis of 7 prospective studies with sample sizes of 2960 to 487 200 and a mean follow-up of 10.6 years examined the association of insomnia symptoms and CVD. Patients with nonrestful sleep, difficulty initiating sleep, and difficulty maintaining sleep had 16% (HR, 1.16 [95% CI, 1.07–1.24]), 22% (HR, 1.22 [95% CI, 1.06–1.40]), and 14% (HR, 1.14 [95% CI, 1.02–1.27]) higher risk of CVD, respectively, compared with those without. Having any insomnia complaint was associated with 13% higher risk (HR, 1.13 [95% CI, 1.08–1.19]).<sup>53</sup>

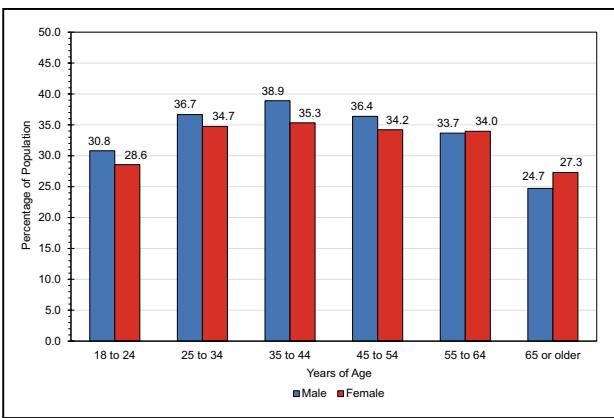
### Costs

- Analysis of direct and indirect costs related to inadequate sleep (defined as reporting difficulty initiating or maintaining sleep or having impaired daytime alertness at least several days per week) in Australia suggested that the approximate cost for a population the size of the US population would be more than \$585 billion for the 2016 to 2017 financial year.<sup>54</sup>



### Global Burden

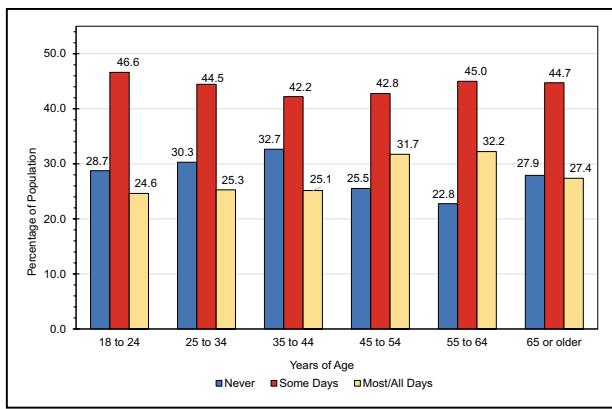
- An analysis of the global prevalence and burden of OSA estimated that 936 million (95% CI, 903–970 million) males and females 30 to 69 years of age have mild to severe OSA and 425 million (95% CI, 399–450 million) have moderate to severe OSA globally. The prevalence was highest in China, followed by the United States, Brazil, and India.<sup>55</sup>



**Chart 13-1. Prevalence of reporting sleep duration <7 h/night in US adults by sex and age, 2020.**

Percentages are adjusted for complex sampling design, including primary sampling units, strata, and sampling weights. The survey question was, "On average, how many hours of sleep do you get in a 24-hour period?"

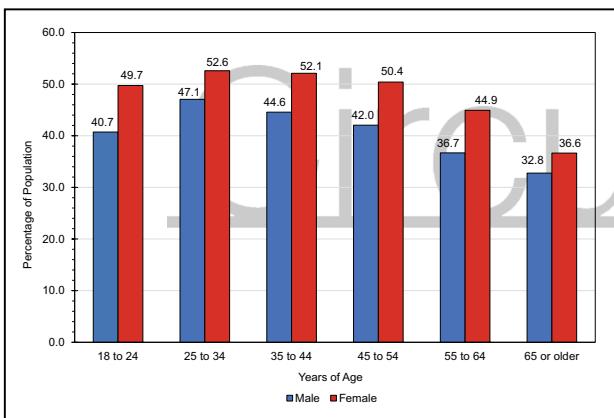
Source: Unpublished tabulation using Behavioral Risk Factor Surveillance Survey.<sup>6</sup>



**Chart 13-3. Prevalence of reporting difficulty falling asleep or maintaining sleep never, some, or most/all days in US adults by age, 2020.**

Percentages are age adjusted for complex sampling design, including primary sampling units, strata, and sampling weights. The survey questions were, "During the past 30 days, how often did you have difficulty falling asleep?" and "During the past 30 days, how often did you have difficulty maintaining sleep?"

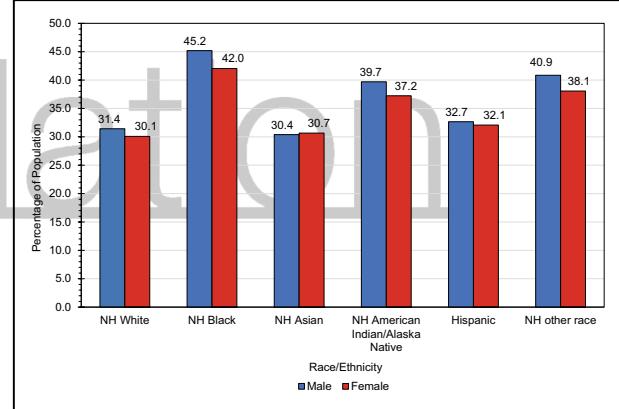
Source: Unpublished tabulation using National Health Interview Survey.<sup>56</sup>



**Chart 13-2. Prevalence of reporting being well rested never or some days by sex and age, 2020.**

Percentages are adjusted for complex sampling design, including primary sampling units, strata, and sampling weights. The survey question was, "During the past 30 days, how often did you wake up feeling well rested?"

Source: Unpublished tabulation using National Health Interview Survey.<sup>56</sup>



**Chart 13-4. Prevalence of reporting sleep duration <7 h/night in US adults by sex and race, 2020.**

Percentages are adjusted for complex sampling design, including primary sampling units, strata, and sampling weights. The 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>6</sup>

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# Circulation

## 14. TOTAL CARDIOVASCULAR DISEASES

**ICD-9 390 to 459; ICD-10 I00 to I99. See Tables 14-1 through 14-3 and Charts 14-1 through 14-16**

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### Prevalence

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

- On the basis of NHANES 2017 to March 2020 data,<sup>1</sup> the prevalence of CVD (comprising CHD, HF, stroke, and hypertension) in adults ≥20 years of age is 48.6% overall (127.9 million in 2020) and increases with age in both males and females. CVD prevalence excluding hypertension (CHD, HF, and stroke only) is 9.9% overall (28.6 million in 2020; Table 14-1). Chart 14-1 presents the prevalence breakdown of CVD by age and sex, with and without hypertension in the CVD definition.
- According to the NHIS<sup>2</sup> 2018:
  - The age-adjusted prevalence of all HD (CHD, angina, or heart attack; excluding hypertension) was 11.2%; the corresponding age-adjusted prevalences of HD among self-described racial and ethnic groups in which only 1 race was reported were 11.5% among NH White, 10.0% among NH Black, 8.2% among Hispanic, 7.7% among Asian, and 14.6% among American Indian or Alaska Native individuals.
  - The age-adjusted prevalences of HD, CHD, hypertension, and stroke in males were 12.6%, 7.4%, 26.1%, and 3.1%, respectively, and in females were 10.1%, 4.1%, 23.5%, and 2.6%, respectively.
  - The age-adjusted prevalences of HD, CHD, hypertension, and stroke among unemployed individuals who had previously worked were as follows: HD, 13.9%; CHD, 7.7%; hypertension, 30.5%; and stroke, 4.7%, respectively. The age-adjusted prevalences of HD, CHD, hypertension, and stroke among currently employed individuals were 9.5%, 4.0%, 21.8%, and 1.6%, respectively.

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

The age-adjusted prevalences of HD, CHD, hypertension, and stroke among individuals who had never worked were 10.2%, 6.7%, 24.6%, and 3.2%, respectively.

- In a cross-sectional study of 56 716 adults ≥40 years of age from northern China, 22.7% had high 10-year risk of CVD according to WHO/International Society of Hypertension risk prediction charts.<sup>3</sup> The age-adjusted prevalences of hypertension, dyslipidemia, obesity, and diabetes among all respondents were 54.3%, 36.5%, 24.8%, and 18.2, respectively.

### Incidence

- In a meta-analysis of 32 studies assessing CVD burden among Asian adults 18 to 92 years of age who were free of CVD at baseline and with >10 years of follow-up, the incidence of fatal CVD was 3.68 (95% CI, 2.84–4.53) events per 1000 person-years.<sup>4</sup> Risk factors for long-term fatal CVD were male sex (1.49, [95% CI, 1.36–1.64]), older age (7.55 [95% CI, 5.59–10.19]), and current smoking (1.68 [95% CI, 1.26–2.24]).

### Lifetime Risk and Cumulative Incidence

- Pooled data from 7 US cohort studies (1960–2015) of Black and White males and females (ARIC, CHS, CARDIA, FHS, FHS Offspring Cohort Study, JHS, and MESA; N=19 630) demonstrated that risk for CVD (MI or stroke) between 55 and 85 years of age ranged from 15.3% to 38.6% in females with fasting glucose <5.0 mmol/L (90 mg/dL) at baseline to 38.6% in females with fasting glucose ≥7.0 mmol/L (126 mg/dL; or taking diabetes medication at baseline).<sup>5</sup> In males, the risk varied between 21.5% in those with fasting glucose of 5.0 to 5.5 mmol/L (90–99 mg/dL) at baseline and 47.7% in those with fasting glucose ≥7.0 mmol/L (or taking diabetes medication at baseline).
- The Cardiovascular Lifetime Risk Pooling Project estimated the long-term risks of CVD among 30 447 participants with a mean age of 55.0 years (SD, 13.9 years) from 7 US cohort studies.<sup>6</sup> After 538 477 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 a 35-year risk of CVD of 38.6% (95% CI, 22.6%–54.7%), but this risk was incalculable for 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 NHANES 2001 to 2016 data collected from 35 416 participants (20 to 79 years of age), BMI increased more in females (from a 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 a 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 188 mg/dL in 2013–2016) than females (from a 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>
- According to data from the COAST study (2000–2012), of 9012 people living with HIV in British Columbia, Canada, and free of 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 compared with 10.01 (95% CI, 7.55–13.27) in 2012.<sup>8</sup> However, incidence rates of hypertension per 1000 person-years increased significantly.

## 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>
- Eating disorders are another risk factor for CVD. 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 (comparison group).

- Among participants of 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>
- Air pollution, as defined by increased ambient exposure to particulate matter (particles with median aerodynamic diameter  $<2.5\text{ }\mu\text{m}$ ), 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>12</sup>
- Among 31 162 adults 35 to 74 years of age in the Henan Rural Cohort Study, each 1- $\mu\text{g}/\text{m}^3$  increase in particulate matter (PM<sub>1</sub> [particles with aerodynamic diameter  $<1\text{ }\mu\text{m}$ ], PM<sub>2.5</sub>, PM<sub>10</sub> [particles with aerodynamic diameter  $<10\text{ }\mu\text{m}$ ], 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 PM<sub>1</sub>, 9.1% (OR, 1.09 [95% CI, 1.08–1.10]) higher 10-year ASCVD risk for PM<sub>2.5</sub>, 4.6% (OR, 1.05 [95% CI, 1.04–1.05]) higher 10-year ASCVD risk for PM<sub>10</sub>, 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>13</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 RR ratio demonstrated a 30% greater risk of all-cause mortality among females and males with diabetes (95% CI, 1.13–1.49). Females with diabetes also had a 58% greater risk of CHD.<sup>14</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>15</sup> However, an increase in potassium intake may be beneficial in lowering BP levels, but excessive potassium supplementation should be avoided.<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 5257 190 person-years of follow-up found that greater adherence to healthy eating patterns was inversely and consistently associated with CVD risk (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]).<sup>17</sup>
- In a systematic review of 19 observational studies aimed at assessing the association between dietary patterns and cardiometabolic risk in adolescents, findings revealed that the highest intake of unhealthy foods was associated with a higher BMI (0.57kg/m<sup>2</sup> [95% CI, 0.51–0.63]) and higher WC (0.57 cm [95% CI, 0.47–0.67]) versus a low intake of unhealthy foods.<sup>18</sup> Children and adolescents with a Western dietary pattern (high intake of beef/lamb/other red meat, wheat, starch fibers, and light colored vegetables) had a significantly higher odds of obesity (OR, 2.04 [95% CI, 1.38–3.02]) compared with youth who followed a healthier eating pattern (milk, yogurt, fruit, vegetables, and less sugar, beef, lamb and other red meat).
  - In a prospective cohort study of 414 588 adults without CVD in the UK Biobank (2006–2010) with follow-up through 2018, perinatal exposure to maternal smoking was associated with higher risk of CVD (aHR, 1.10 [95% CI, 1.05–1.14]), MI (aHR, 1.10 [95% CI, 1.05–1.16]), and stroke (aHR, 1.10 [95% CI, 1.03–1.18]).<sup>19</sup> Furthermore, there were significant interactions between perinatal exposure to maternal smoking and adulthood smoking behaviors on MI and CVD (all  $P < 0.05$ ).
  - Among 116 806 individuals in the UK Biobank who had a mean follow-up of 4.9 years, there were 4245 cases of total CVD, 838 cases of fatal CVD, and 3629 deaths resulting from all causes.<sup>20</sup> Dietary patterns, assessed with a 24-hour online dietary assessment on at least 2 occasions, revealed a positive linear association between diets that were high in chocolate and confectionery, butter, and low-fiber bread and low in fresh fruit and vegetables and total CVD (aHR, 1.40 [95% CI, 1.31–1.50]) and all-cause mortality (aHR, 1.37 [95% CI, 1.27–1.47] in the highest quintile).
  - In a prospective analysis of data of 3612 individuals 17 to 77 years of age from the Framingham Offspring Study who were examined between 1979 and 2014, 533 (15%) were diagnosed with asthma and 897 (25%) developed CVD.<sup>21</sup> Asthma was associated with higher risk of incident CVD (aHR, 1.28 [95% CI, 1.07–1.54]).
  - Among 29 260 adults with type 2 diabetes in the LEAD cohort study (2013 and 2018) with mean follow-up of 4.2 years, there were 3746 incident CVD events.

HbA1c variability, measured by SD, was associated with higher risk of CVD.<sup>22</sup> The aHR for incident CVD was higher across the second (aHR, 1.30 [95% CI, 1.18–1.42]), third (aHR, 1.40 [95% CI, 1.26–1.55]), and fourth (aHR, 1.59 [95% CI, 1.41–1.77]) quartiles of HbA1c SD than the first quartile ( $P_{\text{trend}} < 0.001$ ).

- Among 2 prospective cohorts of US males (HPFS, 1990–2018) and females (Nurses' Health Study, 1990–2018) free of CVD or cancer at baseline,<sup>23</sup> participants who had higher intake of olive oil (>7 g/d or >0.5 tablespoon) had 19% lower risk of CVD mortality (aHR, 0.81 [95% CI, 0.75–0.87]) than those who had lower consumption of olive oil (never or less than once per month).
- In a meta-analysis of 10 studies including 9 cohorts (N=698 707) with 137 969 CVD events, higher adherence to a plant-based diet was associated with lower risk of CVD (aRR, 0.84 [95% CI, 0.79–0.89]) and CHD (aRR, 0.88 [95% CI, 0.81–0.94]) compared with low adherence.<sup>24</sup>

## Social Determinants of Health

- 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 socio-economic factors and CVD risk factors.<sup>25</sup> A 30-percentile-point reduction in neighborhood deprivation was associated with 11% and 19% reduction in total mortality among men and women, respectively, whereas a 30% increase in neighborhood deprivation was associated with an 11% increase in CVD and cancer-related death.
- 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>26</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>27</sup>

## Risk Prediction

- In a meta-analysis of studies assessing the performance of the FRS, ATP III score, and 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>28</sup>

- When added to traditional CVD risk factors (including material deprivation), 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>29</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>30</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) individuals who received care in Northern California between 2006 and 2015, the PCE overestimated ASCVD risk by 20% to 60%.<sup>31</sup>
- SCORE2, a risk prediction algorithm derived from 45 cohorts in 13 European countries (677 684 adults, 30 121 CVD events), was used to estimate the 10-year risk of fatal and nonfatal CVD among adults 40 to 69 years of age who were free of diabetes or CVD, and C indices ranged from 0.67 (95% CI, 0.65–0.68) to 0.81 (95% CI, 0.76–0.86) across the countries.<sup>32</sup> Furthermore, the SCORE2-Older Persons risk prediction algorithm was developed to estimate 5- and 10- year risk of CVD among adults >65 years of age without preexisting ASCVD from the Cohort of Norway (28 503 individuals, 10 089 CVD events) with C indices ranging between 0.63 (95% CI, 0.61–0.65) and 0.67 (95% CI, 0.64–0.69) in 4 geographic risk regions in Europe.<sup>33</sup>
- Among 6701 participants in MESA who were free of ASCVD during a median follow-up of 13.2 years for ASCVD and 12.5 years for ASCVD-CAC, 2 novel LDL-C calculations, LDL<sub>Martin</sub> and LDL<sub>Sampson</sub>, did not underestimate or overestimate ASCVD risk compared with the traditional LDL<sub>Friedewald</sub> equation in primary prevention using AHA/ACC guidelines.<sup>34</sup> However, the LDL<sub>Friedewald</sub> equation underestimated ASCVD risk in adults who were at low risk.
- Higher LTPA promotes cardiovascular wellness. Higher LTPA was associated with lower ASCVD

risk (aHR per 1-SD higher LTPA, 0.91 [95% CI, 0.86–0.96]). The addition of LTPA did not improve the performance of the PCE among 18 824 adults in 3 prospective cohort studies (MESA, ARIC, and CHS).<sup>35</sup> There was no difference in PCE risk discrimination (C statistic, 0.76–0.78) and risk calibration (all  $\chi^2 P>0.10$ ) across 4 LTPA groups (inactive, less than guideline recommended, guideline recommended, and greater than guideline recommended).

A pooled analysis of data from 4 cohort studies,<sup>147 645</sup> individuals from 21 countries in the PURE Study and 40 countries in 3 prospective studies, demonstrated that the association between fish intake and risk of major CVD events varied by CVD status, with a lower risk found among those with established vascular disease but not in general populations (for major CVD,  $P=82.6$ ,  $P=0.02$ ; for death,  $P=90.8$ ,  $P=0.001$ ).<sup>36</sup> Furthermore, among 3 cohorts of patients with vascular disease, risk of major CVD (aHR, 0.84 [95% CI, 0.73–0.96]) was lower among those with intakes of  $\geq 175$  g/wk (or  $\approx 2$  servings/wk) compared with  $\leq 50$  g/mo.

## Borderline Risk Factors/Subclinical/Unrecognized Disease

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- 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>37</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>38</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>39</sup>

## Genetics and Family History

- Genetic contributors to the end points that compose total CVD are described elsewhere (see

- Chapters 8 [High Blood Pressure]), 15 [Stroke (Cerebrovascular Diseases)], 21 [Coronary Heart Disease, Acute Coronary Syndrome, and Angina Pectoris], 22 [Cardiomyopathy and Heart Failure], 25 [Peripheral Artery Disease and Aortic Diseases]).
- Genome-wide data on 47 309 cases and 93 0014 controls identified 12 independent variant associations for HF at 11 genomic loci. These loci are associated with modifiable risk factors such as AF (*PITX2*), BMI (*FTO*), and CAD (*9p21*, *LPA*). At this time, however, there is no conclusive evidence that HF is genetically determined in the majority of cases or that it develops independently of known risk factors such as obesity, hypertension, or AF in the majority of cases.<sup>40</sup>
  - Investigation of data from >450 000 individuals from the UK Biobank found that reduced telomeric length was associated with an increased risk of CVD (HR, 1.08 [95% CI, 1.07–1.09]).<sup>41</sup>
  - The performance of an ASCVD GRS for prediction of ASCVD incidence has been evaluated.<sup>42</sup> With the use of populations with diverse ethnicity and ancestry from the ARIC, MESA, and UK Biobank studies, improved prediction of ASCVD for White, African, and South Asian populations was demonstrated over the PCE when incorporating an ASCVD GRS. Net reclassification improvement was 2.7% (95% CI, 1.1%–4.2%) for self-identified White individuals, 2.5% (95% CI, 0.6%–4.3%) for Black/African American/Black Caribbean/Black African individuals, and 8.7% (95% CI, 3.1–14.4) for individuals of South Asian descent.
  - Among 3259 participants of the CHS, FHS, and WHI with leukocyte telomere collection dates between 1992 and 1998, a participant with a 1-kb 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>43</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 (≥2 times weekly) or walnuts (≥1 time weekly) versus no or almost no consumption of nuts was associated with a total CVD HR of 0.86 (95% CI, 0.81–0.91).<sup>44</sup>
- Among young adults 18 to 30 years of age in the CARDIA study without clinical risk factors, a Healthy Heart Score combined with 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>45</sup>

- According to data from NHANES, REGARDS, and RCTs regarding BP-lowering treatments, it is estimated 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 achieving prior BP goals from the 2003 Seventh Joint National Committee Report and the 2014 Eighth Joint National Committee. However, achieving the 2017 ACC/AHA BP goals could also increase serious adverse events by 3.3 million (UI, 2.2–4.4 million).<sup>46</sup>
- Among 134 480 participants in the Shanghai Men's Health Study (2002–2014) and the Shanghai WHS (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>47</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 ≈230 000 deaths by 2030 and reduce the socioeconomic disparity in CVD mortality by 6%.<sup>48</sup>
- Comparison of 3 healthy eating patterns over a total 52-week period in youth 9 to 18 years of age with BMI >95th percentile, including the AHA, Mediterranean, and plant-based diets, identified significant differences in compliance and CVD risk factors.<sup>49</sup> The plant-based diet was associated with best compliance (96% versus 72% for plant based and 70% for AHA; *P*=0.026). At 52 weeks of follow-up, all 3 healthy eating patterns were associated with improvement in TC, LDL-C, fasting glucose, myeloperoxidase and WC. Median changes in BMI were not significant at 52 weeks.

## Awareness, Treatment, and Control

- According to data from NHANES 2013 to 2016 among 35 416 participants, the prevalence of controlled BP (SBP <130 mm Hg and DBP <80 mm Hg) was 30% in females and 22% in males; the prevalence of controlled diabetes (HbA1c <6.5%) was 30% in females and 20% in males; and the prevalence of TC <240 mg/dL 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>50</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 β-blockers, 0.86 (95% CI, 0.77–0.96) for ACE 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>51</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 modestly from 50.3% in 2007 to 59.9% in 2016; the use of high-intensity statins increased from 25% to 49.2% with an associated slight increase in statin intolerance from 4% in 2007 to 5% in 2016 among patients after stroke or TIA in receipt of high-intensity statin; the out-of-pocket costs for a 30-day supply of statins fell from \$20 to \$2; and the 1-year cumulative risk for a major cardiac adverse event decreased from 8.9% to 6.5%. However, among women and Black, Hispanic, and Asian individuals, statins were less likely to be prescribed or adhered to.<sup>52</sup>

## Mortality

(See Tables 14-2 and 14-3 and Charts 14-2 through 14-13)

**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 but increased again in the later 2010s to 2020.
- CHD (41.2%) was the leading cause of CVD death in the United States in 2020, followed by

stroke (17.3%), other minor CVD causes combined (16.8%), HBP (12.9%), HF (9.2%), and diseases of the arteries (2.6%) (Chart 14-4).

- The age-adjusted death rate attributable to CVD decreased from 235.5 per 100 000 people in 2010 to 224.4 per 100 000 in 2020, which amounts to a 4.7% decrease (unpublished NHLBI tabulation using CDC WONDER<sup>53</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>54</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>55</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.
  - 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 2020 mortality data (unpublished NHLBI tabulation using the NVSS<sup>56</sup>):
  - HD and stroke currently claim more lives each year than cancer and chronic lower respiratory disease combined. In 2020, 207.1 of 100 000 people died of HD and stroke.
  - In 2020, 3 383 729 resident deaths were registered in the United States, which exceeds the 2019 figure by 528 891 deaths. Of all registered deaths, the 10 leading causes accounted for 74.1%. The 10 leading causes of death in 2020 were similar to those in 2019, with the addition of COVID-19 as the No. 3 cause, although 5 causes exchanged ranks: HD (No. 1), cancer (No. 2), unintentional injuries (No. 4), stroke (No. 5), chronic lower respiratory diseases (No. 6), AD (No. 7), diabetes (No. 8), influenza and pneumonia (No. 9), and kidney disease (No. 10). From 2019

to 2020, 6 of the 10 leading causes of death had an increase in age-adjusted death rates. The age-adjusted rate increased 4.1% for HD, 16.8% for unintentional injuries, 4.9% for stroke, 8.7% for AD, 14.8% for diabetes, and 5.7% for influenza and pneumonia. The age-adjusted death rates decreased 1.4% for cancer and 4.7% for chronic lower respiratory disease but did not change appreciably for kidney disease.<sup>57</sup>

- CHD accounted for 382 820 of the total 928 741 CVD deaths in 2020 (unpublished NHLBI tabulation using NVSS<sup>56</sup>).
- The number of CVD deaths for both sexes and by age category is shown in Table 14-2.
- The percentages of total deaths caused by CVD and other leading causes by race and ethnicity are presented in Charts 14-5 through 14-8.
- 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 784 454 in 2010 to 928 741 in 2020 (Chart 14-9). The difference in age-adjusted death rates for HD also narrowed among US racial and ethnic groups between 1999 and 2020. 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 2020, the death rates per 100 000 people for these 2 groups were 228.6 and 90.1, respectively, thus preserving the >2-fold difference in death rates observed in 1999 (unpublished NHLBI tabulation using CDC WONDER<sup>53</sup>).
- The age-adjusted death rates per 100 000 people for CVD, CHD, and stroke differ by US state (Table 14-3) and globally (Charts 14-10 through 14-13).
- Among individuals with additional risk factors associated with increased CVD risk (eg, patients with diabetes and target organ damage; CKD stages 3 to 4; index CVD-related event within 2 years after prior MI or ischemic stroke; and polyvascular disease), risk for MACEs (ie, composite of MI, ischemic stroke, and cardiovascular-related death) persists after initial MI or ischemic stroke despite the use of moderate- or high-intensity statins.<sup>58</sup> Compared with the overall population, risks for incident MI were 2 to 3 times higher among individuals with stated additional risk factors than among individuals without additional stated risk factors. MACE rates are highest in the first 1 to 2 years after the event (MI, ischemic stroke, or cardiovascular-related death).

## 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>59</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>60</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 an RR of 2.25 (95% CI, 1.60–3.17).<sup>61</sup>

## Health Care Use: Hospital Discharges/ Ambulatory Care Visits

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

- Between 2005 and 2016, delays (or nonreceipt) of medical care over the preceding 12 months decreased among individuals <18, 18 to 44, and ≥65 years of age but increased among those 45 to 64 years of age.<sup>54</sup> Among adults 18 to 64 years of age, the percentage who reported delays or failed receipt of medical care because of cost decreased from 11.7% in 2006 to 9.8% in 2016. Those most affected by cost-related delays in care included adults 18 to 64 years of age with family income <100% or at 100% to 199% of the poverty level; these individuals were 3 times as likely as those at ≥400% above the poverty level to experience delays in or failure to receive necessary medical care.
- 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>62</sup>
- From 2009 to 2019, the number of inpatient discharges from short-stay hospitals with CVD as the principal diagnosis decreased from ≈5.5 million to 5.1 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>63</sup>).

- From 1993 to 2019, 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 14-14). However, more recently, hospital discharges have increased.
- In 2018, there were 69 679 000 physician office visits with a primary diagnosis of CVD (unpublished NHLBI tabulation using NAMCS<sup>64</sup>). In 2019, there were 7 545 000 ED visits with a primary diagnosis of CVD (unpublished NHLBI tabulation using HCUP<sup>63</sup>).

## Cost

**(See Chapter 28 [Economic Cost of Cardiovascular Disease] for detailed information.)**

- Direct costs of health care are driven primarily by hospital care (66%), drug/prescription costs (21%), and physician care (12%).<sup>65</sup> The estimated direct and indirect cost of CVD for 2018 to 2019 was \$407.3 billion (MEPS,<sup>66</sup> unpublished NHLBI tabulation).
- Type 2 diabetes accounts for >95% of all cases of diabetes in the United States among individuals >45 years of age.<sup>67</sup> Health care resource use was assessed with data from IBM Watson Health Analytics' MarketScan Commercial and Medicare supplemental databases. Data were collected between January 1, 2014, and September 30, 2018. Cost of CVD-related care among adults with type 2 diabetes was assessed. Costs associated with CVD in the type 2 diabetes population are high. Average all-cause health care cost per patient at baseline is \$38 985 with follow-up costs of \$35 260 per patient for patients with type 2 diabetes experiencing a CVD-related event (MI, TIA, stroke, etc).

## Global Burden

**(See Charts 14-10 through 14-13, 14-15, and 14-16 and Supplementary Material)**

- Death rates for CVD, CHD, stroke, and all CVD in selected countries in 2017 to 2018 are presented in Charts 14-10 through 14-13.
- The GBD 2020 Study produced 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 14-15).
- 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 14-16).
- CVD represents 37% of deaths in individuals <70 years of age that are attributable to noncommunicable diseases.<sup>68</sup>
- In 2019, 27% of the world's deaths were caused by CVD, making it the predominant cause of death globally.<sup>68</sup>
- According to data from the GBD Study, 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>69</sup>
- See Supplementary Material for additional global and regional CVD statistics.

**Table 14-1. CVDs in the United States**

Population group	Total CVD prevalence,* 2017–2020: ≥20 y of age	Prevalence, 2017– 2020: ≥20 y of age†	Mortality, 2020: all ages‡	Hospital discharges, 2019: all ages	Cost, 2018–2019
Both sexes	127 900 000 (48.6%)	28 600 000 (9.9%)	928 741	5 134 000	\$407.3 Billion
Males	65 400 000 (52.4%)	14 800 000 (10.9%)	487 209 (52.5%)§	...	\$253.9 Billion
Females	62 500 000 (44.8%)	13 800 000 (9.2%)	441 532 (47.5%)§	...	\$153.5 Billion
NH White males	51.2%	11.3%	364 143	...	...
NH White females	44.6%	9.2%	333 102	...	...
NH Black males	58.9%	11.3%	66 675	...	...
NH Black females	59.0%	11.1%	61 464	...	...
Hispanic males	51.9%	8.7%	36 966	...	...
Hispanic females	37.3%	8.4%	30 386	...	...
NH Asian males	51.5%	6.9%	14 796	...	...
NH Asian females	38.5%	4.9%	13 524	...	...
NH American Indian/Alaska Native	...	...	5 164	...	...

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>70</sup>

COVID-19 indicates coronavirus disease 2019; CVD, cardiovascular disease; ellipses (...), data not available; NHANES, National Health and Nutrition Examination Survey; 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 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 versus 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 (for underlying cause of CVD): Unpublished NHLBI tabulation using National Vital Statistics System.<sup>56</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 (with a principal diagnosis of CVD): Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project.<sup>63</sup> Cost: Unpublished NHLBI tabulation using Medical Expenditure Panel Survey,<sup>66</sup> average annual 2018 to 2019 (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. CVD and Other Major Causes of Death: All Ages, <85 Years of Age, and ≥85 Years of Age by Sex, 2020**

Cause	ICD code	Total deaths	Deaths, <85 y of age	Deaths, ≥85 y of age
CVD	I00–I99	928 713	580 994	347 719
Males		487 188	352 069	135 119
Females		441 525	228 925	212 600
HD	I00–I09, I11, I13, I20–I51	696 937	442 445	254 492
Males		382 758	278 314	104 444
Females		314 179	164 131	150 048
Cancer	C00–C97	602 347	499 934	102 413
Males		317 730	267 732	49 998
Females		284 617	232 202	52 415
COVID-19	U07.1	350 827	241 298	109 529
Males		192 509	146 020	46 489
Females		158 318	95 278	63 040
Accidents	V01–X59, Y85–Y86	200 932	175 391	25 541
Males		133 184	122 379	10 805
Females		67 748	53 012	14 736

(Continued)

**Table 14-2. Continued**

Cause	ICD code	Total deaths	Deaths, <85 y of age	Deaths, ≥85 y of age
Stroke	I60–I69	160 262	92 485	67 777
Males		69 635	47 619	22 016
Females		90 627	44 866	45 761
CLRD	J40–J47	152 653	111 863	40 790
Males		72 941	56 240	16 701
Females		79 712	55 623	24 089
AD	G30	134 242	48 529	85 713
Males		41 273	18 264	23 009
Females		92 969	30 265	62 704
All other CVD	Residual	71 514	46 064	25 450
Males		34 795	26 136	8 659
Females		36 719	19 928	16 791

Deaths with age not stated are not included in the totals. Accidents includes ICD-10 codes V01 to X59, Y85, and Y86; AD, G30; CLRD, J40 to J47; cancer, C00 to C97; other CVD, I10, I12, I15, and I70 to I99; stroke, I60 to I69; and HD, I00 to I09, I11, I13, and I20 to I51. AD indicates Alzheimer disease; CLRD, chronic lower respiratory disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; HD, heart disease; ICD, International Classification of Diseases; and ICD-10, International Classification of Diseases, 10th Revision.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System data.<sup>56</sup>

**Table 14-3. Age-Adjusted Death Rates per 100 000 People for CVD, CHD, and Stroke by US State, 2018 to 2020**

State	CVD			CHD			Stroke		
	Rank	Death rate	% Change, 2008–2010 to 2018–2020	Rank	Death rate	% Change, 2008–2010 to 2018–2020	Rank	Death rate	% Change, 2008–2010 to 2018–2020
Alabama	51	299.0	-5.0	21	82.7	-26.5	51	52.5	-9.3
Alaska	7	184.8	-11.6	8	68.0	-24.8	26	36.2	-17.5
Arizona	9	187.4	-8.1	24	83.1	-27.6	10	31.3	-9.2
Arkansas	49	282.4	-5.7	52	131.0	-12.2	42	41.9	-24.7
California	14	196.9	-12.9	22	82.7	-31.9	29	37.8	-9.1
Colorado	5	175.5	-7.7	4	61.3	-29.1	21	34.8	-6.9
Connecticut	6	182.4	-11.5	11	73.4	-22.8	5	27.4	-16.5
Delaware	31	219.9	-6.5	25	84.3	-32.4	50	48.1	14.0
District of Columbia	40	241.4	-15.0	43	102.7	-39.5	27	37.5	-1.5
Florida	17	198.5	-7.8	28	88.1	-25.6	39	41.2	13.7
Georgia	38	238.8	-10.2	10	71.2	-25.3	45	42.7	-13.2
Hawaii	4	173.9	-11.4	7	63.9	-18.4	28	37.6	-9.4
Idaho	21	203.0	-5.4	15	77.0	-19.3	25	36.0	-14.9
Illinois	33	221.6	-9.1	17	80.1	-34.0	35	39.5	-9.5
Indiana	39	240.0	-8.1	33	95.8	-21.4	38	40.4	-11.5
Iowa	32	220.9	-7.2	40	101.9	-24.7	12	32.3	-23.2
Kansas	30	219.0	-6.7	35	96.6	-7.0	24	35.8	-21.8
Kentucky	45	257.1	-8.6	41	102.1	-27.4	43	42.1	-14.1
Louisiana	48	272.8	-8.6	34	95.9	-27.1	49	45.8	-6.1
Maine	12	192.5	-8.2	16	78.0	-25.4	15	32.7	-13.8
Maryland	34	222.1	-9.4	29	89.7	-32.7	41	41.5	-1.2
Massachusetts	3	168.8	-17.5	6	63.6	-35.5	3	26.0	-22.9

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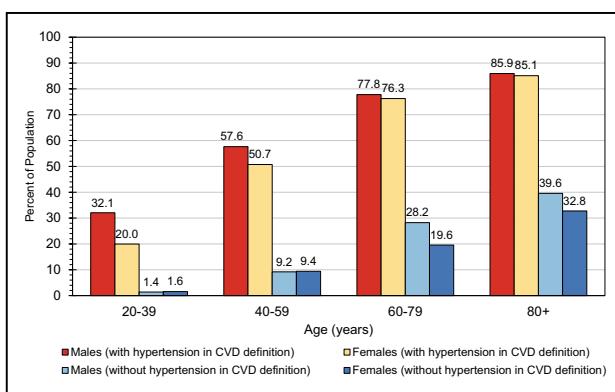
**Table 14-3. Continued**

State	CVD			CHD			Stroke		
	Rank	Death rate	% Change, 2008–2010 to 2018–2020	Rank	Death rate	% Change, 2008–2010 to 2018–2020	Rank	Death rate	% Change, 2008–2010 to 2018–2020
Michigan	44	256.5	-5.0	47	112.3	-23.5	40	41.3	-7.1
Minnesota	2	167.0	-4.7	2	59.3	-17.1	13	32.4	-11.5
Mississippi	52	307.4	-8.4	46	111.0	-23.5	52	52.8	-2.6
Missouri	41	244.3	-10.3	42	102.7	-29.7	32	38.9	-18.3
Montana	24	205.5	-4.1	30	90.5	-5.1	8	30.0	-20.6
Nebraska	16	197.6	-8.5	9	70.5	-17.4	16	33.0	-24.3
Nevada	42	252.4	-0.8	45	104.9	3.1	30	38.3	-5.9
New Hampshire	10	189.3	-7.9	13	76.8	-27.8	6	28.5	-17.7
New Jersey	25	207.6	-10.8	27	87.2	-31.1	9	30.6	-11.2
New Mexico	19	199.2	-3.8	44	103.7	-5.0	17	33.2	-13.0
New York	29	216.4	-16.0	49	118.7	-32.0	2	24.3	-13.4
North Carolina	28	214.2	-12.9	19	81.4	-30.3	44	42.4	-15.5
North Dakota	13	195.5	-9.8	23	82.8	-29.2	14	32.6	-10.7
Ohio	43	253.4	-2.4	39	101.9	-25.3	47	43.4	-3.7
Oklahoma	50	290.7	-6.1	48	114.4	-25.4	36	39.9	-24.0
Oregon	11	189.9	-7.1	3	60.9	-30.5	34	39.3  American Heart Association.	-10.8
Pennsylvania	36	224.8	-10.2	31	93.1	-26.0	23	35.8	-15.1
Puerto Rico	1	146.7	-21.7	7	65.6	-21.7	1	23.7	-37.3
Rhode Island	18	198.8	-11.2	36	97.9	-32.4	4	27.2	-14.6
South Carolina	37	228.9	-12.0	18	80.7	-26.7	48	43.7	-17.0
South Dakota	26	208.6	-6.1	37	100.9	-19.2	18	33.8	-14.3
Tennessee	47	267.3	-7.8	50	120.9	-25.1	46	43.0	-17.3
Texas	35	224.6	-9.6	32	93.7	-24.2	37	40.1	-17.3
Utah	15	197.4	0.2	5	63.4	-15.0	22	35.0	-9.6
Vermont	22	203.5	-1.9	38	101.5	-14.4	7	29.2	-16.8
Virginia	23	203.9	-12.4	12	75.2	-27.8	33	39.0	-13.6
Washington	8	186.3	-12.5	14	76.9	-29.6	20	34.6	-13.7
West Virginia	46	257.1	-11.9	51	125.0	-15.6	31	38.5	-16.6
Wisconsin	27	209.4	-5.5	26	87.2	-17.7	19	34.0	-17.4
Wyoming	20	201.1	-10.6	20	82.4	-18.3	11	31.5	-27.7
Total United States		218.8	-9.8		90.2	-27.2		37.6	-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.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System data.<sup>56</sup>

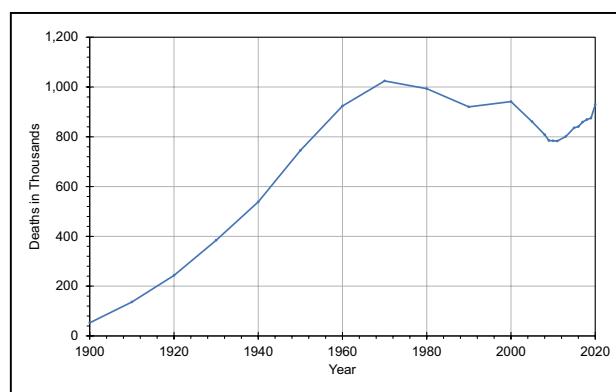


**Chart 14-1. Prevalence of CVD in US adults  $\geq 20$  years of age by age and sex (NHANES, 2017–2020).**

These data include CHD, HF, stroke, and with and without hypertension.

CHD indicates coronary heart disease; CVD, cardiovascular disease; HF, heart failure; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>1</sup>

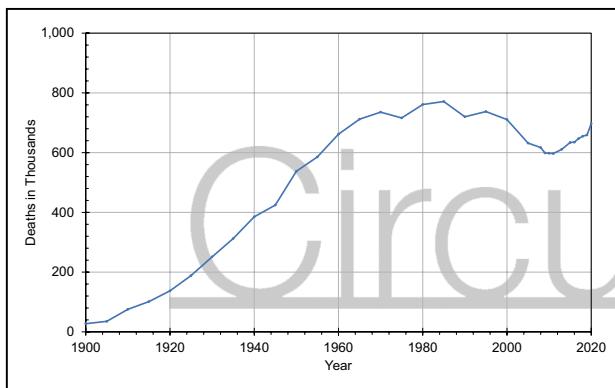


**Chart 14-3. Deaths attributable to CVD, United States, 1900 to 2020.**

CVD (*ICD-10* codes I00–I99) does not include congenital heart disease. Before 1933, data are for a death registration area, not the entire United States.

CVD indicates cardiovascular disease; and *ICD-10, International Classification of Diseases, 10th Revision*.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.<sup>56</sup>

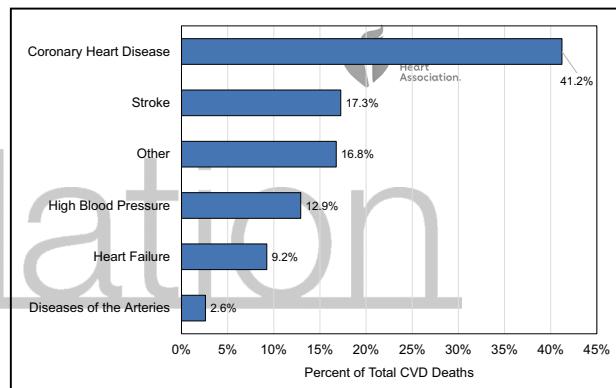


**Chart 14-2. Deaths attributable to diseases of the heart, United States, 1900 to 2020.**

See Glossary (Chapter 30) for an explanation of diseases of the heart. In the years 1900 to 1920, the *ICD* 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.

*ICD* indicates *International Classification of Diseases*.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.<sup>56</sup>

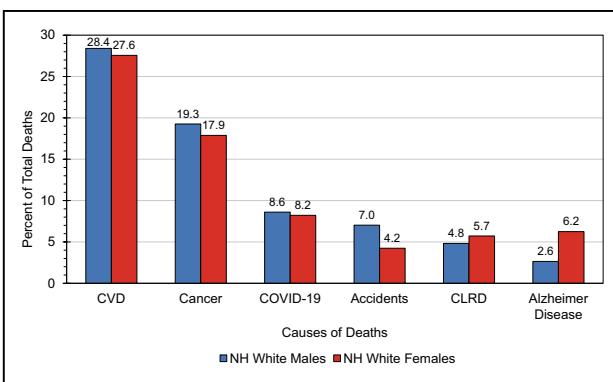


**Chart 14-4. Percentage breakdown of deaths attributable to CVD, United States, 2020.**

Total may not add to 100 because of rounding. CHD includes *ICD-10* codes I20 to I25; stroke, I60 to I69; HF, I50; HBP, I10 to I15; diseases of the arteries, I70 to I78; and other, all remaining *ICD-10* categories.

CHD indicates coronary heart disease; CVD, cardiovascular disease; HBP, high blood pressure; HF, heart failure; and *ICD-10, International Classification of Diseases, 10th Revision*.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.<sup>56</sup>

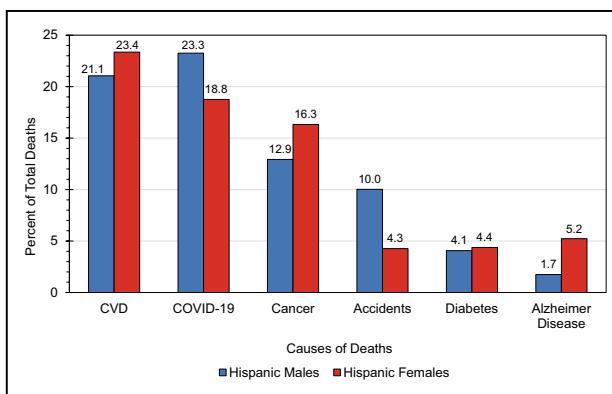


**Chart 14-5. CVD and other major causes of death for NH White males and females, United States, 2020.**

Diseases included CVD (*ICD-10* codes I00–I99); cancer (C00–C97); CLRD (J40–J47); COVID-19 (U07.1); accidents (V01–X59 and Y85–Y86); and AD (G30).

AD indicates Alzheimer disease; CLRD, chronic lower respiratory disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; *ICD-10*, International Classification of Diseases, 10th Revision; and NH, non-Hispanic.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.<sup>56</sup>

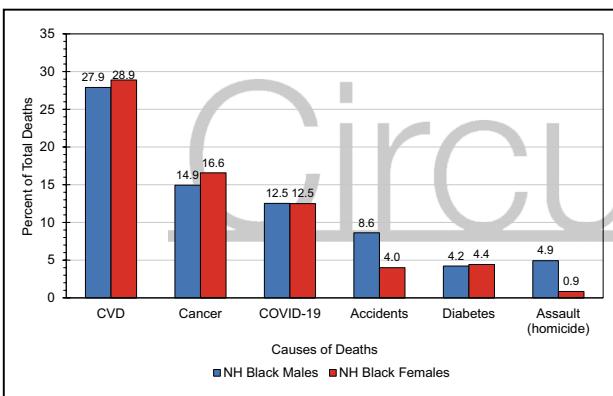


**Chart 14-7. CVD and other major causes of death for Hispanic or Latino males and females, United States, 2020.**

Number of deaths shown may be lower than actual because of underreporting in this population. Diseases included CVD (*ICD-10* codes I00–I99); COVID-19 (U07.1); cancer (C00–C97); accidents (V01–X59 and Y85–Y86); diabetes (E10–E14); and AD (G30).

AD indicates Alzheimer disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; and *ICD-10*, International Classification of Diseases, 10th Revision.

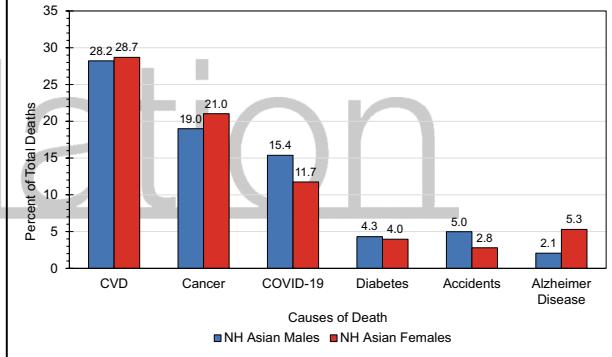
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.<sup>56</sup>



**Chart 14-6. CVD and other major causes of death for NH Black males and females, United States, 2020.**

Diseases included CVD (*ICD-10* codes I00–I99); cancer (C00–C97); COVID-19 (U07.1); 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; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; *ICD-10*, International Classification of Diseases, 10th Revision; and NH, non-Hispanic.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.<sup>56</sup>

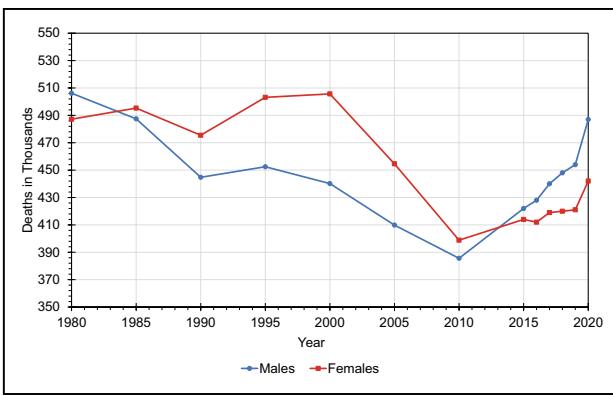


**Chart 14-8. CVD and other major causes of death for NH Asian or Pacific Islander males and females, United States, 2020.**

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 (*ICD-10* codes I00–I99); cancer (C00–C97); COVID-19 (U07.1); accidents (V01–X59, Y85, and Y86); diabetes (E10–E14); and AD (G30).

AD indicates Alzheimer disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; *ICD-10*, International Classification of Diseases, 10th Revision; and NH, non-Hispanic.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.<sup>56</sup>

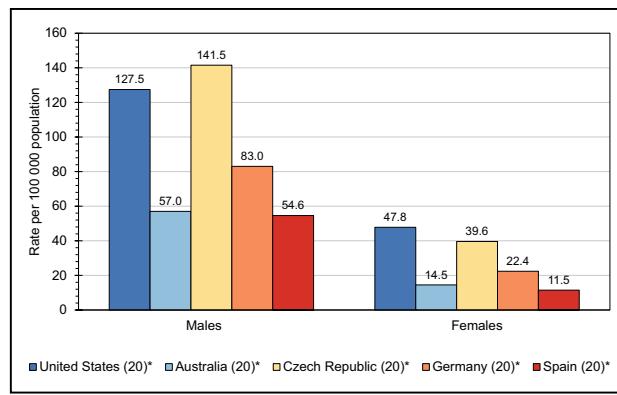


**Chart 14-9. CVD mortality trends for US males and females, 1980 to 2020.**

CVD excludes congenital cardiovascular defects (*ICD-10* codes I00–I99). The overall comparability for CVD between *ICD-9* (1979–1998) and *ICD-10* (1999–2015) is 0.9962. No comparability ratios were applied.

CVD indicates cardiovascular disease; *ICD-9*, *International Classification of Diseases, 9th Revision*; and *ICD-10*, *International Classification of Diseases, 10th Revision*.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.<sup>56</sup>



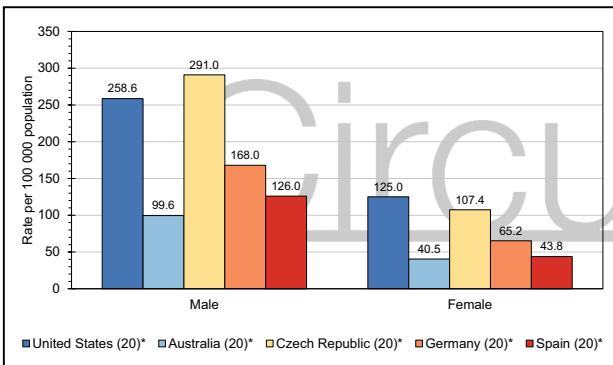
**Chart 14-11. Death rates per 100,000 population for CHD in selected countries for adults 35 to 74 years of age, 2020.**

Rates are adjusted to the European Standard Population. *ICD-10* codes are I20 to I25 for CHD.

CHD indicates coronary heart disease; and *ICD-10*, *International Classification of Diseases, 10th Revision*.

\*Number in parentheses indicates year of most recent data available (20 is 2020).

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.<sup>71</sup>



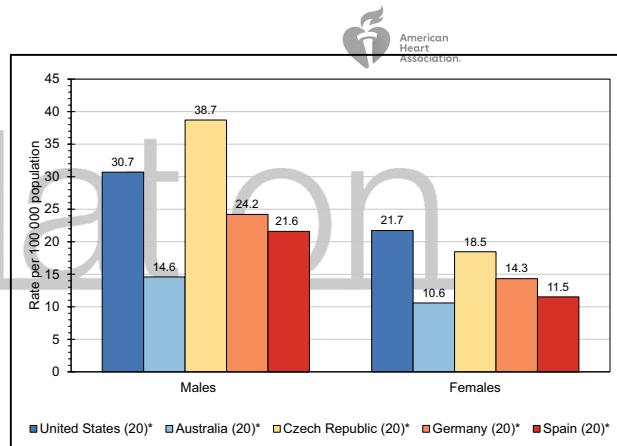
**Chart 14-10. Death rates per 100,000 population for CVD in selected countries for adults 35 to 74 years of age, 2020.**

Rates are adjusted to the European Standard Population. *ICD-10* codes are I00 to I99 for CVD.

CVD indicates cardiovascular disease; and *ICD-10*, *International Classification of Diseases, 10th Revision*.

\*Number in parentheses indicates year of most recent data available (20 is 2020).

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.<sup>71</sup>



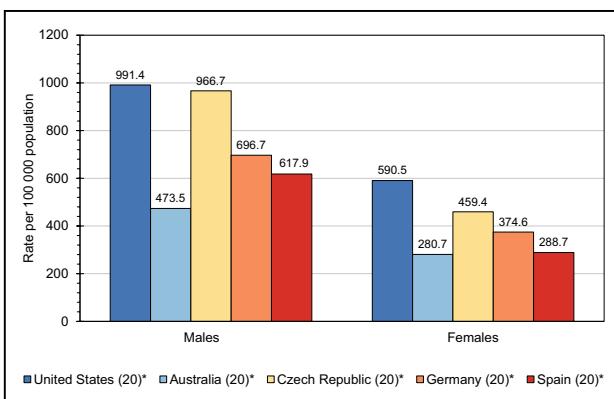
**Chart 14-12. Death rates per 100,000 population for stroke in selected countries for adults 35 to 74 years of age, 2020.**

Rates are adjusted to the European Standard Population. *ICD-10* codes are I60 to I69 for stroke.

*ICD-10* indicates *International Classification of Diseases, 10th Revision*.

\*Number in parentheses indicates year of most recent data available (20 is 2020).

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.<sup>71</sup>



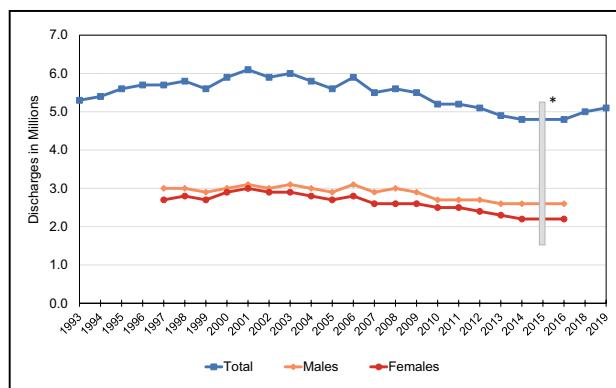
**Chart 14-13. Death rates per 100 000 population for all causes in selected countries for adults 35 to 74 years of age, 2020.**

Rates are adjusted to the European Standard Population. *ICD-10* codes are A00 to Y89 for all causes.

*ICD-10* indicates *International Classification of Diseases, 10th Revision*.

\*Number in parentheses indicates year of most recent data available (20 is 2020).

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.<sup>71</sup>



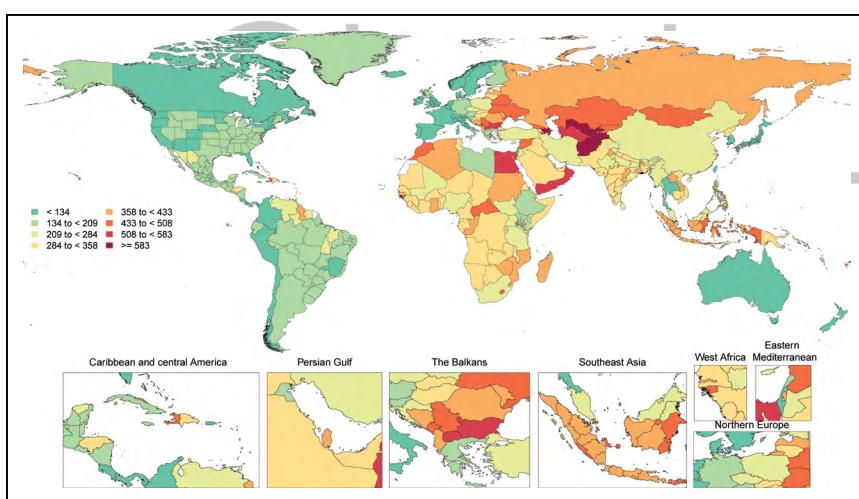
**Chart 14-14. Hospital discharges for CVD, US males and females, 1993 to 2016.**

Hospital discharges include people discharged alive, dead, and status unknown. Data not available for males and females separately from 1993 to 1996 and after 2016.

CVD indicates cardiovascular disease; *ICD-9, International Classification of Diseases, 9th Revision*; and *ICD-10, International Classification of Diseases, 10th Revision*.

\*Data not available for 2015. 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.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.<sup>63</sup>

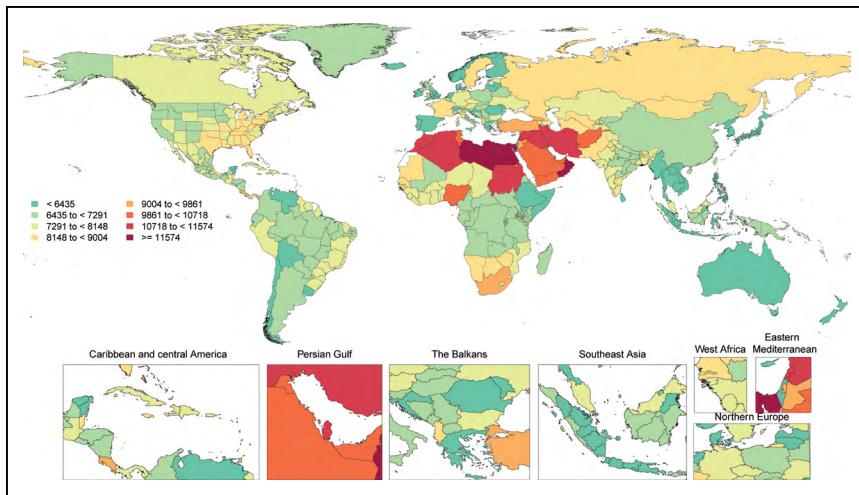


**Chart 14-15. Age-standardized global mortality rates of CVDs per 100,000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

CVD indicates cardiovascular disease; and GBD, Global Burden of Disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>72</sup>


**Chart 14-16. Age-standardized global prevalence rates of CVDs per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

CVD indicates cardiovascular disease; and GBD, Global Burden of Disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>72</sup>

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# Circulation

## 15. STROKE (CEREBROVASCULAR DISEASES)

**ICD-9 430 to 438; ICD-10 I60 to I69. See Table 15-1 and Charts 15-1 through 15-17**

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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 9.4 million Americans  $\geq 20$  years of age self-report having had a stroke (NHANES 2017–2020 data). Overall stroke prevalence during this period was an estimated 3.3% (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 BRFSS<sup>1</sup> 2020 (unpublished NHLBI tabulation), stroke prevalence in adults was 2.8% (median) in the United States, with the lowest prevalence in Puerto Rico (1.2%) and Connecticut (1.9%) and the highest prevalence in Mississippi (4.9%).
- 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).

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

- Projections show that by 2030 an additional 3.4 million US adults  $\geq 18$  years of age, representing 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).
- According to the GBD Study 2019, ischemic strokes accounted for 62.4% of all global incident strokes in 2019 (7.63 million [95% CI, 6.57–8.96 million]), ICH for 27.9% (3.41 million, [95% CI, 2.97–3.91 million]), and SAH for 9.7% (1.18 million [95% CI, 1.01–1.39 million]).<sup>4</sup>

### Secular Trends

- An analysis of data from the GBD Study 2019 found that from 1990 to 2019, the absolute number of incident strokes increased by 70.0% (95% CI, 67.0%–73.0%) and the age-standardized incidence rate for total stroke decreased by 17.0% (95% CI, 15.0%–18.0%).<sup>4</sup> The age-standardized incidence rate for ischemic stroke decreased by 10% (95% CI, 8.0%–12.0%) and ICH decreased by 29% (95% CI, 28.0%–30.0%) during the same period.
- 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>5</sup>
- Data from the Danish Stroke Registry and the Danish National Patient Registry showed that the incidence rate per 100 000 person-years in 2005 and 2018 of ischemic stroke (20.8 versus 21.9, respectively; average annual percentage change,  $-0.6$  [95% CI,  $-1.5$  to  $0.3$ ]) and ICH (2.2 versus 2.5, respectively; average annual percentage change,  $0.6$  [95% CI,  $-1.0$  to  $2.3$ ]) remained steady in younger adults (18–49 years of age), but in older adults ( $>50$  years of age), rates of ischemic stroke and ICH declined, especially in those  $\geq 70$  years of age.<sup>6</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>7</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>8</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>9</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>10</sup>
  - In a US nationwide study of mortality among Asian American individuals from 2003 to 2017, age-standardized cerebrovascular disease mortality declined by an average of 2.2%/y (95% CI, 1.1–3.2) among Asian American females and 2.0%/y (95% CI, 1.3–3.6) among Asian American males.<sup>11</sup> There was heterogeneity among Asian American ethnic subgroups. Average annual percent decline in cerebrovascular mortality was fastest among Japanese American individuals (decline of 3.1 %/y [95% CI, 2.0–4.2] among females and decline of 3.2%/y [95% CI, 2.0–4.2] among males), whereas no decline was observed among Asian Indian American or Vietnamese American females or males.

## 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>12,13</sup>

### High BP

(See Chapter 8 [High Blood Pressure] for more information.)

(See Chart 15-2)

- Among 430977 adults 30 to 79 years of age in China with 5168 stroke deaths during a median

follow-up of 10 years, stroke mortality rates per 100 000 person-years in BP groups were 39 in normal BP, 71 in prehypertension-low, 83 in prehypertension-high, 283 in isolated systolic hypertension, 82 in isolated diastolic hypertension, and 375 in systolic-diastolic hypertension. Compared with normal BP, multiadjusted HRs for stroke mortality were 1.20 (95% CI, 1.06–1.36) in prehypertension-low, 1.53 (95% CI, 1.37–1.70) in prehypertension-high, 2.52 (95% CI, 2.28–2.78) in isolated systolic hypertension, 2.51 (95% CI, 1.94–3.21) in isolated diastolic hypertension, and 5.60 (95% CI, 5.06–6.21) in systolic-diastolic hypertension. For all BP categories relative to normal BP, HRs for hemorrhagic stroke mortality were larger than those for ischemic stroke mortality.<sup>14</sup>

- Among 33357 adults in ALLHAT with 936 strokes during a median follow-up of 4.4 years, heat map plotting of stroke risk at all SBP and DBP combinations showed that stroke risk was lowest in the SBP/DBP range of <110/<60 mm Hg (HRs <0.90 relative to BP of 120/80 mm Hg) and stroke risk was highest in the SBP/DBP range of 170 to 190/85 to 100 mm Hg (HRs >2.00 relative to BP of 120/80 mm Hg; Chart 15-2).<sup>15</sup>
- In a meta-analysis of 66 trials of SBP-lowering interventions including 324 812 participants and 11 437 strokes over an average follow-up of 3.3 years, SBP lowering was associated with 21% lower odds (95% CI, 15%–26% lower) of stroke compared with control. In meta-analyses of stroke types, SBP lowering was associated with 14% lower odds (95% CI, 27% lower–2% higher) of ischemic stroke (6 trials), 28% lower odds (95% CI, 4%–46% lower) of hemorrhagic stroke (6 trials), and 28% lower odds (95% CI, 19%–39% lower) of fatal or disabling stroke (18 trials).<sup>16</sup>

- Among adults treated for hypertension in an ambulatory setting in the United States, tight BP control (<130 mm Hg) was associated with 42% lower incidence of stroke (95% CI, 9%–63% lower) compared with standard BP control (130–139 mm Hg).<sup>17</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  $\geq 60$  years of age who annually attended physical examination in the community health care center in Guangdong, China.<sup>18</sup>
- Among adults in the United Kingdom, genetically predicted pulse pressure was associated with ischemic stroke in those  $\geq 55$  years of age (aOR per SD, 1.23 [95% CI, 1.13–1.34]) independently of genetically predicted mean arterial pressure.<sup>19</sup>
- Among adults  $\geq 35$  years of age recruited from rural areas of Fuxin County, Liaoning Province, China,

ideal BP for stroke prevention varied by BMI: At  $\text{BMI} < 24 \text{ kg/m}^2$ , stroke risk was lowest in those with  $\text{BP} < 130/80 \text{ mmHg}$ , whereas at  $\text{BMI} \geq 24 \text{ kg/m}^2$ , stroke risk was lowest in those with  $\text{BP} < 120/80 \text{ mmHg}$ .<sup>20</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 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>21</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.

### **BP and Recurrent Stroke**

- In a meta-analysis of 10 studies including 13 944 stroke survivors and 1428 recurrent strokes during follow-up ranging from 1 to 5 years, hypertension was associated with 67% higher odds of recurrent stroke (95% CI, 45%–92%).<sup>22</sup> Among 17 916 patients in the PROFESSION trial, every 10-point increment in SBP variability, defined as the SD across repeated measurements, was associated with 15% higher hazard (95% CI, 2%–32%) of recurrent stroke.<sup>23</sup>

## **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, which included 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>24</sup> Compared with males with diabetes, females with diabetes had a 27% greater RR of stroke (pooled ratio of RR, 1.27 [95% CI, 1.10–1.46]).
- Prediabetes, defined as impaired glucose tolerance or impaired fasting glucose, is associated with a modestly increased risk of stroke. A meta-analysis of 53 prospective cohort studies including 161 1339 participants, of which 18 studies reported the association between prediabetes and stroke, revealed that impaired glucose tolerance was associated with a 20% increased risk of stroke (aRR, 1.20 [95% CI, 1.00–1.45]).<sup>25</sup> Impaired fasting glucose, defined as FPG of 100 to 125 mg/dL, was associated increased stroke risk (aRR 1.06

[95% CI, 1.01–1.11]). Diabetes is an independent risk factor for stroke recurrence; a meta-analysis of 27 studies involving 274 631 participants with prior ischemic stroke demonstrated that diabetes was an independent risk factor for stroke recurrence (pooled HR, 1.50 [95% CI, 1.36–1.65]).<sup>26</sup>

- In the GWTG-Stroke registry, diabetes was associated with a higher risk of adverse outcomes 3 years after ischemic 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>27</sup>
- In a meta-analysis of 11 RCTs that included 56 161 patients with type 2 diabetes and 1835 cases of stroke, intensive blood glucose control did not reduce stroke risk compared with conventional glucose control (RR, 0.94 [95% CI, 0.84–1.06]).<sup>28</sup> An RCT of intensive or standard blood glucose control in patients with AIS with hyperglycemia (80% with diabetes) did not demonstrate a difference in favorable functional outcome (aRR, 0.97 [95% CI, 0.87–1.08]) at 90 days.<sup>29</sup> A meta-analysis of 5 RCTs involving 42 910 participants demonstrated that GLP1-RAs reduced stroke risk (OR, 0.87 [95% CI, 0.77–0.98]) compared with placebo.<sup>30</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]). Lower RRs (RR, 0.71 [95% CI, 0.63–0.80]) observed among trials with mean baseline SBP  $\geq 140 \text{ mmHg}$  and no significant associations among trials with baseline SBP  $< 140 \text{ mmHg}$  (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  $< 130 \text{ mmHg}$  and the  $\geq 130 \text{ mmHg}$  groups.<sup>31</sup>

## **Disorders of Heart Rhythm**

(See Chapter 18 [Disorders of Heart Rhythm] for more information.)

### **Atrial Fibrillation**

- Because AF is often asymptomatic<sup>32</sup> and frequently undetected clinically,<sup>33</sup> the stroke risk attributed to AF is likely substantially underestimated. The 12-month prevalence of AF in patients with stroke attributed to large- or small-vessel disease was 12.1% in the STROKE-AF RCT using continuous cardiac monitoring versus 1.8% with usual care; median time to detection was 99 and 181 days, respectively.<sup>34</sup>

- In a meta-analysis of 50 studies, AF was detected in ≈24% (95% CI, 17%–31%) of patients with embolic stroke of undetermined source, depending on duration and type of monitoring used.<sup>35</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>36</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>37</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>38–42</sup> Biomarkers such as high levels of troponin, BNP, NT-BNP, cystatin C, factor VIII antigen, interleukin-6, and growth differentiation factor-15 are associated with an increased risk of stroke or bleeding in AF after adjustment for traditional vascular risk factors.<sup>43,44</sup>
- In patients with AF who are being treated with anti-coagulation, presence of persistent AF versus paroxysmal AF is associated with higher risk of stroke.<sup>45,46</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>47</sup>
- In a meta-analysis of 35 studies (N=2 458 010 patients), perioperative or postoperative AF was associated with an increased risk of early stroke (OR, 1.62 [95% CI, 1.47–1.80]) and later stroke (HR, 1.37 [95% CI, 1.07–1.77]). This risk was found in patients undergoing both noncardiac surgery (HR, 2.00 [95% CI, 1.70–2.35]) and cardiac surgery (HR, 1.20 [95% CI, 1.07–1.34]).<sup>48</sup>
- In a meta-analysis of 28 studies (N=26 128 16 patients), AF after noncardiac surgery was associated with a ≈3 fold increased risk of stroke at 1 month (OR, 2.82 [95% CI, 2.15–3.70]) and ≈4 fold increase in long-term risk of stroke (OR, 4.12 [95% CI, 3.32–35.11]).<sup>49</sup> For the choice of anticoagulant postoperatively, a study from the STS database of 26 522 patients with postcardiac surgery AF (36.8% on DOAC and 36.2% on vitamin K antagonist) showed no association between type of oral anticoagulant and 30-day outcomes (major bleeding, stroke/TIA, or mortality) but did show a half-day reduction in length of stay (B, −0.47 [95% CI, −0.62 to −0.33]).<sup>50</sup>

- In an analysis of 2046 patients admitted with AIS who had AF, mean heart rate during the AIS period was not associated with stroke recurrence but was associated with higher mortality.<sup>51</sup>

### Other Arrhythmias

- In an analysis of inpatient and outpatient claims data from a 5% sample of all Medicare beneficiaries ≥66 years of age (2008–2014), atrial flutter was associated with a lower risk of stroke than AF.<sup>52</sup>
- Paroxysmal SVT<sup>53</sup> and excessive supraventricular ectopic activity<sup>54</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 ≥30 premature atrial contractions per hour or any runs of ≥20 premature atrial contractions, was associated with an increased risk of stroke (HR, 2.19 [95% CI, 1.24–4.02]).<sup>55</sup>
- In a French longitudinal cohort study of 1 692 157 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>56</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>57–60</sup>

### Total Cholesterol

- In a meta-analysis of data from 61 cohorts, TC was weakly associated with risk of total stroke.<sup>61</sup> In the Prospective Studies Collaboration, an association between elevated TC and ischemic and total stroke mortality was present in early middle age (40 to 59 years) but not in older age.<sup>59</sup>
- Elevated TC is inversely associated with hemorrhagic stroke risk. 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 (RR, 0.85 [95% CI, 0.80–0.91]).<sup>62</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>63</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]) but a 17% increased risk of ICH (RR, 1.17 [95% CI, 1.03–1.32]).<sup>64</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>65</sup>
- A meta-analysis of 39 primary and secondary prevention trials including 287 651 participants did not demonstrate an association between lipid-lowering therapy and ICH risk (OR, 1.12 [95% CI, 0.98–1.28]).<sup>66</sup> Another meta-analysis of 8 trials did not demonstrate a difference in the incidence of hemorrhagic stroke among those receiving intensive lipid-lowering therapy (achieved LDL-C <55 mg/dL) compared with those receiving less intensive treatment (OR, 1.05 [95% CI, 0.85–1.31]).<sup>67</sup>
- A mendelian randomization study demonstrated that every 1-mmol/L reduction in genetically predicted LDL-C was associated with a 25% reduced risk of ischemic stroke (RR, 0.75 [95% CI, 0.60–0.95]) but 13% increased risk of ICH (RR, 1.13 [95% CI, 0.91–1.40]).<sup>64</sup> Another mendelian randomization study demonstrated that genetically elevated LDL-C was associated with an increased risk of total ischemic stroke and large-artery atherosclerotic stroke but not other ischemic stroke subtypes.<sup>68</sup>

### HDL Cholesterol

- A meta-analysis of 62 prospective cohort studies including 900 501 participants and 25 678 strokes demonstrated that a 1-mmol/L increase in HDL-C level was associated with an 18% lower risk of total stroke (RR, 0.82 [95% CI, 0.76–0.89]); the RR for ischemic stroke was 0.75 (95% CI, 0.69–0.82) but was 1.21 (95% CI, 1.04–1.42) for ICH.<sup>69</sup> Genetic predisposition to higher HDL-C has been associated with lower risk of small-vessel ischemic stroke in mendelian randomization analyses.<sup>68,70</sup>

### Triglycerides

- In a population-based cohort study of 5 688 055 Korean young adults (20–39 years of age) with a median follow-up of 7.1 years, serum triglyceride concentration was associated with an increased risk of stroke (HR, 2.53 [95% CI, 2.34–2.73]).<sup>71</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>72</sup>

- In an RCT of 8179 participants with established CVD or diabetes and other vascular risk factors and elevated serum triglycerides despite the use of statin therapy, icosapent ethyl treatment reduced nonfatal stroke risk compared with placebo (HR, 0.71 [95% CI, 0.54–0.94]).<sup>73</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>74</sup>
- A meta-analysis of 141 cohort studies showed that low cigarette consumption ( $\approx$ 1 cigarette/d) carries a risk of developing stroke up to 50% of the risk associated with high cigarette consumption ( $\approx$ 20 cigarettes/d).<sup>75</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>75</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>76,77</sup>
  - 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,  $96.4 \pm 20.8$  per 100 person-years versus  $56.7 \pm 4.8$  per 100 person-years;  $P=0.026$ ).<sup>78</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>79</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>80</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>81</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>82</sup>
- In a cross-sectional study from 2016 to 2018 of the US CDC BRFSS surveys (N=6 867 786 stroke survivors), the estimated prevalence of e-cigarette use among stroke survivors in the United States was 13.5% (95% CI, 11.8%–15.3%).<sup>83</sup> Among cigarette smokers, users of e-cigarette were more likely to have tried to quit cigarette smoking in the past year than those not using e-cigarettes (73% versus 60.7%; OR, 1.63 [95% CI, 1.21–2.19]).

### **Physical Inactivity**

(See Chapter 4 [Physical Activity and Sedentary Behavior] for more information.)

- The GBD Study 2019 estimated that low physical inactivity accounted for 1.7% of stroke-related disability globally (95% CI, 0.3%–4.5%) and 2.9% in high-income countries (95% CI, 0.5%–8.0%).<sup>4</sup>
- In a case-control study of NHANES participants, self-reported recent moderate-intensity activity (OR, 0.8 [95% CI, 0.7–0.9]), vigorous-intensity activity (OR, 0.6 [95% CI, 0.5–0.8]), and muscle-strengthening exercises (OR, 0.6 [95% CI, 0.5–0.8]) were associated with lower odds of stroke.<sup>84</sup>
- Physical inactivity is a significant risk factor for stroke in middle-aged and elderly populations.<sup>85,86</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>87</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 also observed in individuals  $\geq 75$  years of age.<sup>88</sup>
- In the Cooper Center Longitudinal Study, cardiorespiratory fitness in midlife as measured by exercise treadmill testing was inversely associated with risk of stroke hospitalization in older age, including after adjustment for the interim development of diabetes, hypertension, and AF.<sup>89</sup>
- In the California Teachers Study of 61 256 females with PA data, meeting AHA recommendations of moderate PA was associated with a lower risk of ischemic stroke (aHR, 0.70 [95% CI, 0.55–0.88]). No association was observed between meeting

AHA guidelines for strenuous activity and risk of total stroke.<sup>90</sup>

- A prospective study among 437 318 participants in China found that physical inactivity was associated with an increased risk of incident total stroke (aHR, 1.52 [95% CI, 1.37–1.70]), ischemic stroke (aHR 1.49 [95% CI, 1.33–1.67]), and hemorrhagic stroke (aHR, 1.83 [95% CI, 1.30–2.59]).<sup>91</sup>
- In a systematic review of 7 observational studies that included 41 800 stroke survivors, prestroke PA was associated with lower stroke severity at hospital admission.<sup>92</sup>
- In an analysis of the Taiwan National Stroke Registry, among 39 835 stroke cases, prestroke PA (of at least 30 min/d for 3 d/wk in the preceding 6 months) was associated with a lower risk of in-hospital mortality (aHR, 0.95 [95% CI, 0.85–0.99]) and a higher odds of functional independence 6 months after stroke (aOR, 0.88 [95% CI, 0.83–0.92]).<sup>93</sup>

### **Cardiorespiratory Fitness**

- The REGARDS study ( $\geq 45$  years of age) reported a race-specific association between cardiorespiratory fitness and incident stroke. 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 stroke: HR, 1.98 [95% CI, 0.87–4.52]).<sup>94</sup>
- The Oslo Ischemia Cohort Study assessed change in cardiorespiratory fitness levels, assessed by a bicycle electrocardiographic test, between baseline and  $>7$  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>95</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, 0.68–0.153]).<sup>96</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>97</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>98</sup>

### Nutrition

(See Chapter 5 [*Nutrition*] for more information.)

- Diet quality:
  - Among 7841 adults in the Guizhou Population Health Cohort Study in China with 142 incident ischemic strokes over a mean follow-up of 6.6 years, the least favorable quartile of diet quality (assessed by Chinese Diet Balance Index) versus most favorable was associated with 3.31 times the hazard of ischemic stroke (95% CI, 1.57–6.97), and inadequate dietary variety was associated with 5.40 times the hazard of ischemic stroke (95% CI, 1.70–17.2), adjusted for sociodemographic, behavioral, and clinical risk factors.<sup>99</sup>
  - Among 26 547 adults in the Malmö Diet and Cancer Study in Sweden with 2339 incident ischemic strokes over a median follow-up of 21.2 years, high diet quality by Swedish nutrition recommendations was associated with 17% lower hazard of ischemic stroke (95% CI, 3%–28% lower), adjusted for established risk factors and comorbidities.<sup>100</sup>
  - Among 4701 young adults in the CARDIA study in the United States with 80 incident strokes over a median follow-up of 32 years, each 1-SD increment in diet quality assessed by the A Priori Diet Quality Score was associated with 30% lower hazard of incident stroke (95% CI, 1%–50% lower).<sup>101</sup>
- Vegetarian diet: In a meta-analysis of 7 cohort studies including 29 705 vegetarians with 408 incident strokes and 627 728 nonvegetarians with 13 026 incident strokes, vegetarian diet was associated with 14% lower hazard of stroke, with a wide CI (95% CI, 33% lower–11% higher). Precision was inadequate to assess ischemic stroke and hemorrhagic stroke separately. The 7 individual cohort studies had substantial heterogeneity ( $P=68\%$ ), with HR estimates of incident stroke of 0.51 (95% CI, 0.25–1.05) in vegetarians and 1.20 (95% CI, 1.02–1.41) in nonvegetarians.<sup>102</sup>
- Fruits and vegetables:
  - In a study based on GBD Study 2017 data for China, the association of low fruit intake with stroke mortality was stronger for males than for females and stronger for older adults than for younger adults.<sup>103</sup> The age-standardized stroke mortality attributed to low fruit intake was 6% lower for males and 41% lower for females in 2017 (versus 1992).
- Among 87 177 adults in Japan with 4091 incident strokes over a median follow-up of 13.1 years, higher intake of flavonoid-rich fruits (such as citrus, strawberries, and grapes) was associated with 30% lower hazard of stroke among females (95% CI, 16%–42% lower) but not among males (7% lower hazard [95% CI, 21% lower–9% higher]).<sup>104</sup>
- In a meta-analysis of 6 cohort studies, the highest level of green leafy vegetable intake was associated with 7% lower hazard of total stroke (95% CI, 3%–10% lower), 8% lower hazard of ischemic stroke (95% CI, 4%–12% lower), and 5% lower hazard of hemorrhagic stroke (95% CI, 14%–4% higher); heterogeneity of cohort-specific results was moderate ( $P=36\%$ ).<sup>105</sup>
- 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. The people who consumed 25 to 29 g/d fiber had the greatest health benefits.<sup>106</sup>
- Coffee:
  - In a meta-analysis of 21 studies including >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; heterogeneity of cohort-specific results was moderate ( $P=32\%$ ). Dose-response meta-analysis suggested a U-shaped relationship, with 3 to 4 cups of coffee per day associated with the lowest risk: 21% lower stroke risk compared with abstaining from coffee.<sup>107</sup>
  - In a different meta-analysis of 7 studies, the lowest category of coffee consumption was associated with 8% lower hazard of total stroke (95% CI, 1%–14% lower;  $P=50\%$ ), 17% lower hazard of ischemic stroke (95% CI, 12%–26% lower;  $P=0\%$ ), and 10% lower hazard of hemorrhagic stroke (95% CI, 3%–18% lower;  $P=4\%$ ). A U-shaped relationship was not seen.<sup>108</sup> Among 9964 adults in the Jichi Medical School Cohort Study in Japan with 244 stroke deaths over 18.4 years of follow-up, there was a U-shaped relationship between coffee consumption and stroke mortality among males, with 1 to 2 cups of coffee per day associated with the lowest stroke mortality: 37% lower stroke mortality than abstaining from coffee (95% CI, 5%–58% lower). The U-shaped association was not found in females.<sup>109</sup>
- Milk:
  - Among 110 585 adults in the Japan Collaborative Cohort, daily milk consumption was associated

- with 20% (95% credible interval, 7%–31%) lower stroke mortality among males but not among females (5% lower mortality [95% CI, 20% lower–17% higher]).<sup>110</sup>
- Among 14 121 adults in the Iwate-KENCO Study in Japan with 478 strokes over 10.7 years of follow-up, intake of 7 to <12 cups of milk per week compared with <2 cups of milk per week was associated with 47% lower hazard of ischemic stroke (95% CI, 12%–68% lower) in females but not in males (7% higher hazard [95% CI, 34% lower–71% higher]).<sup>111</sup>
  - In a meta-analysis of 3 studies including 163 128 adults and 3691 ischemic strokes, the highest category of milk intake was associated with 12% lower risk of ischemic stroke (2%–21% lower;  $P=0\%$ ) compared with the lowest category.<sup>112</sup>
  - ASBs: The FHS (N=2888; >45 years of age) showed that those who consumed ≥1 artificially sweetened soft drinks per day (eg, diet cola) had 1.97 times (95% CI, 1.1–3.55) and 2.34 times (95% CI, 1.24–4.45) the risk of total and ischemic stroke, respectively, compared with those who consumed 0 artificially sweetened soft drinks per week.<sup>113</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>114</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 that of individuals not taking omega-3 supplements (RR, 1.04 [95% CI, 0.83–1.31]).<sup>115</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>116</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>117</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>118</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>119</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>120</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>121</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>122</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>123</sup>
- Among 232 236 patients in the CWTG-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>124</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>125</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 hypertension, the magnitude of risk of a poor functional outcome associated with low eGFR was less than in individuals without hypertension (aOR, 1.30 [95% CI, 1.11–1.52];  $P_{\text{interaction}}=0.046$ ).
- 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>126</sup>

- In CRIC, a prospective cohort study of 1778 females and 2161 males with CKD, no significant sex differences in the risk of stroke were found (aHR, 0.83 [95% CI, 0.54–1.28]).<sup>127</sup> Notably, the mean eGFR was  $43.9 \pm 17.4 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$  in females (22% had an eGFR  $<30 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ) and  $45.7 \pm 16.4 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$  in males (18% had an eGFR  $<30 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ).
- In the Q-Cohort Study (N=3045 participants; median follow-up time, 8.8 years), a multicenter cohort study of patients on maintenance hemodialysis from Japan, a 10-unit decrease in the geriatric nutritional risk index (calculated from serum albumin and BMI) was associated with an increased risk of ischemic stroke (aHR, 1.49 [95% CI, 1.05–2.12]) and hemorrhagic stroke (aHR, 1.89 [95% CI, 1.1–3.2]) after adjustment for potential confounders.<sup>128</sup>
- In the ARIC study cohort (N=12588 participants; median follow-up time, 24.2 years), those in the top quartile of concentration of the liver enzyme  $\gamma$ -glutamyl transpeptidase compared with those in the lowest quartile 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>129</sup> There was a dose-response association ( $P_{\text{linear trend}} < 0.001$ ).
- In a case-cohort analysis in the REGARDS cohort, advanced liver fibrosis was classified with the use of validated cutoffs of the Fibrosis-4 score and Nonalcoholic Fatty Liver Disease Fibrosis Score.<sup>130</sup> Advanced liver fibrosis was associated with stroke in females (aHR, 3.51 [95% CI, 1.00–12.34]) but not males (aHR, 0.70 [95% CI, 0.16–3.16];  $P_{\text{interaction}} = 0.098$ ).

### Stroke After Procedures and Surgeries

- In-hospital stroke rates after TAVR declined from 2.2% in 2012 to 1.6% in 2019.<sup>131</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>132</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>133</sup> Axillary cannulation and retrograde cerebral perfusion were associated with lower risk of postoperative stroke.
- In a nationwide prospective cohort study from Denmark (N=78 096 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>134</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>135</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 100 000 pregnancies (95% CI, 18.8–47.9). The crude rates per 100 000 pregnancies were 18.3 (95% CI, 11.9–28.2) for antenatal/perinatal stroke and 14.7 (95% CI, 8.3–26.1) for postpartum stroke.<sup>136</sup>
- Among 80 191 parous females in the WHI Observational Study, those who reported breastfeeding for at least 1 month had a 23% lower risk of stroke than those who never breastfed (HR, 0.77 [95% CI, 0.70–0.83]). The strength of the association increased with increasing breastfeeding duration (1–6 months: HR, 0.81 [95% CI, 0.74–0.90]; 7–12 months: HR, 0.75 [95% CI, 0.66–0.85];  $\geq 13$  months: HR, 0.74 [95% CI, 0.65–0.83];  $P_{\text{trend}} < 0.01$ ). The strongest association was observed among NH Black females (HR, 0.54 [95% CI, 0.37–0.71]).<sup>137</sup>
- In a systematic review and meta-analysis of 78 studies including >10 million participants, any HDP, 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, HDP, PTB, and stillbirth were associated with a greater risk of any stroke.<sup>138</sup>
- In an analysis from the FHS of 1435 females with at least 1 pregnancy before menopause, hysterectomy, or 45 years of age, females with a history of preeclampsia had a higher risk of stroke in later life compared with females without a history of preeclampsia after adjustment for time-varying covariates (RR, 3.79 [95% CI, 1.24–11.60]).<sup>139</sup>
- In the UK Million Women Study, there was a U-shaped relationship between age at menarche and risk of incident stroke.<sup>140</sup> Compared with females experiencing menarche at 13 years of age, both those experiencing menarche at  $\leq 10$  years of age and those experiencing menarche at  $\geq 17$  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=74 928 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  $\geq 5$  kg) but not in males.<sup>141</sup>
- In a population-based matched cohort study in the United Kingdom (n=56 090 females with endometriosis and 223 669 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>142</sup>
  - In a case-control analysis of data from the Longitudinal Health Insurance Database 2000 of the Taiwan National Health Research Institutes, among 24 955 females 15 to 49 years of age with dysmenorrhea, nonsteroidal anti-inflammatory drug use and duration of use were associated with increased incidence of stroke. The aHR for nonsteroidal anti-inflammatory drug use was 1.47 (95% CI, 0.93–2.32).<sup>143</sup> The aHR for nonsteroidal anti-inflammatory drug use  $\geq 24$  d/mo was 2.29 (95% CI, 1.36–3.84).
  - 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>144</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  $\geq 45$  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>145</sup>
  - In a retrospective cohort study in the Taiwan National Health Insurance Research Database, among females 40 to 65 years of age treated with postmenopausal hormone therapy, the incidence of ischemic stroke was 1.17-fold higher in females treated with conjugated equine estrogen than in those treated with estradiol (4.24 per 1000 person-years versus 3.61 per 1000 person-years; aHR, 1.23 [95% CI 1.05–1.44]).<sup>146</sup>
  - Among people living with HIV, females had a higher incidence of stroke or TIA than males, especially at younger ages.<sup>147</sup> Compared with females without HIV, females living with HIV had a 2-fold higher incidence of ischemic stroke.<sup>148</sup>
  - In a record linkage study among 487 767 primiparous females 15 to 44 years of age with singleton pregnancies giving birth in New South Wales, Australia, from 2003 to 2015, a history of stroke

before pregnancy was associated with early-term delivery (37–38 weeks; RR 1.49 [95% CI, 1.17–1.90]) and a prelabor caesarean section (RR 2.83 [95% CI, 2.20–3.63]).<sup>149</sup> There were no differences in other APOs for females with a history of stroke.

### 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>150</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>151</sup>
- OSA is also common after stroke.<sup>152</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>153</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>154</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  $\geq 10$ , than NH White people after adjustment for confounders (PR, 1.21 [95% CI, 1.01–1.46]).<sup>152</sup>
- In a meta-analysis of 75 studies including 8670 patients with stroke, the prevalence of sleep apnea was nominally higher in those with hemorrhagic (82.7% [95% CI, 64.4%–92.7%]) compared with patients with ischemic (67.5% [95% CI, 63.2%–71.5%];  $P=0.098$ ) stroke and in those with supratentorial (64.4% [95% CI, 56.7%–71.4%]) compared with infratentorial (56.5% [95% CI, 42.2%–60.0%];  $P=0.171$ ) stroke.<sup>155</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  $\geq 8$  to 9 h/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>156</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>157</sup>
- Among 4785 Chinese adults >65 years of age in the 2011 China Health and Retirement Longitudinal Study, short and long sleep durations were not associated with stroke risk in those who reported good general health status.<sup>158</sup> In individuals who reported poor health status, compared with normal sleep duration (7–8 h/d), short sleep duration (aOR, 2.11 [95% CI, 1.30–3.44]) and long sleep duration (aOR, 1.86, [95% CI, 1.08–3.21]) were associated with increased stroke risk.
- 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>159</sup>
- In a mendelian randomization study including 40 585 stroke cases and 406 111 controls and using 36 SNPs associated with daytime sleepiness as instrumental variables, daytime sleepiness was associated with large-artery stroke (OR, 6.75 [95% CI, 1.49–30.57]) but not with all stroke, all ischemic stroke, cardioembolic stroke, or small-artery stroke.<sup>160</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>161</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>162</sup>
- History of depression and persistent depressive symptoms increase the risk of incident stroke. The association was even stronger in Black participants without diabetes (HR, 2.64 [95% CI, 1.48–4.72]).<sup>163</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 a low level of psychological distress.<sup>164</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>165</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>166</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>167</sup>
- Among 13 930 patients with ischemic stroke and 28 026 control subjects in the NINDS Stroke Genetics Network, each 1-SD increase in the Psychiatric Genomics Consortium PRS 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>168</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>169</sup>

### Social Determinants and Health Equity

#### Sex

- Each year, ≈55 000 more females than males have a stroke (GCNKSS, NINDS).<sup>170</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>171</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>172</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>172,173</sup>
- Racial and ethnic disparities in stroke risk may persist or even increase in elderly females from underrepresented races and ethnicities.<sup>73</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>174</sup> This increased risk was not present among elderly Black or Hispanic males compared with White males.

#### Race and Ethnicity

- The BASIC project demonstrated an increased incidence of ischemic stroke among Mexican American people compared with NH White people.<sup>175</sup> According to population-based surveillance data from 2000 to 2010, the age- and sex-adjusted IRR in Mexican American individuals/White individuals was as follows: 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>176,177</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 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 (age-adjusted HR, 1.47 [95% CI, 1.33–1.63]).<sup>178</sup> Adjustment for socio-economic 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>179</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>180</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 Secular Trends section).<sup>5</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>181</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>182</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%;  $P<0.01$ ).

- 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>183</sup>
- In a retrospective analysis of the BRFSS 2016, 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>184</sup>

## TIA: Prevalence, Incidence, Racial and Ethnic Disparities, and Prognosis

- 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>185</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>186</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>187</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>188</sup>
- In the Oxford Vascular Study, acute lesions on MRI were identified in 13% of participants with TIA.<sup>189</sup> In age- and sex-adjusted analyses, these participants had a higher risk of recurrent ischemic stroke compared with individuals with TIA and a negative MRI (HR, 2.54 [95% CI, 1.21–5.34];  $P=0.014$ ).
- In a meta-analysis of 68 studies from 1971 to 2019, the estimated risk of subsequent ischemic stroke after a TIA was 2.4% (95% CI, 1.8%–3.2%) within 2 days, 3.8% (95% CI, 2.5%–5.4%) within 7 days, 4.1% (95% CI, 2.4%–6.3%) within 30 days, and 4.7% (95% CI, 3.3%–6.4%) within 90 days.<sup>190</sup> However, when studies were categorized according to date of publication (before 1999, 1999–2007, after 2007), the risk of subsequent ischemic stroke appears to have slightly declined.

- 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>191</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>192</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>193</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>194</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>195</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>196</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) than for ischemic recurrence (HR, 1, 1.03, 1.37, and 1.61). 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>197</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>198</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>199</sup>
- Data from 2015 to 2019 in 1458 hospitals in China found that an increase of 10  $\mu\text{g}/\text{m}^3$  in PM1 was associated with a 1.64% increment in stroke recurrence.<sup>200</sup>
- A meta-analysis of 11 clinical trials from 1970 to 2021 with 20 163 patients with stroke found that intensive LDL-C-lowering statin-based therapies reduced the risk of recurrent ischemic stroke (RR, 0.88 [95% CI, 0.80–0.96]) compared with less intensive LDL-C-lowering statin-based therapies.<sup>201</sup> This relationship was even stronger in populations with atherosclerosis (RR, 0.79 [95% CI, 0.69–0.91]). 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>202</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>203</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>204</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>205</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.
- Employment status was linked to outcomes in a study of 377 symptomatic patients with stroke from the Jikei stroke registry in Tokyo. Patients with regular employment compared with those with nonregular employment were more likely to have a hyperacute stroke on Monday in reference to Sunday (OR, 2.56 [95% CI, 1.00–6.54];  $P=0.049$ ) but were also more likely to have a favorable outcome defined as a modified Rankin Score of 0 to 2 at 3 months (OR, 2.89 [95% CI, 1.38–6.05];  $P=0.005$ ).<sup>206</sup>
- 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>207</sup>

## Genetics and Family History

- Ischemic stroke is heritable, although heritability estimates vary by ischemic stroke subtype.<sup>208</sup> A study of n=3752 patients with ischemic strokes and n=5972 controls estimated ischemic stroke heritability to be 37.9%. Estimated heritability was higher for large-vessel disease (40.3%) and lower for small-vessel disease (16.1%).
- SAH is moderately heritable. Using data from the Nordic Twin Cohort, SAH heritability was estimated at 41%.<sup>209</sup> Similarly, SAH concordance proportions by zygosity indicate a higher SAH concordance in monozygotic twins (3.1%) than dizygotic twins (0.27%).
- ICH also appears to have a genetic component, with heritability estimates of 34% to 74%, depending on the subtype.<sup>210</sup>

- Rare 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, and lactic acidosis.<sup>211</sup>
- The largest multiethnic GWAS of stroke conducted to date reported 32 genetic loci for any stroke or stroke subtypes.<sup>212</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 stroke genetic loci may be subtype specific.<sup>212</sup> For example, *EDNRA* and *LINC01492* were associated exclusively with large-artery stroke. However, shared genetic influences between stroke subtypes were also evident. For example, *SH2B3* showed shared influence on large-artery and small-vessel stroke and *ABO* on large-artery and cardioembolic stroke; *PMF1-SEMA4A* has been associated with both nonlobar ICH and ischemic stroke.
- A GWAS 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>210</sup> Other genes strongly implicated in ICH are *PMF1* and *SLC25A44*, which have been linked to ICH with small-vessel disease.<sup>213,214</sup>
- 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>215,216</sup>
- A multiethnic GWAS of SAH in 10754 cases and 306882 controls of European and East Asian ancestry identified 17 risk loci, 11 of which were not previously reported.<sup>217</sup>
- An initial GWAS of small-vessel stroke from the International Stroke Consortium (n=4203 cases and n=50728 controls) identified a novel association with a region on chromosome 16q24.2.<sup>218</sup> A follow-up study that included n=7338 cases and n=254798 controls identified 5 loci in European or transethnic meta-analysis (*ICA1L-WDR12-CARF-NBEAL1*, *ULK4*, *SPI1-SLC39A13-PSMC3-RAPSN*, *ZCCHC14*, and *ZBTB14-EPB41L3*).<sup>219</sup> By extending analyses to simultaneously consider cerebral white matter hyperintensities and small-vessel stroke, multitrait GWASs identified an additional 7 loci (*SLC25A44-PMF1-BGLAP*, *LOX-ZNF474-LOC100505841*, *FOXF2-FOXQ1*, *VTA1-GPR126*, *SH3PXD2A*, *HTRA1-ARMS2*, and *COL4A2*). Two of these loci (*COL4A2* and *HTRA1*) are implicated in monogenic forms of small-vessel stroke.
- 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>220</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>221</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.
- Genetically determined higher levels of monocyte chemoattractant protein-1/chemokine (C-C motif) ligand 2 concentrations were 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. These results implicate inflammation in stroke pathogenesis.<sup>222</sup>
- Genetic determinants of coagulation factors, including factor XI and factor VII, have been implicated in the pathogenesis of ischemic stroke.<sup>223,224</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>225</sup>
- GRSs may independently predict ischemic stroke.<sup>226</sup> In N=51288 participants (n=960 participants with an ischemic stroke), a GRS composed of 32 previously reported stroke SNPs was independently associated with ischemic stroke risk ( $P_{\text{trend}}=0.009$ ). Stroke GRS performance was stronger in patients without a prior stroke.

## 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>227</sup>
- In the 357 participants who completed the South Asian Health Awareness About Stroke program from 2014 to 2017, those  $\leq 60$  years of age had a 2.9-point greater increase in score on educational questionnaires than those  $>60$  years of age ( $P<0.0001$ ) after a culturally specific educational presentation on stroke awareness.<sup>228</sup>

- 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>229</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>230</sup>

## Stroke Mortality

(See Table 15-1 and Charts 15-3 through 15-7)

- In 2020 (unpublished NHLBI tabulations using CDC WONDER<sup>231</sup> and the NVSS<sup>232</sup>):
  - On average, every 3 minutes 17 seconds, someone died of a stroke.
  - Stroke accounted for ≈1 of every 21 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, COVID-19, and unintentional injuries/accidents.
  - The number of deaths with stroke as an underlying cause was 160 264 (Table 15-1); the age-adjusted death rate for stroke as an underlying cause of death was 38.8 per 100 000, whereas the age-adjusted rate for any mention of stroke as a cause of death was 70.9 per 100 000.
  - Approximately 67% 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 56.5% of US stroke deaths in 2020.
- Conclusions about changes in stroke death rates from 2010 to 2020 are as follows<sup>231</sup>:
  - The age-adjusted stroke death rate decreased 0.8% (from 39.1 per 100 000 to 38.8 per 100 000), whereas the actual number of stroke deaths increased 23.8% (from 129 476 to 160 264 deaths).
  - Age-adjusted stroke death rates increased 1.3% for males and decreased 2.3% for females.
  - Crude stroke death rates increased most among people 55 to 64 years of age (14.0%; from 29.3 to 33.4 per 100 000), 45 to 54 years of age (7.6%; from 13.1 to 14.1 per 100 000), 35 to 44 years of age (4.3%; from 4.6 to 4.8 per 100 000), and >85 years of age (2.4%; from 993.8 to 1017.9 per 100 000). In comparison, the crude stroke

death rates declined among those 75 to 84 years of age (−8.8%; 288.3 to 262.9 per 100 000) and 65 to 74 years of age (−0.9%; from 81.7 to 81.0 per 100 000). There was no change among those 25 to 34 years of age (1.3 per 100 000 in 2010 and 2020). Despite the improvements noted since 2010, there has been a recent flattening of or increase in death rates among all age groups (Charts 15-3 and 15-4).

- There are substantial geographic disparities in stroke mortality, with higher rates in the southeastern United States known as the Stroke Belt (2015–2017; Chart 15-5). This area is usually defined to include the 8 southern states of North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. Historically, the overall average stroke mortality has been ≈30% higher in the Stroke Belt than in the rest of the nation and ≈40% higher in the Stroke Buckle (North Carolina, South Carolina, and Georgia).<sup>233</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 15-6 and 15-7).

## Racial and Ethnic Disparities

See Charts 15-6 through 15-8



- In 2020, NH Black males and females had higher age-adjusted death rates for stroke than NH White, NH Asian, NH American Indian or Alaska Native, and Hispanic males and females in the United States (Chart 15-8).
- Age-adjusted stroke death rates declined among some racial and ethnic groups but increased in others; however, in 2020, rates remained higher among NH Black people (56.8 per 100 000; change since 2010, 4.6%) than among NH White people (37.1 per 100 000; −1.9%), NH Asian/Pacific Islander people (31.9 per 100 000; −4.5%), NH American Indian/Alaska Native people (33.7 per 100 000; −6.1%), and Hispanic people (34.9 per 100 000; 8.7%).<sup>231</sup>
- The probability of death within 1 year of a stroke was lowest in Black males 45 to 64 years of age (Chart 15-6). The probability of death within 5 years of a stroke was lowest for White males 45 to 64 years of age (Chart 15-7).
- On the basis of 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 ratio 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 ratio

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>234</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>5</sup>
- Projections of stroke mortality from 2012 to 2030 differ on the basis of the factors included in the forecasting.<sup>235</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>235</sup>

## Complications and Recovery

### (See Chart 15-9)

- Recurrent stroke is common (Chart 15-9).

### Rehabilitation and Readmission

- 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>236</sup>

### Disability

- 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>237</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 ≥3) at 12 months<sup>238</sup>: no comorbidity, 24.8%; 1 comorbidity, 34.7%; 2 to 3 comorbid conditions, 45.2%; and ≥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 to 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>239</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>240</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>241</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 ≥3 complications.<sup>242</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 ( $P_{\text{interaction}}=0.001$ ). 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>243</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>244</sup>
  - In the PROFESSIONAL Outcomes of Stroke Evaluation and Evaluation of Stroke Survival (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>245</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>246</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>247</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>248</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>249</sup>
  - Among 190 mildly 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>250</sup>
  - In CHS, among 509 participants with recovery data, those in the lowest quintiles of prestroke walking speed and grip strength had approximately twice the risk of poststroke decline in both cognition (aOR, 2.00 [95% CI, 1.18–3.39] for walking speed; aOR, 1.86 [95% CI, 1.05–3.32] for grip strength)

and activities of daily living (aOR, 2.19 [95% CI, 1.33–3.62] for walking speed; OR, 1.74 [95% CI, 1.01–3.02] for grip strength).<sup>251</sup> Inflammatory biomarkers were associated with an increased risk of poststroke cognitive decline among males (aOR, 1.48 [95% CI, 1.14–1.92] per doubling of CRP; aOR, 2.02 [95% CI, 1.28–3.20] per doubling of CRP), and frailty was associated with a 3-fold increase in risk of decline in activities of daily living among females (aOR, 3.21 [95% CI, 1.27–8.13]).

- 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>21</sup> Pretreatment (aOR, 0.91 [95% CI, 0.84–0.98]) and posttreatment (aOR, 0.70 [95% CI, 0.57–0.87]) SBP values were also inversely related to lower likelihood of 3-month functional independence.
- Among 938 patients with ischemic stroke in the Spanish Stroke-Chip study, 19 patients (2%) had acute decompensated HF, and a 3-biomarker panel including vascular adhesion protein-1 >5.67, NT-proBNP >4.98, and d-dimer >5.38 predicted this outcome with a sensitivity of 89.5% and specificity of 71.7%.<sup>252</sup> Eighty-six patients (9.1%) had respiratory tract infections, and a panel of interleukin-6 >3.97, von Willebrand factor >3.67, and d-dimer >4.58 predicted respiratory tract infection with sensitivity of 82.6% and specificity of 59.8%. The addition of the panel to clinical predictors significantly improved AUCs of the receiver-operating characteristic curves for both outcomes.

### 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>253</sup> Suicidality is also increased after stroke.<sup>254</sup>
- In a retrospective cohort study among US Medicare beneficiaries admitted for ischemic stroke from July 1, 2016, to December 31, 2017, females (n=90 474) were 20% more likely to develop poststroke depression over 1.5 years of follow-up than males (n=84 427) in adjusted models (HR, 1.20 [95% CI, 1.17–1.23]).<sup>255</sup>
- In a secondary analysis of a randomized, multicenter, placebo-controlled trial among 308 patients with spontaneous intracranial hemorrhage who completed the Center for Epidemiologic Studies Depression Scale, poststroke depression occurred in 36% of patients at 180 days.<sup>256</sup> Correlates of depression included female sex (aOR, 1.93, [95% CI, 1.07–3.48]), Hispanic ethnicity (aOR, 3.05 [95%

CI, 1.19–7.85]), intraventricular hemorrhage (aOR, 1.88 [95% CI, 1.02–3.45]), right-sided lesions (aOR, 3.00 [95% CI, 1.43–6.29]), impaired cognition at day 30 (aOR, 2.50 [95% CI, 1.13–5.54]), and not being at home at day 30 (aOR, 3.17 [95% CI, 1.05–9.57]).

- 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>257</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>258</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>259</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>260</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>261–264</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>262</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>265</sup>

- In a review of 5 articles on the role of the single nucleotide polymorphism (G/A) at nucleotide 196 in the human brain-derived neurotrophic factor (*BDNF*) gene, which produces an amino acid substitution (valine to methionine) at codon 66 (Val66Met), patients with stroke with the AA genotype had worse recovery outcomes than those with GA+GG genotypes (OR, 1.90 [95% CI, 1.17–3.10];  $P=69.2\%$ ).<sup>266</sup> Overall, the A allele may be more common in Asian patients than White patients.

### 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>263</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 an MMSE score threshold of <27 and in 61% with a Montreal Cognitive Assessment score threshold of <25.<sup>267</sup>
- In a study among 4 centers in Shanghai (N=383 patients with AIS), the prevalence of cognitive impairment (Montreal Cognitive Assessment Scale score <22) was 49.6% at 2 weeks and 34.2% at 6 months.<sup>268</sup> Age, lower level of education, higher glucose level, and severe stroke were correlates of poststroke cognitive impairment, and LDL-C level was associated with higher cognitive scores. The DREAM-LDL score had an area under the receiver-operating curve of 0.93 for predicting cognitive impairment at 6 months.
- Among 109 patients with ischemic stroke, NIHSS score ( $\beta=-0.54$  [95% CI, –0.99 to –0.89]) and preexisting leukoaraiosis 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>269</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>270</sup>

### Risk Factors

- Significant risk factors for perinatal stroke in a case-control study of 40 patients with perinatal arterial ischemic stroke matched to 80 controls found that emergency cesarean section (OR, 13.79 [95% CI, 3.51–54.13]), primiparity (OR, 11.74 [95% CI, 3.28–42.02]), birth asphyxia (OR, 40.55 [95% CI, 3.08–532.94]), and Apgar score of 7 after 5 minutes (OR, 13.75 [95% CI, 1.03–364.03]) were significantly associated with perinatal arterial ischemic stroke in multivariate analysis.<sup>271</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>272</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>273</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 study of 66 infants with perinatal hemorrhagic stroke, 66.7% were in preterm infants compared with 33.3% in term infants. Respiratory insufficiency, perinatal asphyxia, respiratory distress syndrome, neonatal sepsis, use of invasive mechanical ventilation, use of noninvasive mechanical ventilation, and prolonged hospitalization were more common in preterm infants than term infants ( $P<0.05$ ), whereas mucosal bleeding, primiparity, and multiple lobe involvement were more common in term infants ( $P<0.05$ ).<sup>274</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>275</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>276</sup> In contrast, a population-based controlled study suggested a minimal association between perinatal stroke and thrombophilia<sup>277</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>278,279</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>192</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>280</sup> The recurrence risk after perinatal stroke, however, was negligible.
- Among survivors of ICH in childhood, 13% developed delayed seizures and epilepsy within 2 years.<sup>281</sup> The cumulative risk of delayed seizures after later childhood stroke is 13% at 5 years and 30% at 10 years.<sup>282</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>283</sup>
- More than 25% of survivors of perinatal ischemic strokes develop delayed seizures within 3 years; those with larger strokes are at higher risk.<sup>284</sup> A retrospective study of data from the Alberta Perinatal Stroke Program Edmonton database compared patients with perinatal arterial ischemic stroke who developed infantile spasms (n=9) with a seizure-free control group (perinatal arterial ischemic stroke only; n=16). A greater proportion of patients with perinatal arterial ischemic stroke who developed infantile spasms had injury to deep cerebral structures (67%) than patients with perinatal arterial ischemic stroke only (25%). Infarct size was significantly associated with infantile spasm development as determined by modified pediatric ASPECTS ( $P=0.002$ ).<sup>285</sup>



- Pediatric stroke teams and stroke centers<sup>286</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>287</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>288</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>289</sup>

## Stroke in Young Adults and in Midlife

- Approximately 10% to 5% of strokes occur in individuals 18 to 45 years of age.<sup>290</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>291</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 years of age (from 37.7 to 68.2 per 10 000 hospitalizations). 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.
- Data from the Danish Stroke Registry and the Danish National Patient Registry found that the incidence rate per 100 000 person-years of ischemic stroke was steady from 2015 to 2018 in younger adults (20.8 in 2005 versus 21.9 in 2018; average annual percentage change, −0.6 [95% CI, −1.5 to 0.3]).<sup>6</sup> 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>292</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>293</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>172</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>173</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>291</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>291</sup> Among males, the prevalence of ≥3 risk factors among patients with stroke increased from 9% to 16% at 18 to 34 years of age, 19% to 35% at 35 to 44 years of age, 24% to 44% at 45 to 54 years of age, and 26% to 46% at 55 to 64 years of age. Among females, the prevalence of ≥3 risk factors among patients with stroke increased from 6% to 13% at 18 to 34 years of age, 15% to 32% at 35 to 44 years of age, 25% to 44% at 45 to 54 years of age, and 27% to 48% at 55 to 65 years of age ( $P_{trend}<0.001$ ).
- A prospective multicenter study of young adults 18 to 55 years of age in Argentina found that among 269 patients with ischemic stroke, 25.7% had no vascular risk factors, 26.3% had 1 vascular risk factor, and 48% had ≥2 vascular risk factors. Males had significantly higher sedentary, arterial hypertension, obesity, alcohol consumption, and diabetes compared with females.<sup>294</sup>

### 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>295</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>296</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>297</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>87</sup>
- The proportion of ischemic strokes attributable to AF increases with age and may reach  $\geq 40\%$  in very elderly patients with stroke.<sup>298</sup>
- Very elderly patients have a higher risk-adjusted mortality,<sup>299</sup> have greater disability,<sup>299</sup> have longer hospitalizations,<sup>300</sup> receive less evidence-based care,<sup>301,302</sup> and are less likely to be discharged to their original place of residence.<sup>300</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>303</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>304</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 by only 0.83 QALY; for patients with baseline disability, intravenous thrombolysis

yielded only an additional 0.27 QALY over endovascular thrombectomy.<sup>305</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>306</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>307</sup> A retrospective study assessed the role of noninvasive vascular imaging at referral centers in outcomes, including endovascular therapy, using data from a population-based registry in Catalonia (CICAT registry) from 2016 to 2020. Patients with vascular imaging and without vascular imaging were compared. A total of 5128 patients with ischemic stroke were admitted at referral centers: 59.8% had vascular imaging; 35.5% were transferred to a CSC; and 11.7% received endovascular therapy. Among patients with severe stroke (NIHSS score  $>16$ ) at referral centers, multivariate analysis adjusted for sex found that lower age (OR, 0.981 [95% CI, 0.971–0.992];  $P < 0.001$ ), thrombolytic treatment (OR, 1.824 [95% CI, 1.353–2.458];  $P < 0.001$ ), and vascular imaging (OR, 1.48 [95% CI, 1.12–1.96];  $P = 0.006$ ) were independent factors associated with endovascular therapy.<sup>308</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 minutes 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>309</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>310</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 2009 to 2019, the number of inpatient discharges from short-stay hospitals with stroke as the principal diagnosis decreased slightly, from 888 000 in 2009 to 931 000 in 2019 (Table 15-1).
- In 2019, there were 869 000 ED visits with stroke as the principal diagnosis (HCUP,<sup>311</sup> unpublished NHLBI tabulation), and in 2011, there were 209 000 outpatient visits with stroke as the first-listed diagnosis (NHAMCS,<sup>312</sup> unpublished NHLBI tabulation). In 2018, physician office visits for a first-listed diagnosis of stroke totaled 1 942 000 (NAMCS,<sup>313</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>314</sup>
- An analysis of the NIS 2011 to 2012 for AIS found that after risk adjustment, all underrepresented racial and ethnic groups except Native American people had a significantly higher likelihood of length of stay ≥4 days than White people.<sup>315</sup>

## Operations and Procedures

- In the HCUP 2013 to 2016 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>316</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 an analysis of NIS 2014 to 2016, among 376 956 patients with AIS, 6 230 (1.54%) underwent

endovascular thrombectomy, of whom 1 547 (24.83%) were ≥80 years of age.<sup>317</sup> The rate of endovascular thrombectomy in patients ≥80 years of age doubled from 0.83% in 2014 to 1.83% by 2016, 1 year after the publication of studies demonstrating the efficacy of endovascular thrombectomy for patients with large-vessel occlusion. The rate of discharge to home or an acute rehabilitation center was significantly lower in patients ≥80 years of age (9%) than in younger patients (26%;  $P<0.001$ ).

- In 2018, an estimated 115 000 inpatient CEA and CAS procedures were performed in the United States. CEA is the most frequently performed surgical procedure to prevent stroke (HCUP,<sup>311</sup> unpublished NHLBI tabulation).

### CEA Compared With CAS for Stroke Prevention

- 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>318</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>319</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>320</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>321</sup>

## Cost

### (See Table 15-1)

- In 2018 to 2019 (average annual; MEPS,<sup>322</sup> unpublished NHLBI tabulation):
  - The direct and indirect cost of stroke in the United States was \$56.5 billion (Table 15-1).
  - The estimated direct medical cost of stroke was \$36.5 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 \$9157.
- 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>188</sup>
- In an analysis of trends in physician reimbursement from 2000 to 2019, after adjustment for inflation, the average reimbursement for stroke (ICD160-I63) procedures decreased by an average of 0.43%/y (11.2% from 2000–2019).<sup>323</sup> The adjusted reimbursement rate for telestroke codes decreased by 12.1% from 2010 to 2019, and from 2005 to 2019, the reimbursement for alteplase rose by 163.98% (average of +7.3%/y).
- 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>324</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>324</sup>

## Global Burden of Stroke

The GBD Study 2020 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 2020).

### Prevalence

#### (See Charts 15-10 through 15-13)

In 2020 (data courtesy of the GBD 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 15-10).
- 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 the eastern United States and sub-Saharan Africa (Chart 15-11).
- 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 15-12).
- 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 15-13).

### Incidence

In 2020 (data courtesy of the GBD 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 15-14 through 15-17)

In 2020 (data courtesy of the GBD Study 2020):

- Globally, the number of deaths attributable to stroke was 7.08 million (95% UI, 6.48–7.60 million). 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 15-14).
- 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 15-15).
- Globally, the number of deaths attributable to ICH in 2020 was 3.25 million (95% UI, 2.99–3.53 million). 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 15-16).
- 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 15-17).

**COVID-19 and Stroke**

- A review by the World Stroke Organization on the global impact of the COVID-19 pandemic on stroke care found the following<sup>325</sup>.
  - Stroke occurs in ≈1.4% of patients hospitalized with COVID-19 infection with these patients showing an excess of large-vessel occlusion and increased mortality.
  - Stroke presentations fell during the pandemic with newer data suggesting that total stroke mortality may have risen with increased stroke deaths at home and in care homes.
  - Strategies/guidelines were developed to adapt stroke services worldwide and to protect health care workers. Adaptations included increasing use of telemedicine for all aspects of stroke care.
  - The pandemic exacerbated already marked global inequalities in stroke incidence and mortality.

- A retrospective observational study using data from the Italian stroke network during a period of high incidence of COVID-19 assessed whether the in-hospital rerouting and the switch from a drip-and-ship to a mothership model (direct transport of all patients with suspected stroke to the hub) could ensure an adequate volume of acute treatments. The study looked at the volume of stroke cases managed in the ED and reperfusion therapies. Data from March 2020 were compared with data from March 2019. A decrease of 28% in confirmed stroke cases managed in the ED, a negative correlation between stroke cases in ED and COVID-19 progression ( $r_s = -0.390$ ,  $P = 0.030$ ), and a similar number of treatments in March 2020 and March 2019 were found. The adoption of the mothership model did not delay alteplase infusion (median call-to-needle time,  $P = 0.126$ ; median door-to-needle time,  $P = 0.142$ ) but did lead to a significant reduction in median call-to-groin time ( $P = 0.018$ ) and door-to-groin time ( $P = 0.010$ ).<sup>326</sup>
- A retrospective review of patients with a discharge diagnosis of AIS from the GWTG database from 2 CSCs in New York was performed from January 1, 2019, to July 1, 2020, comparing the pre-COVID-19 (January/February), peak COVID-19 (March/April), and post-COVID-19 time periods.<sup>327</sup> Stroke volumes were found to be significantly lower during the peak COVID-19 period in 2020 compared with that in 2019 (absolute decline, 49.5%;  $P < 0.001$ ). Patients were more likely to present after 24 hours from last known well during the 2020 peak COVID-19 period ( $P = 0.03$ ), but there was not a significant difference in the rate of treatment with either tPA or mechanical thrombectomy during the peak COVID-19 period. Relative treatment rates increased during the 2020 post-COVID-19 period to 11.4% ( $P = 0.01$ ).<sup>327</sup>
- A cohort study of patients with COVID-19 admitted to Yale-New Haven Health between January 3, 2020, and August 28, 2020, with and without AIS and a subcohort of hospitalized patients with COVID-19 demonstrating a neurologic symptom with and without AIS was conducted. A total of 1827 patients were included (AIS, n=44; no AIS, n=1783). Among all hospitalized patients with COVID-19, history of stroke and platelet count  $>200 \times 1000/\mu\text{L}$  at hospital presentation were independent predictors of AIS (derivation AUC, 0.89; validation AUC, 0.82), regardless of COVID-19 severity. In the subcohort of patients with a neurologic symptom (n=827), the risk of AIS was significantly higher among patients with a history of stroke who were  $<60$  years of age (derivation AUC, 0.83; validation AUC, 0.81). In an ischemic stroke control cohort without COVID-19 (n=168), patients with AIS were significantly older and less likely to have had a prior stroke.<sup>328</sup>

- A systematic review looked at the clinical features and etiological characteristics of patients with ischemic stroke with COVID-19 infection. Data from 14 articles including 93 patients were assessed. Median age was 65 years (IQR, 55–75 years); 75% were male; stroke occurred after a median of 6 days from COVID-19 infection diagnosis; and patients had a median NIHSS score of 19. Cryptogenic strokes

were more frequent (51.8%), followed by cardioembolic strokes (26.5%). A significant association was observed between the etiological classification and the interval between the COVID-19 diagnosis and the cerebrovascular event ( $P_{\text{trend}}=0.039$ ). The clinical severity of stroke was significantly associated with the severity grade of COVID-19 infection ( $P_{\text{trend}}=0.03$ ).<sup>329</sup>

**Table 15-1. Stroke in the United States**

Population group	Prevalence, 2017–2020, ≥20 y of age	New and recurrent at-tacks, 1999, all ages	Mortality, 2020, all ages*	Hospital discharges, 2019, all ages	Cost, 2018–2019
Both sexes	9 400 000 (3.3% [95% CI, 2.8%–3.8%])	795 000	160 264	931 000	\$56.5 Billion
Males	4 000 000 (2.9%)	370 000 (46.5%)†	69 637 (43.5%)†	...	...
Females	5 400 000 (3.6%)	425 000 (53.5%)†	90 627 (56.5%)†	...	...
NH White males	2.7%	325 000‡	49 490	...	...
NH White females	3.6%	365 000‡	67 262	...	...
NH Black males	4.8%	45 000‡	10 276	...	...
NH Black females	5.4%	60 000‡	12 128	...	...
Hispanic males	2.5%	...	6374	...	...
Hispanic females	2.5%	...	6996	...	...
NH Asian males	1.8%	...	2981§	...	American Heart Association
NH Asian females	1.5%	...	3674§	...	...
NH American Indian or Alaska Native	...	...	848	...	...

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.

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>330</sup>

COVID-19 indicates coronavirus disease 2019; ellipses (...), data not available; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

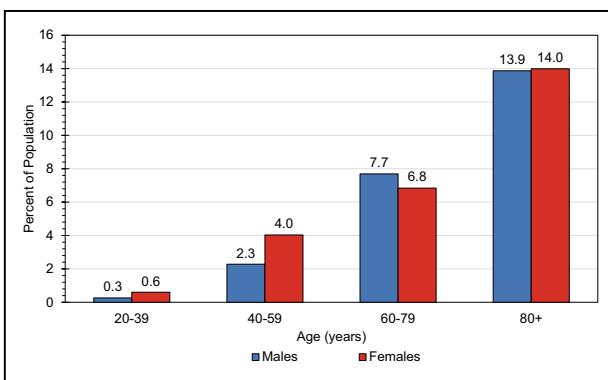
\*Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting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

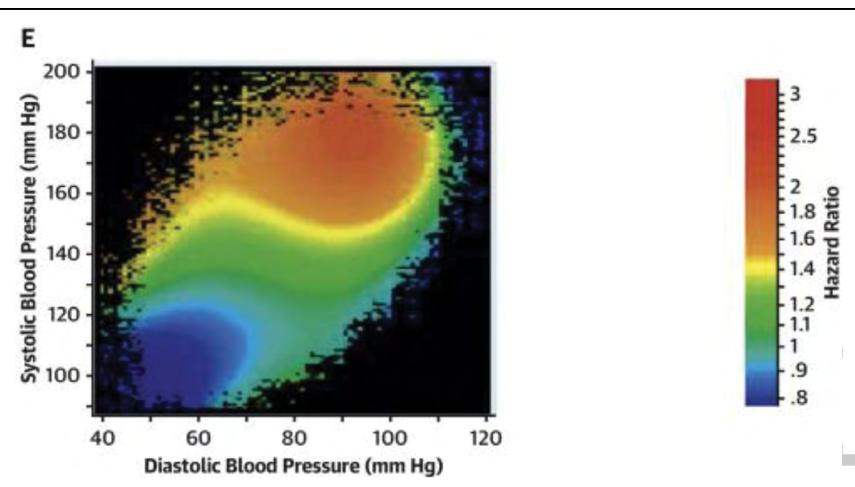
§Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander people.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES.<sup>331</sup> Percentages for racial and ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2020 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>332</sup> Data include children. Mortality (for underlying cause of stroke): Unpublished NHLBI tabulation using National Vital Statistics System.<sup>333</sup> These data represent underlying cause of death only. Mortality for NH Asian people includes Pacific Islander people. Hospital discharges (with a principal diagnosis of stroke): Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project.<sup>334</sup> Data include those inpatients discharged alive, dead, or status unknown. Cost: Unpublished NHLBI tabulation using Medical Expenditure Panel Survey.<sup>332</sup> Data include estimated direct and indirect costs for 2018 to 2019 (average annual).



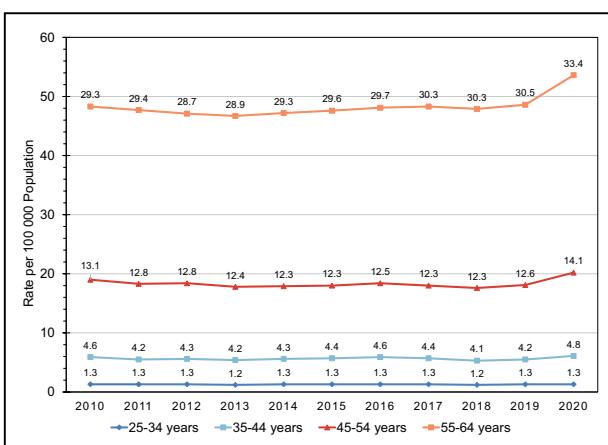
**Chart 15-1. Prevalence of stroke, by age and sex, United States (NHANES, 2017–2020).**

NHANES indicates National Health and Nutrition Examination Survey.  
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>331</sup>



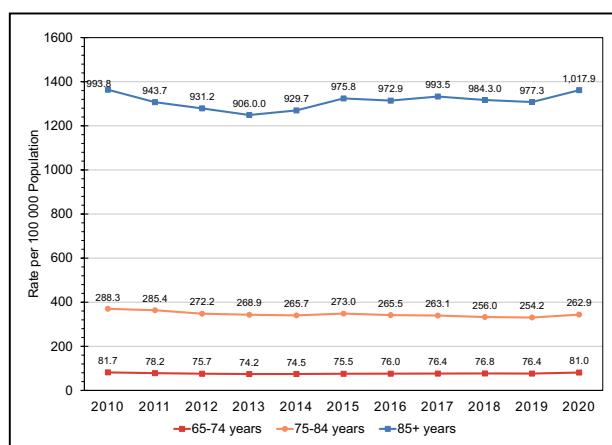
**Chart 15-2. Heat map of stroke risk at all combinations of SBP and DBP observed in ALLHAT.**

ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; DBP, diastolic blood pressure; and SBP, systolic blood pressure.  
Source: Reprinted from Itoga et al.<sup>15</sup>  
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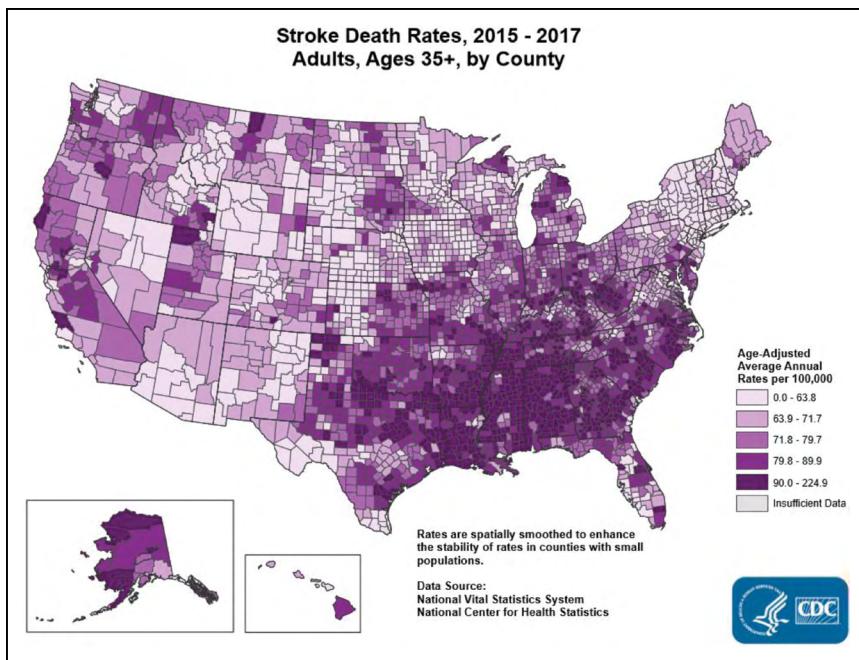
**Chart 15-3. Crude stroke mortality rates among young US adults (25–64 years of age), 2010 to 2020.**

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>231</sup>



**Chart 15-4. Crude stroke mortality rates among older US adults (>65 years of age), 2010 to 2020.**

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>231</sup>

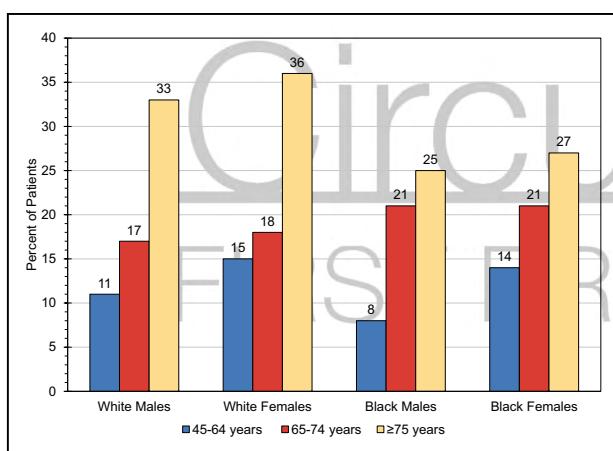


**Chart 15-5. Stroke death rates, 2015 through 2017, among adults  $\geq 35$  years of age, by US county.**

Rates are spatially smoothed to enhance the stability of rates in counties with small populations.

ICD-10 codes for stroke: I60 through I69. ICD-10 indicates International Classification of Diseases, 10th Revision.

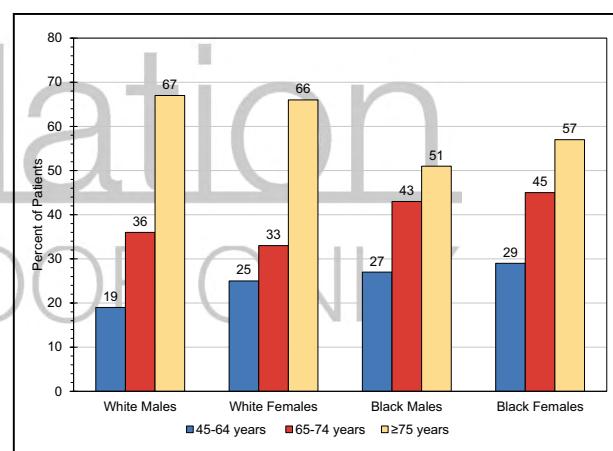
Source: Reprinted from National Vital Statistics System.<sup>333</sup>



**Chart 15-6. Probability of death within 1 year after first stroke, United States, 1995 to 2011.\***

\*Data years 1986 to 2011 for those who were 45 to 64 years of age because of the small number of events.

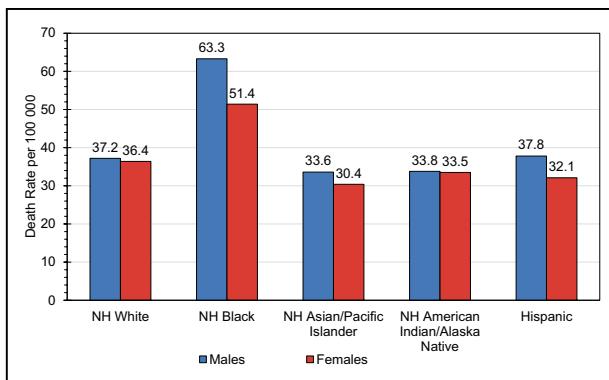
Source: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using pooled data from the Framingham Heart Study, Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis, Coronary Artery Risk Development in Young Adults, and Jackson Heart Study of the NHLBI.



**Chart 15-7. Probability of death within 5 years after first stroke, United States, 1995 to 2011.\***

\*Data years 1986 to 2011 for those who were 45 to 64 years of age because of the small number of events.

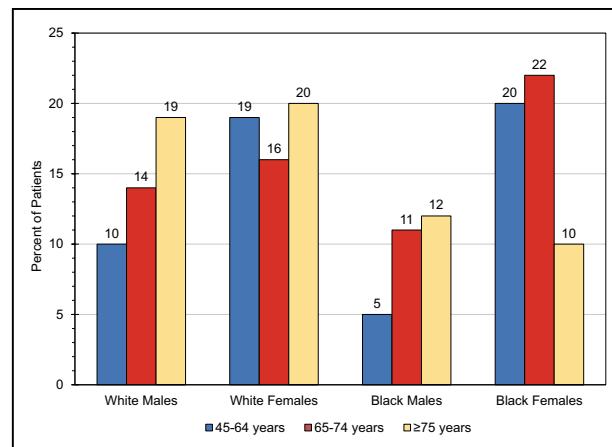
Source: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using pooled data from the Framingham Heart Study, Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis, Coronary Artery Risk Development in Young Adults, and Jackson Heart Study of the NHLBI.



**Chart 15-8. Age-adjusted death rates for stroke by sex and race and ethnicity, United States, 2020.**

Death rates for the American Indian or Alaska Native and Asian or Pacific Islander populations are known to be underestimated. Stroke includes ICD-10 codes I60 through I69 (cerebrovascular disease). Mortality for NH Asian people includes Pacific Islander people. ICD-10 indicates *International Classification of Diseases, 10th Revision*; and NH, non-Hispanic.

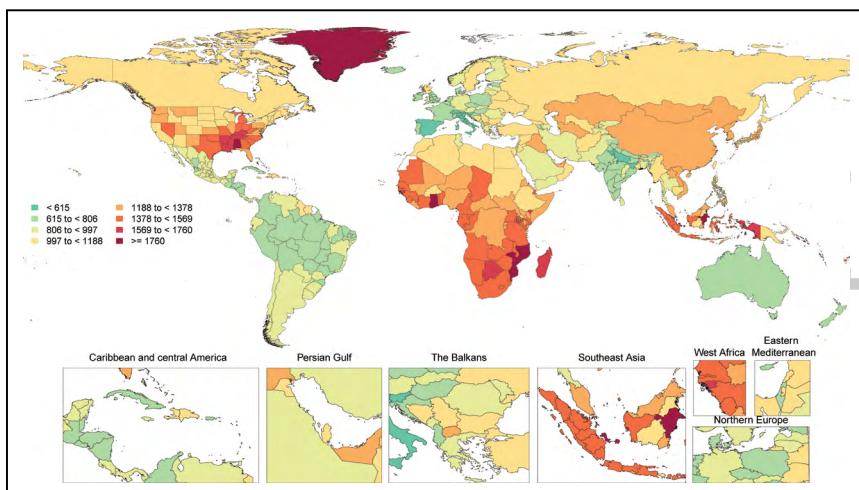
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>231</sup>



**Chart 15-9. 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.

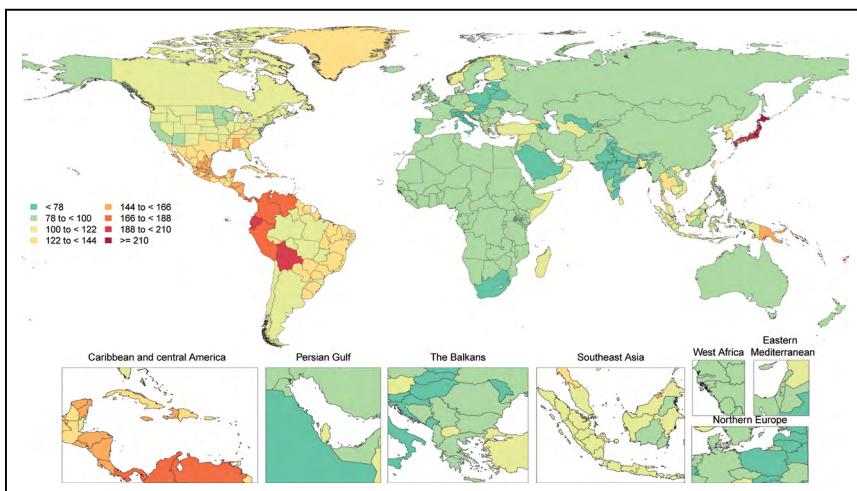
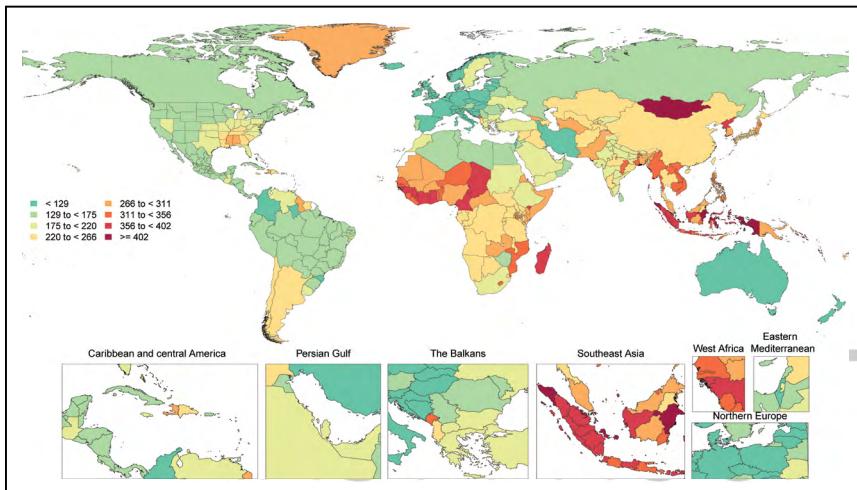
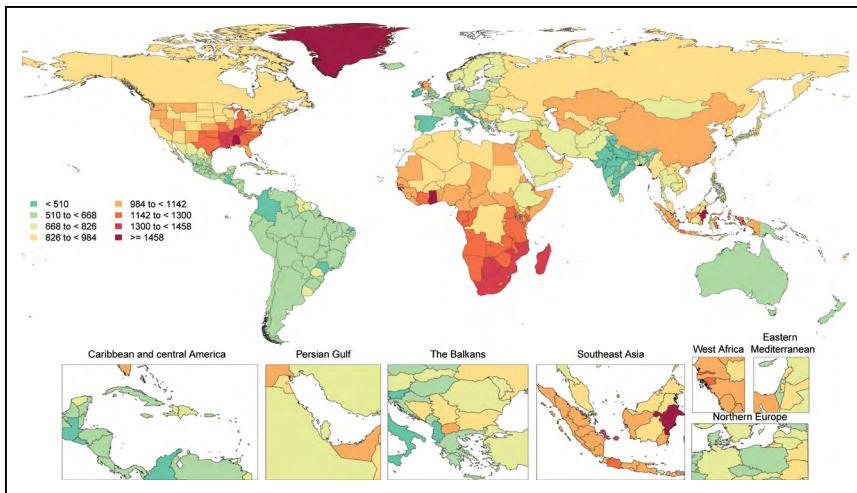
Source: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using pooled data from the Framingham Heart Study, Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis, Coronary Artery Risk Development in Young Adults, and Jackson Heart Study of the NHLBI.

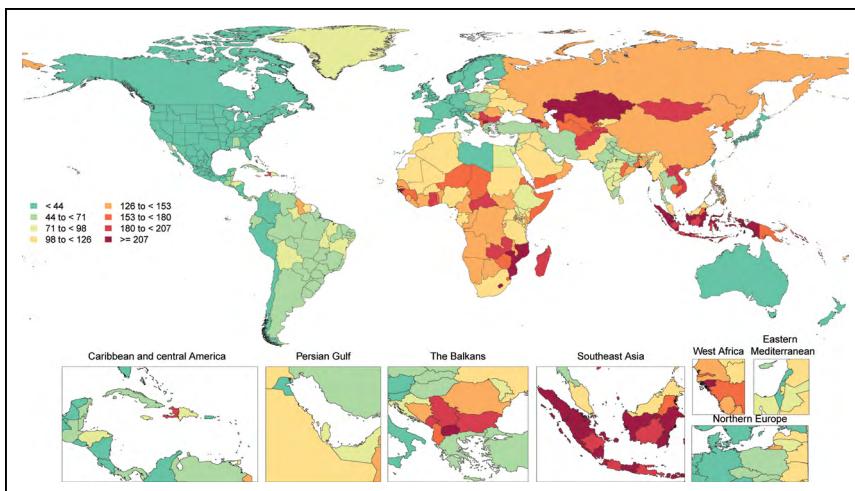


**Chart 15-10. Age-standardized global prevalence rates of total stroke (all subtypes) per 100,000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease. Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>334</sup>



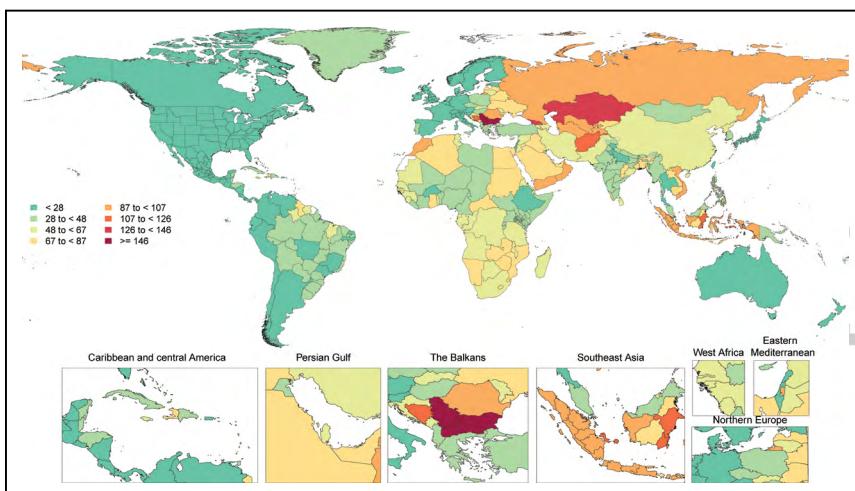


**Chart 15-14. Age-standardized global mortality rates of total stroke (all subtypes) per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>334</sup>

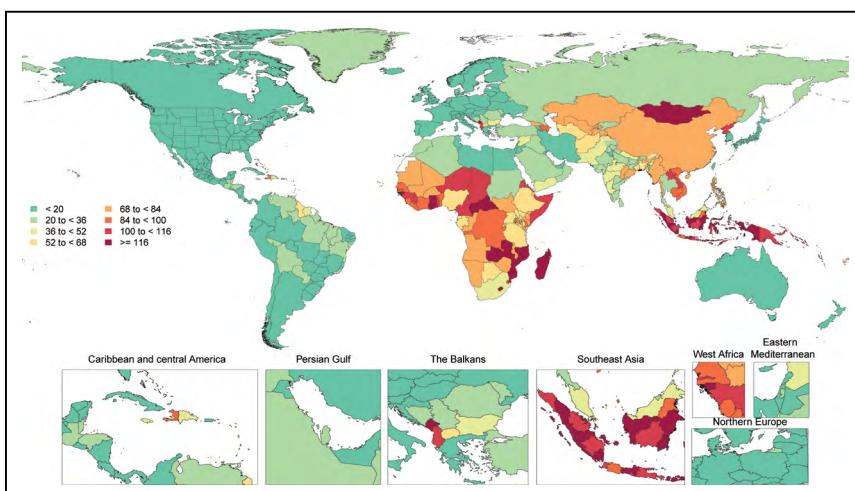


**Chart 15-15. Age-standardized global mortality rates of ischemic stroke per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>334</sup>

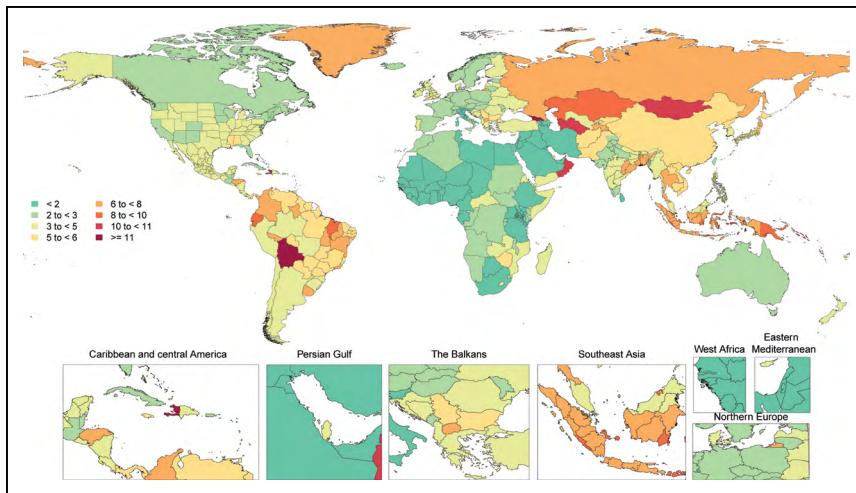


**Chart 15-16. Age-standardized global mortality rates of ICH per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and ICH; intracerebral hemorrhage.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>334</sup>



**Chart 15-17. Age-standardized global mortality rates of SAH per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and SAH, subarachnoid hemorrhage.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>334</sup>

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## 16. BRAIN HEALTH

**ICD-9 290, 291.2, 291.8, 294, 331; ICD-10 F00–F03, G30–G31.**

**See Tables 16-1 through 16-3 and Charts 16-1 and 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 AD, made when patients are alive, are wrong.<sup>2</sup> Vascular dementia prevalence and incidence are likely underestimated because most dementia cases have multiple pathologies and vascular disease is common.<sup>3,4</sup> The list of *ICD* codes at the beginning of this chapter matches the list of codes for dementia used in the GBD Study, which encompasses all common types of dementia.<sup>5</sup> ADRD refers to AD-related dementias, which are conditions that overlap with and are difficult to distinguish from AD, including vascular contributions to cognitive impairment and dementia, frontotemporal degeneration, Lewy body dementia, and dementias of multiple causes.<sup>6</sup>

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

### Prevalence

#### Dementia

- The estimated prevalence of dementia in US adults ≥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>7</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 ≥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>8</sup>
- A systematic analysis of data from the GBD Study showed that AD/ADRD was the fourth most prevalent neurological disorder in the United States in 2017, affecting 2.9 million people (95% UI, 2.6–3.2 million).<sup>9</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.
- According to administrative claims data of US Medicare fee-for-service beneficiaries ≥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>10</sup> AD/ADRD prevalence increased with age (65–74 years of age, 3.6%; 75–84 years of age, 13.6%; and ≥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.

#### Alzheimer Disease

- Results of a multistate model using biomarker data and US population predictions show that ≈3.7 million Americans ≥30 years of age had clinical AD in 2017, and this number is projected to increase to 9.3 million by 2060.<sup>11</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 according to updated data from 1078 consecutive deceased individuals with autopsy (mean age at death, 89 years; 32% male) from the ROS and the MAP.<sup>4</sup>

#### Vascular Dementia

- More than 80% of those with probable AD had vascular pathology (defined as microinfarcts, moderate to severe atherosclerosis, arteriolosclerosis,

and cerebral amyloid angiopathy), and merely 4.9% of those with probable AD had vascular pathology only according to data from the ROS and the MAP.<sup>4</sup>

## Incidence

### Dementia

- In 2017, AD/ADRD had the fifth leading incidence rate of neurological disorders in the United States according to GBD Study data.<sup>9</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>8</sup>
- Among 3605 members of Group Health (Seattle, WA) ≥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>12</sup> Among individuals ≥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.

### Alzheimer Disease

- Among 2794 individuals from CHAP, the annual incidence of clinically diagnosed AD was 3.6% (95% CI, 3.3%–3.9%).<sup>13</sup> Black individuals had a higher annual incidence of clinically diagnosed AD (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 increased with age in Black and White individuals.

### Vascular Dementia

- Estimates of vascular dementia incidence in the United States are lacking.
- Data from the nationally representative MHAS 2012 and 2015 waves found that the age- and sex-standardized incidence of vascular dementia among individuals ≥50 years of age in Mexico was 2.0 (95% CI, 1.3–2.7) per 1000 person-years.<sup>14</sup>

## Lifetime Risk and Cumulative Incidence

### Dementia

- In a population-based Japanese cohort of individuals ≥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>15</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>16</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 ≈24.0%, higher for females (29.4%) than males (18.3%).<sup>17</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>18</sup>
- In a population-based Japanese cohort of individuals ≥60 years of age, the lifetime risk of AD was ≈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>15</sup>

### Vascular Dementia

- In a population-based Japanese cohort of individuals ≥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>15</sup>

## Secular Trends

### Dementia

- According to an analysis of 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>9</sup>
- Between 1990 and 2019, the GBD Study estimated a significant increase in age-standardized

- mortality rates from dementia for males of 5.1% (95% CI, 0.4%–12.0%) and a nonsignificant increase for females of 3.0% (95% CI, –2.6% to 11.0%).<sup>19</sup> The all-age mortality rate from dementia increased 100.1% (95% CI, 89.1%–117.5%).
- The GBD Study estimated secular trends from 1990 to 2017 in dementia prevalence, incidence, DALYs, and mortality, globally and for high-income countries.<sup>20</sup> Globally, prevalent cases increased by 119% (95% UI, 115%–123%), annual incident cases increased by 113% (95% UI, 109%–118%), DALYs increased by 115% (95% UI, 109%–120%), and annual deaths increased by 146% (95% UI, 140%–151%). However, global age-standardized prevalence decreased by 4% (95% UI, 4%–5%), age-standardized annual incidence decreased by 5% (95% UI, 5%–6%), age-standardized DALYs decreased by 6% (95% UI, 4%–8%), and age-standardized annual mortality decreased by 4% (95% UI, 2%–6%). For high-income countries, percent increases in absolute burden measures were smaller than globally: Prevalent cases increased by 93% (95% UI, 87%–99%), annual incident cases increased by 87% (95% UI, 81%–94%), DALYs increased by 90% (95% UI, 86%–94%), and annual deaths increased by 126% (95% UI, 122%–130%). The age-standardized prevalence in high-income countries decreased by 5% (95% UI, 4%–7%), age-standardized annual incidence rate decreased by 6% (95% UI, 4%–7%), age-standardized DALYs decreased by 7% (95% UI, 6%–9%), and age-standardized annual mortality rate decreased by 4% (95% UI, 3%–6%).
  - A forecasting analysis based on the GBD Study 2019 projected stable age-standardized prevalence but an increase in the number of people living with dementia from 2019 to 2050, attributed largely to population growth and aging.<sup>21</sup> More females were estimated to be living with dementia in 2019 and 2050 compared with males.
  - 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>22</sup>
  - Incidence of 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>23</sup>
  - An analysis of Medicare data estimates that the AD/ADRD prevalence in the US population will

increase to 3.3% and affect 13.9 million Americans by 2060.<sup>10</sup>

- 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>24</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]).
- In a cohort study of older adults  $\geq 65$  years of age, from 2005 to 2018, the incidence of dementia declined 22.5% in males and 34.2% in females.<sup>25</sup> The decline in incidence was seen across subgroups defined by sex, age or birth cohort, educational attainment, and household wealth.
- An analysis of 7 population-based cohort studies in the United States and Europe demonstrated that for individuals  $> 65$  years of age, the incidence of all-cause dementia declined by 13% per calendar decade since 1998 (95% CI, 7%–19%) with a more pronounced reduction in males (24% [95% CI, 14%–32%]) than in females (8% [95% CI, 0%–15%]).<sup>26</sup>
- A meta-analysis of 53 cohorts demonstrated a decrease in dementia incidence across 3 older age groups (65–74, 75–84, and  $\geq 85$  years of age).<sup>27</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 those 75–84 years of age; and OR, 0.72 [95% CI, 0.58–0.90] for individuals  $\geq 85$  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>28</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>29</sup> The reduction in incidence was greatest among NH White participants and Black participants and lowest among Hispanic participants.

## Alzheimer Disease

- For FHS participants ≥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>30</sup>
- In an analysis of 7 population-based cohorts in the United States and Europe from the Alzheimer Cohort Consortium, among individuals >65 years of age, the incidence of clinical AD declined by 16% per calendar decade since 1998 (95% CI, 8%–24%).<sup>26</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 ≥85 years of age).<sup>27</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.
- A population-based cross-sectional study of US data from the WHO Mortality Database showed that age-adjusted mortality for AD increased by 1.2-fold from 2007 to 2016 (from 244.3 per 1 000 000 individuals in 2007 to 301.1 per 1 000 000 individuals in 2016).<sup>31</sup> In contrast, age-adjusted stroke mortality decreased by 21.6% during the same time period (from 358.4 per 1 000 000 in 2007 to 281.2 per 1 000 000 in 2016).

## Vascular Dementia

- For FHS participants ≥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>30</sup>
- Based on a population-based cross-sectional study of US data from the WHO Mortality Database, age-adjusted mortality for vascular dementia increased by 2-fold from 2007 to 2016 (from 19.2 per 1 000 000 individuals in 2007 to 38.5 per 1 000 000 individuals in 2016).<sup>31</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>32</sup>
- In the Whitehall II cohort study (N=8639; 33% females), elevated BP, defined as SBP≥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>33</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>34</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>35</sup>
- In a meta-analysis of 8 studies including between 1000 and 8000 participants, depending on cognitive domain, arterial hypertension was cross-sectionally associated with poorer performance on measures of processing speed (standardized mean difference, 0.40 [95% CI, 0.25–0.54]), working memory (0.28 [95% CI, 0.15–0.41]), short-term memory and learning (−0.27 [95% CI, −0.37 to −0.17]), and delayed recall (−0.20 [95% CI, −0.35 to −0.05]).<sup>36</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>34,37,38</sup> Among 17 286 older adults (mean age, 74.5 years) in 7 pooled cohorts in Europe and the United States with 2799 incident dementia cases over a median of 7.3 years of follow-up, SBP at baseline had a U-shaped association with dementia risk, and the lowest dementia

- risk was observed at SBP of 185 mmHg (95% CI, 161–230).<sup>39</sup> The U-shaped relationship was more prominent in the oldest age groups, with lowest-risk SBP of 170 mmHg (95% CI, 160–260) at 75 to 85 years of age and lowest-risk SBP of 162 mmHg (95% CI, 153–240) at 85 to 95 years of age.
- 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 ( $\beta=-0.033 \text{ cm}^3$  [95% CI, -0.062 to -0.003];  $P=0.03$ ).<sup>40</sup>
  - Among 3319 older adults in the SAGES 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:  $\beta=-0.12$  [SE, 0.06], -0.20 [SE, 0.06], and -0.20 [SE, 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>41</sup> Among 12298 adults in HRS and ELSA who were dementia-free at baseline, each 10% increment in coefficient of variation of visit-to-visit SBP variability was associated with 0.026-SD/y faster (95% CI, 0.016–0.036) global cognitive decline and each 10% increment in DBP variability with 0.022-SD/y faster (95% CI, 0.017–0.027) global cognitive decline.<sup>42</sup> Among 19114 participants in the ASPREE trial, males in the highest SBP variability tertile versus the lowest had higher incidence of dementia (HR, 1.68 [95% CI, 1.19–2.39]), but females in the highest tertile did not (HR, 1.01 [95% CI, 0.98–1.32]).<sup>43</sup> Among 13284 adults  $\geq 50$  years of age in the National Alzheimer's Coordinating Center study who were dementia-free at baseline, those in the highest quintile of visit-to-visit SBP variability had 2.64 times the odds (95% CI, 2.29–3.04) of conversion from normal cognition to cognitive impairment or dementia.<sup>44</sup>
  - Among 8493 older adults (mean age, 80.6 years) in the Chinese Longitudinal Healthy Longevity Survey, those whose SBP increased from 130 to 150 mmHg at baseline to  $>150$  mmHg at follow-up had 48% higher odds (95% CI, 13%–93%) of incident cognitive impairment and those whose SBP decreased from 130 to 150 mmHg at baseline to  $<130$  mmHg at follow-up had 28% higher odds (95% CI, 2%–61%) of incident cognitive impairment compared with those who maintained stable SBP from 130 to 150 mmHg.<sup>45</sup>
  - 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>46</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 SBP or  $\geq 7$  mmHg in DBP 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 results from 4 other studies of orthostatic hypotension, with a pooled risk ratio of dementia of 1.21 (95% CI, 1.09–1.35).<sup>47</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>48</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>49</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>50</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 MMSE than those without HF (10.2 points [95% CI, 8.6–11.8] versus 5.8 points [95% CI, 5.3–6.2]).<sup>51</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>52</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>53</sup> Among 25 980 adults in REGARDS, those with AF at baseline declined in mean word list learning score over 10 years of follow-up (decline in mean score from 16.3 [SD, 0.15] to 16.0 [SD, 0.23]), whereas those without AF at baseline increased in mean word list learning score (increase in mean score from 16.3 [SD, 0.05] to 16.9 [SD, 0.06];  $P=0.03$  for AF vs no AF); however, there were no significant differences in trajectories of semantic fluency, word list delayed recall, or Montreal Cognitive Assessment score.<sup>54</sup> In a meta-analysis of 18 studies including 3.5 million participants with >900 000 cases of incident dementia, AF was associated with 41% higher (28%–54%) hazard of dementia ( $P=94\%$  indicating high heterogeneity, although 15 of 18 study-specific HRs fell between 1.10 and 2.00).<sup>55</sup>

- Evidence for the possible benefits of anticoagulant therapy to mitigate this risk relationship is conflicting, with some studies reporting benefits and others not.<sup>56,57</sup> In 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 non-users with AF.<sup>56</sup> In a meta-analysis of 9 studies including 613 920 patients with AF, anticoagulant treatment was associated with 28% lower (14%–40% lower) risk of dementia compared with no treatment, albeit with high heterogeneity of study-specific findings ( $P=97\%$ ).<sup>58</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>57</sup>
- Among 39 200 new users of oral anticoagulants in the General Practice Research Database in the United Kingdom with 1258 cases of incident dementia, treatment with DOACs was associated with 16% lower hazard of dementia (95% CI, 2%–27% lower) and 26% lower hazard of MCI (95% CI, 16%–35% lower) than treatment with vitamin K antagonists.<sup>59</sup> Among 53 236 new users of oral anticoagulants in the Korean National Health Insurance Service database identified in 2013 to 2016 with 2194 cases of incident dementia through the end of 2016, treatment with DOACs was associated with 22% lower

hazard (95% CI, 10%–31% lower) of dementia than treatment with warfarin.<sup>60</sup> However, in another analysis among 72 846 new users of oral anticoagulants in the Korean National Health Insurance Service database identified in 2014 to 2017 with 4437 cases of incident dementia through the end of 2018, treatment with DOACs versus warfarin was not associated with dementia risk (HR, 0.99 [95% CI, 0.93–1.06]).<sup>61</sup> Among 12 068 patients with AF in the Taiwan National Health Insurance Research database, treatment with DOACs was associated with 18% lower hazard (8%–27% lower) of dementia than treatment with warfarin.<sup>62</sup> Last, in a meta-analysis of 9 studies including 611 069 participants, treatment with DOACs was associated with 44% lower odds (85% CI, 6%–66% lower) of incident dementia than treatment with warfarin.<sup>63</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>64</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>65–67</sup>
- In MESA (N=4999; mean age, 61 years; 47% males; 26% Black, 22% Hispanic, 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>66</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>68,69</sup>
- Heart rate variability in CARDIA (N=2118; mean age, 45 years; 42% Black individuals; 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>70</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 102174 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>71</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. Among 63117 postmenopausal females in the WHI observational study in the United States with 8340 cases of incident AD over a median follow-up of 20 years, diabetes was associated with 22% higher hazard (95% CI, 13%–31% higher) of AD. Incidence of AD was 8.5 cases per 1000 person-years (95% CI, 8.0–9.0) for females who had diabetes versus 7.1 cases per 1000 person-years (95% CI, 6.9–7.2) for females without diabetes.<sup>72</sup>

- In a mendelian randomization study of 115875 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>73</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>34,74,75</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>76</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>77</sup> In a meta-analysis of 9 studies of older adults treated with glucose-lowering drugs, experiencing hypoglycemic episodes was associated with 50% higher odds (95% CI, 29%–74% higher) of dementia.<sup>78</sup>
- Investigators have observed associations between lower fasting insulin and risk of dementia. In the PPSW (N=1212 females without diabetes; 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>79</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>80</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>81</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·min<sup>−1</sup>·1.73 m<sup>−2</sup>.<sup>82</sup>
- Among 10567 older adults undergoing hemodialysis with 1302 cases of incident dementia over a median follow-up of 3.8 years, patients in the highest quartile of dialysis adequacy had 31% lower hazard of dementia (HR, 0.69 [95% CI, 0.58–0.82]) and 31% lower hazard of AD (HR, 0.69 [95% CI, 0.57–0.84]) than patients in the lowest quartile of dialysis adequacy.<sup>83</sup>

### 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>84</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 in processing speed and executive function.<sup>85</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>86</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>87</sup> In a systematic review of 34 studies, of which 30 were cross-sectional and 4 were prospective, obesity was associated with lower gray matter volume or cortical thickness in most studies; no quantitative meta-analysis was conducted because of the heterogeneity of obesity measures (BMI, WC, waist-to-hip ratio, plasma leptin levels) and of brain MRI measures used in the included studies.<sup>88</sup>

- The evidence for obesity and BMI in late life is less clear,<sup>89</sup> with some studies suggesting that obesity is protective or that weight loss may be a prodrome of late-life dementia.<sup>90,91</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>90</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 10–20 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>92</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>93</sup>

### SDB/Sleep Apnea

- In a meta-analysis of 18 longitudinal studies (N=246 786 participants), SDB was associated with all-cause dementia (pooled RR,  $1.18$  [95% CI,  $1.02$ – $1.36$ ]), 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>94</sup>
- In another 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>95</sup>

- 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>96</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 associated with greater amyloid burden in addition to greater gray matter volume, perfusion, and metabolism in the cingulate cortex and precuneus.<sup>97</sup>
- Sleep apnea was 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>98</sup> and with brain WMH, most notably periventricular frontal and dorsal WMH volumes (N=529 participants; age, 52 years; 53% females).<sup>99</sup>
- In a retrospective study of Medicare beneficiaries with OSA (N=53 321, adults  $\geq 65$  years of age; 41% females), the odds of incident AD and dementia not otherwise specified over 3 years<sup>100</sup> were lower among older adults prescribed treatment for positive airway pressure therapy (OR,  $0.65$  [95% CI,  $0.56$ – $0.76$ ] and OR,  $0.69$  [95% CI,  $0.5$ – $0.85$ ]).<sup>100</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>101–103</sup>
- 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>102</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>101</sup>

- Among 2993 participants in the Framingham Offspring Study, those exposed to >1 pack/d of secondhand smoke during the first 18 years of life had 2.86 times the risk of dementia (HR, 2.86 [95% CI, 1.00–4.09]) and 3.13 times the risk of AD (HR, 3.13 [95% CI, 1.80–5.42]) compared with those with no exposure to second-hand smoke.<sup>104</sup>

### **Cardiovascular Risk Factor Burden**

(See Table 16-1)

- The AHA's ideal CVH metrics are associated with reduced cognitive decline. Among 1033 participants in NOMAS (mean age at initial cognitive assessment, 72±8 years; 39% male; 65% Hispanic, 19% Black, and 16% White individuals), 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>105</sup> Having more ideal CVH factors was associated with less decline on 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>106</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>107</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>108</sup>
- Among 229 976 participants in the UK Biobank with 2143 cases of incident dementia over a median follow-up of 9 years, each 1-point increment in Life's Simple 7 score was associated with 11% lower hazard of dementia (HR, 0.89 [95% CI, 0.88–0.91]).<sup>109</sup> Each 1-point increment in the biological component score (based on BP, cholesterol, and glucose) was associated with 7% lower hazard of dementia (HR, 0.93 [95% CI, 0.89–0.96]). However, a 1-point increment in the lifestyle component score (based on smoking, BMI, diet, and PA) was not associated with dementia (HR, 0.99 [95% CI, 0.96–1.02]).

- Conversely, greater cardiovascular risk factor burden is associated with increased risk of cognitive decline and dementia.<sup>110,111</sup>
- In CARDIA,<sup>110</sup> Framingham 10-Year Coronary Heart Disease Risk Score ≥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>112</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>113</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 participants), 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>114</sup> The association between vascular risk score and markers of brain health was strongest in early adulthood compared with midlife and late life.
- In the HRS, cognitive impairment-free life expectancy at 55 years of age was estimated as 23.0 years (95% CI, 22.6–23.4) for participants with no hypertension, HD, diabetes, or stroke; 21.2 years (95% CI, 20.9–21.5) for those with any 1 of those conditions; 18.1 years (95% CI, 17.7–18.4) for those with any 2 conditions; and 14.0 years (95% CI, 13.5–14.5) for those with any 3 or all 4 conditions.<sup>115</sup> The association of CVD burden with lower cognitive impairment-free life expectancy was also observed at 65, 75, and 85 years of age with lower absolute life expectancies (Table 16-1).

### **Social Determinants of Health**

#### **Race and Ethnicity**

- A retrospective analysis of the BRFSS 2016 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>116</sup> Compared with White adults, adults from racial and ethnic underrepresented groups 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 Hispanic/Latino individuals 45 to 74 years of age from HCHS/SOL examined the association between cognition and BP measures.<sup>117</sup> In age-, sex-, and education-adjusted models, investigators 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>118</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.
- 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 SBP, suggesting that Black individuals' higher cumulative BP levels might contribute to racial disparities in cognitive decline.<sup>119</sup>

### **Education**

- A meta-analysis looked at factors predicting reversion from MCI to normal cognition.<sup>120</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 factors positively predicted reversion, including 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>121</sup> Professional/university education was also associated with lower dementia risk (HR, 0.74 [95% CI, 0.60–0.91]).
- PARs for established potentially modifiable risk factors for dementia among different groups were calculated using data from the SADHS 2016 study. The risk factor contributing the greatest PAR was low education (weighted PAR, 12% [95% CI, 7%–18%]). The PAR for low education differed by wealth strata but not sex (*P* for interaction with sex=0.1880, *P* for interaction with wealth <0.0000).<sup>122</sup>

### **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>123</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>121</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/Rural-Urban**

- 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>124</sup> These results suggest that early-life behavioral and other

patterning may influence late-life development of dementia.

- In a US nationwide ecological study of Medicare beneficiaries from 2008 to 2015, county-level annual prevalence of AD/ADRД was ≈0.5 to 1.0 cases per 100 population lower in rural counties than in urban counties, whereas county-level annual incidence of AD/ADRД was ≈0.4 new cases per 100 population higher in rural counties than in urban counties, adjusted for county-level demographic and health care factors.<sup>125</sup>

## Risk Prediction

### Polygenic Risk Scores

- According to genetic data from 60 801 cases of CAD and 17 008 cases of LOAD, each increment in PRS for CAD was associated with 7% higher odds of LOAD (95% CI, 1%–15%).<sup>126</sup> This association was no longer present after removal of the *APOE* locus from the PRS.
- All-cause dementia GRSs have been used to examine whether lifestyle factors can offset high dementia genetic risk.<sup>127</sup> In a study of N=196 383 participants, although a healthy lifestyle was associated with lower risk of incident dementia among participants with low or high genetic risk, no significant interaction between dementia genetic risk and lifestyle factors on incident dementia was detected ( $P=0.99$ ).

### Risk Scores That Emphasize Vascular Risk Factors

- Among 60 patients with vascular dementia and 70 control patients at a single center in China, the Framingham 10-Year Coronary Heart Disease 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>128</sup> The combination of white matter lesions and Framingham 10-Year Coronary Heart Disease 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 versus low LIBRA score in midlife, 2.36 [95% CI, 1.53–3.64]; HR for high versus low LIBRA score 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>129</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>130</sup>

- Among 34 083 female and 39 998 male patients with AF with no history of dementia, CHADS<sub>2</sub>-VASc scores ≥3 (versus ≤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>131</sup>

## Subclinical/Unrecognized Disease

- Among 896 people in 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 1 SD of MRI score, 1.68 [95% CI, 1.44–1.96]).<sup>132</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]; aHR, 1.35 [95% CI, 1.00–1.82]).<sup>133</sup>
- Among 152 patients diagnosed with MCI and cerebral small vessel disease, 41 (27%) had ≥1 cerebral microbleeds.<sup>134</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 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 MMSE (standardized mean difference,  $-0.47$  [95% CI,  $-0.72$  to  $-0.22$ ]).<sup>135</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 after adjustment 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>136</sup>

- In 113 people who were imaged at baseline and a follow-up 3 to 5 years later, people with idiopathic normal pressure hydrocephalus at follow-up had more WMHs and, despite being asymptomatic, had evidence of subclinical cognitive decline and worse executive function, memory, and Trail-Making Test B scores.<sup>137</sup>

## Genetics and Family History

- AD is highly heritable with a complex genetic cause. According to data from 11 884 twin pairs >65 years of age from the Swedish Twin Registry, AD heritability was estimated to range from 58% to 79%.<sup>138</sup>
- Rare forms of early-onset autosomal dominant AD may reflect highly penetrant mutations in *APP*, *PSEN1*, or *PSEN2*.<sup>139</sup>
- Cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy and familial cerebral amyloid angiopathy are 2 rare, highly heritable forms of vascular dementia that show autosomal dominant inheritance patterns.<sup>140,141</sup> Missense mutations in *NOTCH3* are largely responsible for cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy, whereas mutations in *APP*, *CST3*, or *ITM2B* underlie familial cerebral amyloid angiopathy.
- The heritability of sporadic vascular dementia is estimated to be very low (<1%).<sup>142</sup>

## APOE

- The *APOE* ε4 allele is an established AD genetic risk factor, lowering age at onset and increasing AD lifetime risk in a dose-dependent manner.<sup>143</sup>
- The *APOE* ε4 allele also is associated with vascular dementia risk.<sup>144</sup> Among 549 cases of vascular dementia and 552 controls without dementia in Europe, having ≥1 *APOE* ε4 alleles was associated with 1.85 times the odds of vascular dementia (95% CI, 1.35–2.52), and having ≥1 *APOE* ε2 alleles was associated with 0.67 times the odds of vascular dementia (95% CI, 0.46–0.98).
- The frequency of the *APOE* ε4 allele shows marked variation (range, 3%–49%) across diverse ancestral populations.<sup>145</sup>
- Among 8263 Latino people in the United States, prevalence of ≥1 *APOE* ε4 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>146</sup> Prevalence of ≥1 *APOE* ε2 alleles (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%]).

## Other Dementia Loci

- To date, the largest GWAS of clinically diagnosed AD was performed by the International Genomics of Alzheimer's Project Consortium.<sup>147</sup> With a final n=35 274 cases and n=59 163 controls, this study identified 25 AD loci, 5 of which were novel. Pathway analyses implicated tau binding proteins and amyloid precursor protein metabolism in LOAD, suggesting a shared genetic architecture with early-onset autosomal dominant AD.
- Although not examining clinically diagnosed AD, other GWASs have examined AD proxy traits. As an example, a GWAS of 116 196 UK Biobank participants compared participants who reported having a parent with AD (proxy cases) with control subjects who reported having no parent with AD.<sup>148</sup> These findings also were meta-analyzed with published GWASs. When analyzed alone, this study replicated previous associations with *APOE*. When pooled with published GWASs, this study identified 4 novel loci ( $P<5\times 10^{-8}$ ) on chromosomes 5 (near *HBEFGF*), 10 (near *ECHDC3*), 15 (near *SPPL2A*), and 17 (near *SCIMP*).
- In total, AD GWASs have mapped 40 AD susceptibility loci, which harbor 89 unique lead variants.<sup>149</sup> Twenty-four of these loci have been replicated at genome-wide significance, and functional genomics studies suggest *APOE*, *CR1*, *BIN1*, *TREM2*, *CLU*, *SORL1*, *ADAM10*, *ABCA7*, *CD33*, *SPI1*, and *PILRA* as the most likely causal genes.

## Prevention

### Exercise

- 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 ≥1 *APOE* ε4 alleles.<sup>150</sup>
- Meta-analyses examining RCTs indicate that PA interventions benefit cognition in both AD (7 RCTs; N=501; improvement on MMSE, 0.458

[95% CI, 0.097–0.819]) and MCI (15 RCTs; N=1156; improvement on MMSE, 0.631 [95% CI, 0.244–1.018]).<sup>151</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 individuals), targeting an SBP <120 mmHg compared with targeting an SBP <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>152</sup> A secondary analysis from SPRINT suggests that antihypertensive treatment regimens that stimulate angiotensin II receptors were associated with reduced risk of cognitive impairment compared with angiotensin inhibitor-only regimens.<sup>153</sup>
- A post hoc analysis from the PreDIVA trial (54% women; mean age, 74.5 years) also found that angiotensin II-stimulating antihypertensive medications were significantly associated with reduced risk of dementia (HR, 0.86 [95% CI, 0.64–1.16]) compared with angiotensin II-inhibiting medications.<sup>154</sup>
- In a systematic review of 15 prospective cohort studies and 7 randomized control trials (N=649 790), treatment with antihypertensive medication, especially calcium channel blockers and angiotensin II receptor blockers, was associated with a reduced risk of incident dementia.<sup>155</sup>
- In a randomized clinical trial of older adults with MCI and hypertension (N=176; mean age, 66 years; 57% women; 64% Black individuals), participants treated with candesartan over 1 year had better outcomes on executive function ( $-0.03$  [95% CI,  $-0.08$  to  $0.03$ ]) compared with those treated with lisinopril.<sup>156</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>157</sup>
- A 2021 Cochrane review of hypertension treatment in adults without prior cerebrovascular disease reported low-certainty evidence for a small benefit in cognition (4 placebo-controlled trials; mean difference on MMSE score, 0.20 [95% CI,

0.10–0.29]) but no significant benefit for dementia (5 placebo-controlled trials).<sup>158</sup>

### Blood Lipid Control/Statin Therapy

- 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>159</sup>
- In an observational study of 18 846 older adults (median age, 74 years; 56% women) with no history of cardiovascular events, statin therapy was not associated with risk of dementia, MCI, or cognitive decline.<sup>160</sup>

### Aspirin Therapy

- In a randomized placebo-controlled trial, the ASPREE study, rates of incident dementia, probable AD, and MCI did not differ between the low-dose daily aspirin treatment group and the placebo group after almost 5 years of follow-up (N= 19 114; age, 65 to 98 years; 44% male).<sup>161</sup>

### Glycemic Control

- 
- In a secondary analysis of 2880 participants (mean age, 63.1 years; 67% females) of the DPP, neither exposure to intensive lifestyle intervention nor use of metformin was associated with cognition at 8 years.<sup>162</sup>
  - In adults  $\geq 60$  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>163</sup>
  - A meta-analysis of RCTs found that intensive glucose control compared with conventional glucose control may delay cognitive decline slightly in patients with type 2 diabetes (4 cohorts with N=5444;  $\beta=-0.03$  [95% CI,  $-0.05$  to  $-0.02$ ]).<sup>164</sup>

### Multidomain Prevention Strategies

- In the 4-year DR's EXTRA trial (N=1401; mean age, 66.5 years), there was a trend toward better cognition in older adults randomized to a combined aerobic exercise and healthy diet intervention compared with the control group (global cognition [CERAD-TS] increase, 1.4 points [95% CI, 0.1–2.7];  $P=0.06$ ).<sup>165</sup> Effects were not significant for the resistance exercise alone, aerobic exercise alone, diet alone, or combined resistance exercise and diet groups.
- A pooled analysis of 2 multidomain intervention trials focused on cardiovascular and lifestyle strategies

(MAPT and PreDIVA; N=4162 participants; median age, 74 years) found no significant overall association between multidomain prevention and cognitive decline.<sup>166</sup> Cognitive benefits were observed among participants with lower baseline cognitive function (MMSE score <26; n=250; mean difference in change, 0.84 [95% CI, 0.15–1.54];  $P<0.001$ ).

- A 2021 Cochrane review of RCTs found no conclusive evidence that multidomain interventions reduce the incidence of dementia in older adults (2 RCTs; n=7256); however, there was high-certainty evidence for a small effect on cognition (3 RCTs; n=4617; mean difference on composite cognitive Z score based on neuropsychological test battery, 0.03 [95% CI, 0.01–0.06]).<sup>167</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>168</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>169</sup>

## Mortality

### (See Table 16-2)

- In 2020 (unpublished NHLBI tabulations using CDC WONDER<sup>170</sup> and the NVSS<sup>171</sup>):
  - On average, every 1 minute 44 seconds, someone died of dementia.
  - Dementia accounted for  $\approx 1$  of every 11 deaths in the United States.
  - The number of deaths with dementia as an underlying cause was 303984 (Table 16-2); the age-adjusted death rate for dementia as an underlying cause of death was 73.3 per 100 000, whereas the age-adjusted rate for any mention of dementia as a cause of death was 120.6 per 100 000.
  - More females than males die of dementia each year because of the higher prevalence of elderly females compared with males. Females accounted for 67.4% of US dementia deaths in 2020.
- Conclusions about changes in dementia death rates from 2010 to 2020 are as follows<sup>170</sup>:
  - The age-adjusted dementia death rate increased 24.7% (from 58.8 per 100 000 to 73.3 per

100 000), whereas the actual number of dementia deaths increased 54.8% (from 196371 to 303984 deaths).

- Age-adjusted dementia death rates increased 18.4% for males and 29.1% for females.

### 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>172</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.

## 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 an STEMI and in 5.7% of those presenting with an NSTEMI.<sup>173</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%). Last, 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 assessed with the NIHSS compared with no 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>174</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>175</sup>
- In a meta-analysis of 29 studies including 61 824 individuals with AD followed up for incident stroke, incidence of total stroke (20 studies) was 15.4 per

1000 person-years (95% CI, 10.6–20.3), incidence of ischemic stroke (11 studies) was 13.0 per 1000 person-years (95% CI, 7.6–18.5), and incidence of ICH (16 studies) was 3.4 per 1000 person-years (95% CI, 2.3–4.6).<sup>176</sup> Individuals with AD compared with controls without AD (3 studies) had 1.31 times the incidence of total stroke (95% CI, 1.07–1.59), 1.22 times the incidence of ischemic stroke (95% CI, 0.95–1.57), and 1.67 times the incidence of ICH (95% CI, 1.43–1.96).

- Among 3111 community-dwelling older adults in the Taiwan Longitudinal Study on Aging, prevalence of disability in instrumental activities of daily living was 71.8% among participants who had cognitive impairment without stroke, 56.8% among participants who had stroke without cognitive impairment, and 91.5% among participants who had cognitive impairment and stroke compared with 24.2% among participants who were cognitively intact with no stroke ( $P<0.001$ ).<sup>177</sup>

## Health Care Use

- In Japan, among 8897 patients discharged from a general acute care hospital who had undergone cognitive screening before admission, having moderate cognitive impairment was associated with 1.42 times (95% CI, 1.01–2.00) higher risk for readmission within 90 days and having severe cognitive impairment was associated with 2.21 times (95% CI, 1.21–4.06) higher risk for readmission within 90 days compared with normal cognitive screening.<sup>178</sup>
- In Italy, among 108 patients with cognitive impairment who were contacted by video call for a telemedicine neurological evaluation, 74 (68.5%) successfully connected for the televisit, and 34 (31.5%) were unable to connect for the televisit.<sup>179</sup> Successful connection for the televisit was higher (86%) when a child or grandchild of the patient was present than in the absence of a child or grandchild (49%).
- Patients with stroke with preexisting cognitive impairment or dementia may receive different care compared with cognitively normal patients with stroke. Among 836 adults with AIS in the Brain Attack Surveillance in Corpus Christi project, having preexisting dementia versus being cognitively normal was associated with lower odds of receiving antithrombotic therapy by day 2 (OR, 0.39 [95% CI, 0.16–0.96]) and echocardiogram (OR, 0.42 [95% CI, 0.26–0.67]).<sup>180</sup> Preexisting MCI versus normal cognition was associated with lower odds of receiving intravenous tPA (OR, 0.36 [95% CI, 0.14–0.96]), rehabilitation assessment (OR, 0.28 [95% CI, 0.10–0.79]), and echocardiogram (OR, 0.48 [95% CI, 0.32–0.73]). A composite quality measure

of care received versus care eligible to receive was not significantly associated with dementia (OR, 0.79 [95% CI, 0.55–1.12]) or with MCI (OR, 1.06 [95% CI, 0.77–1.45]). Among 7070 patients with acute stroke in the Australian Stroke Foundation national audit, those with dementia were more likely to receive no rehabilitation (OR, 1.88 [95% CI, 1.25–2.83]) and to be discharged to residential care (OR, 2.36 [95% CI, 1.50–3.72]).<sup>181</sup>

- A structured dementia care program was examined with regard to health care use and cost outcomes.<sup>182</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.

## 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>183</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>184</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 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>185</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>186</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 the 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.
- 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.<sup>182</sup>

## Global Burden

All prevalence and mortality estimates cited here are from the GBD Study 2020 and pertain to all types of dementia combined (data courtesy of the GBD Study 2020). The GBD Study 2020 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 Study 2020

(See Table 16-3 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 16-3).
- 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 Study 2020

(See Table 16-3 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 16-3).
- 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).

## Coronavirus Disease 2019

- In a meta-analysis of 19 studies of post-COVID-19 syndrome (long COVID) with 11 324 participants with COVID-19, prevalence of cognitive dysfunction was assessed ≥3 months after COVID-19 onset.<sup>187</sup> Prevalence of memory issues (5 studies; 5268 participants) was 27% (95% CI, 18%–36%), prevalence of attention disorder (3 studies; 1207 participants) was 22% (95% CI, 10%–34%), and prevalence of brain fog (3 studies; 4329 participants) was 32% (95% CI, 9%–55%).
- In a study of 263 older adults in France who had cognitive measures obtained longitudinally for up to 15 years before the COVID-19 pandemic and during the COVID-19 pandemic, decline in global cognitive ability accelerated during the pandemic ( $\beta=-0.289$  [ $P<0.001$ ]), suggesting that the circumstances of the pandemic such as isolation and loneliness may contribute to cognitive decline.<sup>188</sup>
- In a study of 401 UK Biobank participants who had brain imaging before and after COVID-19 infection and 385 controls who had brain imaging at 2 time points without COVID-19 infection, those who had COVID-19 had significantly reduced gray matter thickness in certain regions, changes to tissue damage biomarker levels, reduced global brain size, and increased time to complete Trail-Making Tests relative to control subjects without COVID-19, suggesting that COVID-19 infection affects brain structure and hastens cognitive decline.<sup>189</sup>
- In a cohort study evaluating cognitive decline during the first year after COVID-19 infection among 1438 COVID-19 survivors and 438 uninfected spouses, the authors found that 12.5% of those with COVID-19 had incident cognitive impairment within 12 months.<sup>190</sup> Compared with uninfected spouses and with adjustment for demographics and comorbidities, survivors of severe COVID-19 had 4.87 times the odds of cognitive decline at 6 months followed by remaining stable through 12 months (95% CI, 3.30–7.20), 7.58 times the odds of cognitive decline only at 12 months after being stable at 6 months (95% CI, 3.58–16.03), and 19.00 times the odds of progressive cognitive decline at both 6 months and 12 months (95% CI, 9.14–39.51).
- Dementia is a risk factor for mortality in patients with COVID-19. In a meta-analysis of 3 studies including 130 patients with COVID-19 with dementia and 805 patients with COVID-19 without dementia, having dementia was associated with 3.69 times the odds of mortality (95% CI, 1.99–6.83).<sup>191</sup> Mortality among 223 patients with COVID-19 >50 years of

age in South Korea who had underlying dementia was 33.6% compared with 20.2% among 223 propensity-matched patients with COVID-19 who did not have dementia (adjusted OR, 3.05 [95% CI, 1.80–5.30]); dementia was also associated with requiring a ventilator (24.1% versus 22.0% without dementia;  $P<0.001$ ).<sup>192</sup> In a meta-analysis of 10 studies including 56 577 patients with COVID-19 with 10% prevalence of dementia, having dementia was associated with 1.80 times the adjusted odds of death (95% CI, 1.45–2.24).<sup>193</sup>

- COVID-19 is also a risk factor for subsequent dementia. Among 7133 COVID-19 survivors and 299 444 control subjects without COVID-19 in the

Korean National Health Insurance Service database, all free of dementia at baseline, COVID-19 survivors had 1.39 times the hazard of new-onset dementia compared with people without COVID-19 (95% CI, 1.05–1.85).<sup>194</sup> A systematic review and meta-analysis of the impact of dementia on the clinical outcomes of COVID-19 used 10 studies including 119 218 individuals.<sup>195</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 in 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]).

**Table 16-1. Health Expectancies by Number of Cardiovascular Conditions Across Age Groups, HRS in the United States, 1996 to 2014**

	No. of cardiovascular conditions*			
	0 y (95% CI)	1 y (95% CI)	2 y (95% CI)	≥3 y (95% CI)
<b>At 55 y of age</b>				
CIFLE	23.0 (22.6–23.4)	21.2 (20.9–21.5)	18.1 (17.7–18.4)	14.0 (13.5–14.5)
CILE	6.7 (6.4–7.0)	6.2 (6.0–6.4)	5.5 (5.3–5.8)	4.6 (4.2–5.0)
TLE	29.7 (29.3–30.2)	27.4 (27.0–27.8)	23.6 (23.1–24.0)	18.6 (18.0–19.2)
<b>At 65 y of age</b>				
CIFLE	15.0 (14.6–15.3)	13.3 (13.1–13.6)	10.9 (10.7–11.2)	7.9 (7.6–8.3)
CILE	6.4 (6.1–6.7)	5.8 (5.6–6.0)	5.2 (5.0–5.4)	4.3 (4.0–4.6)
TLE	21.3 (20.9–21.8)	19.2 (18.9–19.5)	16.1 (15.8–16.4)	12.2 (11.9–12.6)
<b>At 75 y of age</b>				
CIFLE	8.4 (8.1–8.6)	7.1 (6.9–7.3)	5.6 (5.4–5.7)	3.7 (3.5–3.9)
CILE	5.7 (5.4–5.9)	5.1 (4.9–5.3)	4.5 (4.3–4.6)	3.7 (3.5–3.9)
TLE	14.0 (13.7–14.4)	12.2 (12.0–12.5)	10.0 (9.8–10.3)	7.4 (7.1–7.6)
<b>At 85 y of age</b>				
CIFLE	3.8 (3.6–4.0)	3.1 (2.9–3.2)	2.3 (2.1–2.4)	1.4 (1.2–1.5)
CILE	4.5 (4.3–4.7)	3.9 (3.8–4.1)	3.4 (3.3–3.6)	2.7 (2.5–2.8)
TLE	8.3 (8.0–8.6)	7.0 (6.8–7.2)	5.7 (5.5–5.8)	4.1 (3.9–4.2)

CIFLE indicates cognitive impairment-free life expectancy; CILE, cognitive impairment life expectancy; HRS, Health and Retirement Study; and TLE, total life expectancy.

\*Cardiovascular conditions included hypertension, heart disease, diabetes, and stroke. Source: Adapted from Zheng et al.<sup>115</sup> with permission. Copyright © 2021 Oxford University Press.

**Table 16-2. Dementia Mortality in the United States**

Population group	Mortality, 2020: all ages*
Both sexes	303 984
Males	99 157 (32.6%)†
Females	204 827 (67.4%)†
NH White males	81 841
NH White females	168 786
NH Black males	8235
NH Black females	17 681
Hispanic males	6151
Hispanic females	12 383
NH Asian or Pacific Islander males	2417‡
NH Asian or Pacific Islander females	5088‡
NH American Indian or Alaska Native	966

Data represent underlying cause of death only using *ICD-10* codes F01, F03, and G30 through G31. (*ICD-10* codes F00 and F02 are not listed as underlying or multiple causes of death in the NVSS.)

ICD-10 indicates *International Classification of Diseases, 10th Revision*; NH, non-Hispanic; and NVSS, National Vital Statistics System.

\*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.

Source: Mortality: Unpublished National Heart, Lung, and Blood Institute tabulation using NVSS.<sup>171</sup>

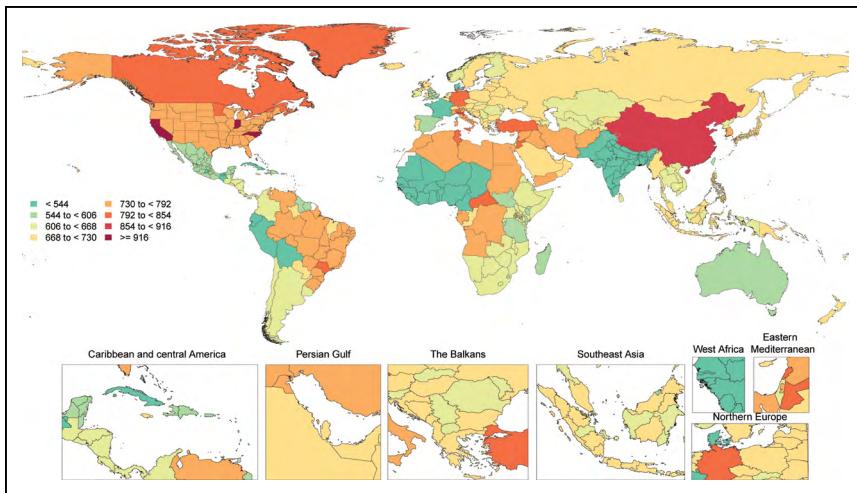
**Table 16-3. Global Mortality and Prevalence of AD and Other Dementias by Sex, 2020**

	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)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AD indicates Alzheimer disease; GBD, Global Burden of Disease; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>196</sup>

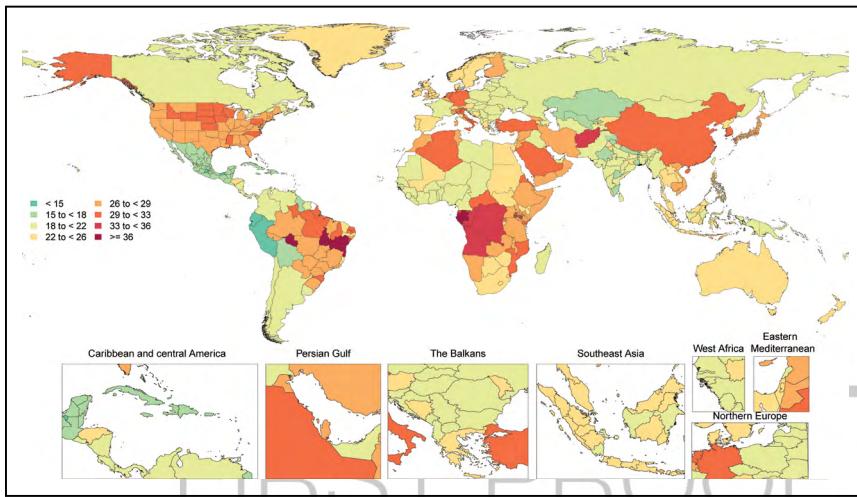


**Chart 16-1. Age-standardized global prevalence rates of AD and other dementias per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AD indicates Alzheimer disease; and GBD, Global Burden of Disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>196</sup>



**Chart 16-2. Age-standardized global mortality rates of AD and other dementias per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AD indicates Alzheimer disease; and GBD, Global Burden of Disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>196</sup>

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# Circulation

## 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.<sup>1</sup> 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>2</sup> on par with what is seen in other chronic pediatric health conditions,<sup>3</sup> as well as deficits in cognitive functioning<sup>4</sup> and neurodevelopmental outcomes.<sup>5</sup> However, health outcomes generally continue to improve for CCDs, including survival.<sup>6</sup>

### 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>7</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>7</sup> The change was greatest in low- and middle-income countries, attributed to both increasing population growth and improving survival.<sup>7</sup>

In 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>8</sup> This figure represents a fairly drastic downshift from the 32nd Bethesda Conference estimate (2000 estimate,

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

800 000)<sup>9</sup> and estimates provided by the CDC (2010 estimate, 1.4 million adults and 1 million children),<sup>10</sup> reflecting a change in GBD Study modeling strategy. In prior estimates, every person born with a CCD, regardless of type or severity, was assumed to have a CCD across their life span. In 2017, the GBD Study took a more nuanced approach that allowed for “cure” of simple lesions such as ASDs 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>8</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>8</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>8</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>11</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>12</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>13</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>11</sup>

### Risk Factors

- Numerous nongenetic risk factors are thought to contribute to CCDs.<sup>14,15</sup>

- Maternal exposure to teratogens 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>16</sup>
- Maternal lifestyle factors have been associated with increased risk of CCDs.
  - Smoking<sup>17–19</sup> during the first trimester of pregnancy is associated with a ≥30% increased risk of fetal ASD, pulmonary valvar stenosis, truncus arteriosus, TGA,<sup>20</sup> and septal defects (particularly for heavy smokers [ $\geq 25$  cigarettes daily]).<sup>21</sup> Exposure to secondhand smoke also has been implicated as a risk factor for CCDs.<sup>19</sup>
  - Maternal alcohol intake of >1 drink/wk has been correlated with CCDs.<sup>19</sup>
  - Smoking and binge drinking together may also increase risk. 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>22</sup>
- Maternal health factors have been associated with increased risk of CCDs.
  - Higher maternal BMI has been identified as a risk factor for CCDs in some but not all studies. A systematic review including 8 studies that assessed the relationship between maternal obesity and CCDs found a significant association between maternal obesity and CCDs in 5 studies, whereas 3 studies found no association between CCDs and maternal obesity.<sup>23</sup> A second meta-analysis (14 studies) found a dose-response effect between overweight, moderate obesity, and severe obesity and a pregnancy with a CCD (the pooled ORs: OR, 1.08 [95% CI, 1.02–1.15]; OR, 1.15 [95% CI, 1.11–1.20]; and OR, 1.39 [95% CI, 1.31–1.47], respectively), an association that persisted when controlling for the presence of diabetes.<sup>24</sup>
  - Maternal diabetes, including type 1, type 2, and gestational diabetes, is strongly associated with fetal CCDs (aRR, 4.00 [95% CI, 3.51–4.53]), with higher risk among women with previous diabetes-related complications (RR, 7.32 [95% CI, 5.32–10.6]).<sup>25</sup>
  - Approximately 2670 (95% UI, 1795–3795) cases of CHDs could potentially be prevented annually if all women in the United States with pregestational diabetes achieved glycemic control before pregnancy.<sup>26</sup>
  - Folate deficiency is a well-documented risk for CCDs.<sup>14</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>27</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>28</sup> An observational study from Quebec, Canada, of 1.3 million births from 1990 to 2005 found a 6%/y reduction in severe CCDs with the use of 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>29</sup>

- Maternal infections, including rubella and chlamydia, have been associated with CCDs.<sup>30,31</sup>
- Paternal occupational exposures may also be associated with fetal CCDs.<sup>32</sup> More specifically, there are attributable fractions of fetal TOF attributable 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>34</sup>



## Screening

It has been almost a decade since pulse oximetry screening for CCDs was instituted as part of the uniform US screening panel for newborns and endorsed by the AHA and the American Academy of Pediatrics.<sup>35,36</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>37</sup> and several studies have demonstrated the benefit of such screening.<sup>38–40</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 have nonsyndromic CCDs versus 880 (95% UI, 700–1080) false-negative screenings (no CCD).<sup>41</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>42</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>43</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>44</sup> with a sensitivity and specificity of pulse oximetry screening for critical CCDs of 100% and 99.7%, respectively.

### Social Determinants

Multiple studies assessing the impact of social determinants of health on CCD incidence and prevalence, infant mortality, and postsurgical outcomes found the following:

- A 2021 scoping review showed that poverty was associated with higher incidence and prevalence of CCDs; reported associations between lower SES, parental education attainment, and prenatal diagnosis of CCDs suggest lower rates of prenatal diagnosis in association with stated risk factors, as well as increased infant mortality, adverse postsurgical outcomes, decreased health care access, and impaired neurodevelopmental outcome.<sup>45</sup>
- Among >2.4 million infants born in the state of California, CCD incidence was higher among infants born in neighborhoods in the lowest compared with the highest SES quartile (OR, 1.31 [95% CI, 1.21–1.42]) and environmental exposure quartiles (OR, 1.23 [95% CI, 1.15–1.31]).<sup>46</sup>
- Among infants with HLHS living within the Metropolitan Atlanta Congenital Defects Program, survival rates were worse for those residing in high-poverty census tracts (9%) compared with those residing in low-poverty census tracts (25%;  $P<0.001$ ).<sup>47</sup>
- Lower SES and poverty have been associated with worse HLHS survival, in-hospital mortality, increased resource use after orthotopic heart transplantation, higher interstage mortality, higher mortality after congenital heart surgery, and worse 1-year transplantation-free survival after a stage 1 palliation procedure.<sup>45</sup> Longer length of stay, higher unplanned readmission rates, and higher resource use were also associated with lower school functioning among parents of children who had undergone cardiac surgery.
- Neurodevelopmental outcomes and quality of life measures were lowest among children living in poverty, children of parents with low educational attainment, and children of parents with transportation barriers.<sup>45</sup>
- Lower socioeconomic quartile was associated with decreased rates of prenatal detection of HLHS and TGA, particularly among children with TGA (OR for socioeconomic quartile 1, 0.78 [95% CI, 0.64–0.85] compared with quartile 4). Hispanic ethnicity (RR, 0.85 [95% CI, 0.72–0.99]) and rural residence (RR,

0.78 [95% CI, 0.64–0.95]) were also associated with lower rates of prenatal detection of TGA.<sup>48</sup>

- Maternal socioeconomic and environmental factors have been associated with risk of CCDs.
  - In Ontario, CCDs were more common among children of mothers who lived in neighborhoods in the lowest compared with the highest income quartile (OR, 1.29 [95% CI, 1.20–1.38]) and neighborhoods with the lowest compared with the highest percentage of individuals with university or advanced degrees (aOR, 1.34 [95% CI, 1.24–1.44]).<sup>49</sup>
  - Maternal exposure to 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>50</sup>
- SES is a major contributor to identified differences in infant mortality among infants with critical CCDs, with greater mortality among socioeconomically deprived patients (OR, 1.7 [95% CI, 1.4–2.07]).<sup>51</sup>
- The income status of the neighborhood in which a child lives is associated with increased risk for death after congenital heart surgery and greater intensive care resource use.<sup>52</sup> Among patients undergoing cardiac surgery, children from the lowest neighborhood income quartile versus the highest had a 1.31 times increased mortality risk (OR, 1.21 [95% CI, 1.14–1.51]) after cardiac surgery independently of age, race, insurance type, geographic region, or low versus high procedure complexity.
  - However, the relationship between neighborhood household income and mortality among children with CHD is nonlinear. Higher risk for mortality exists at lower and higher income levels. The risk of death nadirs between annual neighborhood household income of \$72 000 to \$80 000.<sup>53</sup>
- Lower maternal education is associated with higher infant mortality in the first year among infants with critical CHDs (OR, 1.32 [95% CI, 1.2–1.45]).<sup>51</sup>

### Genetics and Family History

- Eight percent to 10% of CCDs can be attributed to chromosomal aberrations (eg, DiGeorge syndrome, Down syndrome, Turner syndrome) and 5% to 15% to single-nucleotide or pathogenic copy number variants.<sup>54</sup>

- CCDs can have a heritable component, and parental consanguinity is a known risk factor.<sup>16</sup> There is a greater concordance of CCDs in monozygotic than dizygotic twins.<sup>55</sup> A report from Kaiser Permanente data showed that monochorionic twins were at particularly increased risk for CCDs (RR, 11.6 [95% CI, 9.2–14.5]).<sup>56</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>57</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>58</sup>
- Large chromosomal abnormalities are found in 8% to 10% of individuals with CCDs.<sup>58</sup> For example, aneuploidies such as trisomy 13, 18, and 21 account for 9% to 18% of CCDs.<sup>59</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>60</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>61</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>62</sup>
- De novo variants have been reported in ≈8% of patients with CCDs (≈3% in isolated CCDs and ≈28% in those with extracardiac features along with CCDs).<sup>58</sup> Carriers of de novo variants also have been reported to have worse transplantation-free survival and longer extubation duration.<sup>63</sup>
- Point variants in single genes are found in 3% to 5% of CCDs<sup>58</sup> and include variants in a core group of cardiac transcription factors (*NKX2.5*, *TBX1*, *TBX2*, *TBX3*, *TBX5*, *GATA4*, and *MEF2*),<sup>62,64,65</sup> *ZIC3*, and the *NOTCH1* gene (dominantly inherited and found in ≈5% of cases of bicuspid aortic valve) and related *NOTCH* signaling genes.<sup>66</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>67</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>68</sup> A GWAS in 5 cohorts including 1025 conotruncal case-parent trios, 509 LV obstructive tract defect case-parent trios, 406 conotruncal defect cases, and 2976 controls found intronic variants in the *MGAT4C* gene associated with conotruncal defects; in meta-analyses, 1 genome-wide significant association was found in an intragenetic SNP associated with LV outflow tract defect.<sup>69</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>70</sup> These results suggest that noncoding de novo variants play a significant role in CCDs in addition to coding de novo variants.
- Recently, in addition to previously recognized 14 genes associated with CCDs, 7 new genes (*FEZ1*, *MYO16*, *ARID1B*, *NALCN*, *WAC*, *KDM5B*, and *WHSC1*) have been identified as being associated with CCDs.<sup>71</sup> A recent GWAS in patients of European ancestry with CCDs has identified *MACROD2*, *GOSR2*, *WNT3*, and *MSX1* to have an essential role in embryonic and postnatal cardiac morphogenesis and to contribute to the development of structural cardiac defects.<sup>72</sup>
- Rare monogenic CCDs also exist, including monogenic forms of ASD, heterotaxy, severe mitral valve prolapse, and bicuspid aortic valve.<sup>62</sup>
- Complications related to CCDs also may have a genetic component; whole-exome sequence study identified *SOX17* as a novel candidate gene for PAH in patients with CCDs.<sup>73</sup>
- Genetic variants associated with CCDs may also occur within cancer risk genes.<sup>74</sup>
- There is no exact consensus currently on the role, type, and utility of clinical genetic testing in people with CCDs,<sup>62</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 CCDs and extracardiac manifestations.<sup>9,75</sup>
- The diagnostic yield for CCD genetic panels in familial, nonsyndromic cases is 31% to 46% and is even lower in nonfamilial disease.<sup>76,77</sup> Use of whole-exome genetic testing has been shown to improve rates of detection.<sup>78</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>79</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>8</sup>
- In 2020, mortality related to CCDs was 2817 deaths (Table 17-2) in the United States, a 11.9% decrease from the number of deaths in 2010 (unpublished NHLBI tabulation using NVSS<sup>80</sup>).
- CCDs (*ICD-10* Q20–Q28) were the most common cause of infant deaths resulting from birth defects (*ICD-10* Q00–Q99) in 2020; 20.4% of infants who died of a birth defect had a heart defect (*ICD-10* Q20–Q24; unpublished NHLBI tabulation using NVSS<sup>80</sup>).
- In 2020, the age-adjusted death rate (deaths per 100 000 people) attributable to CCDs was 0.9, an 18.2% decrease from 2010 (unpublished NHLBI tabulation using CDC WONDER<sup>81</sup>).
- Death rates attributed to CCDs decrease as gestational age advances to 40 weeks.<sup>82</sup> In-hospital mortality of infants with a major CCD is independently associated with late PTB (OR, 2.70 [95% CI, 1.69–4.33]) compared with delivery at later gestational ages.<sup>83,84</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>85</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>86</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 patients with CCDs 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>87</sup>
- In Mexico, 70 741 deaths were attributed to CCDs 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>88</sup>
- Analysis of the NIS 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>89</sup>
- A meta-analysis of outcomes for 848 patients with heterotaxy who underwent a Fontan procedure before May 2018 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>90</sup>
- Trends in overall age-adjusted death rates attributable to CCDs showed a decline from 1999 to 2017 with a relative plateau between 2017 and 2020 (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 to 2018 and 2019 to 2020 for NH White, rates fell for NH Black people and Hispanic people between 2019 and 2020. From 1999 to 2020, death rates generally 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, although 2017 to 2020 showed a relative plateau in trends.
- 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 2020 (Chart 17-4).
- The US 2020 age-adjusted death rate (deaths per 100 000 people) attributable to CCDs was 0.99 for NH White males, 1.29 for NH Black males, 0.77 for Hispanic males, 0.79 for NH White females, 0.97 for NH Black females, and 0.67 for Hispanic females (Chart 17-5). Infant (<1 year of age) mortality rates were 24.9 for NH White infants, 34.1 for NH Black infants, and 24.2 for Hispanic infants (unpublished NHLBI tabulation using CDC WONDER<sup>81</sup>).
- Prenatal diagnosis can help to reduce mortality rates associated with CCDs, but prenatal diagnosis has not been consistently demonstrated to reduce mortality rates among neonates with complex CCDs such as HLHS.<sup>91</sup> Even among children diagnosed prenatally, greater distance between the birth center and cardiac surgical center (>90 miles) has been associated with greater mortality. Time required to drive from the birth center to the cardiac surgical center of <10, 10 to 90, and >90 minutes has been associated with 21%, 25.2%, and 39.6% mortality, respectively.
- Multiple pregnancies versus singleton pregnancy is associated with higher mortality during the first year

- of life among infants with critical CHD (1.61 [95% CI, 1.042–2.5]).<sup>51</sup>
- Efforts have been made to link data from multiple sources for the purpose of providing risk-adjusted outcome, resource use, health expenditure, and health disparity-related data for patients <18 years of age with CCDs. The New York Congenital Heart Surgeons Collaborative for Longitudinal Outcomes and Utilization of Resources has linked locally held data from 10 of 11 New York congenital heart centers to Medicaid claims data. In total, 7.7%, 8.4%, and 10.0% of children died at 3, 5, and 10 postoperative years, respectively.<sup>92</sup>
    - For adults with CCDs, both the number of instances of clinic nonattendance (HR, 1.08 [95% CI, 1.05–1.12 per clinic nonattendance];  $P<0.001$ ) and the ratio of clinic nonattendance to follow-up period (HR, 1.23 [95% CI, 1.04–1.44 per clinic nonattendance per year];  $P=0.013$ ) are independent predictors of mortality.<sup>93</sup>
  - Survival and health-related quality of life among individuals with CCDs are affected by genetic, epigenetic, environment, intervention-related, and disease-related outcomes.<sup>94</sup>

### Complications

Long-term effects of CCDs include arrhythmias, IE, and HF. Adults with CCDs who survive to 50 years of age have a significant chance of experiencing physical and mental health complications.<sup>95–98</sup>

- Individuals with CCDs are at increased risk of AF. In an analysis in Sweden including 21982 patients with CCDs and 219816 control patients, the risk of developing AF was 22 times higher (HR, 22.0 [95% CI, 19.3–25.1]) in those with CCDs compared with controls without congenital HD.<sup>99</sup> By 42 years of age, ≈8% of patients with CCDs had been diagnosed with AF.
- HF rates are 40%, 25%, and 50% among TOF, coarctation, and TGA/Fontan-repaired adult survivors, respectively.<sup>98</sup>
- Arrhythmia is very common and occurs among 35%, 32%, and 60% of TOF, coarctation, and TGA/Fontan-repaired adult survivors, respectively.<sup>98</sup>
- Adults with CCDs are at risk for reoperation, congestive HF, cerebrovascular events, and subacute bacterial endocarditis. Estimated reoperation rates among adults with TOF, coarctation of the aorta, and TGA and Fontan are 40%, 50%, and 10%, respectively.<sup>98</sup>
- Children with CCDs may be at risk for adverse neurodevelopmental outcomes, including mild motor impairments,<sup>100</sup> increased attention-deficit/hyperactivity disorder-related behaviors, difficulties in social interaction,<sup>101</sup> and depression and anxiety.<sup>102,103</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>104</sup> Of 121 patients with adult CCDs in Australia with moderate or complex CCDs, just more than 60% of those with TOF or CoA remained employed, and approximately half had been diagnosed with anxiety or depression.<sup>98</sup>
  - In patients with HLHS, an older age at Fontan procedure and a history of sepsis were independent predictors of poor neurocognitive outcomes.<sup>105</sup>
- A diagnosis of anxiety is made in ≈5% to 50% of adult CCD survivors with lowest reported rates for individuals with history of coarctation repair and highest among adult survivors after Fontan surgery.<sup>98</sup>
- There are inconclusive data showing an increased risk of serious adverse events from COVID-19 infection in children and adults with CCDs.<sup>106</sup>

### Health Care Use: Hospitalizations

(See Table 17-2)

- In 2019, the total number of first-listed hospital discharges for CCDs for all ages was 44 000 (Table 17-2).
- Hospitalization of infants with CCDs is common; one-third of patients with CCDs require hospitalization during infancy,<sup>107,108</sup> often in an ICU.
- Socioeconomic and sociodemographic factors affect hospitalization rates and length of stay. However, adjustments to length of hospital stay (eg, longer length of stay) may help to mitigate previously identified higher mortality risk for Black infants with CCDs.<sup>109</sup>
- The number of 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>110</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, 2.0–3.1]), 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>111</sup>
- Among adults with commercially purchased insurance, those with CCDs had more health care visits and higher expenditures than those without CCDs, even when controlling for baseline characteristics and comorbidities.<sup>112</sup>
- Among adolescents and adults with CCDs, residence within the census tracts with highest area

deprivation index (most deprived areas) was associated with a 51% higher odds of inpatient admission, 74% higher odds of ED visit, 41% higher odds of cardiac surgeries, and 45% higher odds of major adverse cardiac events compared with residence within the census tracts with the lowest deprivation index.<sup>113</sup>

### Cost

- Using HCUP NIS 2013 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>114</sup>
- Among pediatric hospitalizations (0–20 years of age) in the HCUP 2012 Kids' Inpatient Database<sup>115</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 \$51302 (IQR, \$32088–\$100058) in children who underwent cardiac surgery, \$21920 (IQR, \$13068–\$51609) in children who underwent cardiac catheterization, \$4134 (IQR, \$1771–\$10 253) in children who underwent noncardiac surgery, and \$23 062 (IQR, \$5529–\$71 887) in children admitted for medical treatments.
  - The mean cost of CCDs was higher in infancy (\$36 601) than in older ages and in those with critical CCDs (\$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>116</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>117</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>118</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>119</sup>
- A cross-sectional survey from the NHIS of US households (2011–2017) found that nearly half (48.9%) of families of children with CCDs 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>120</sup>

- Cost of CCD care may be affected by center volume. Data from the Pediatric Health Information Systems database show cost of care associated with infant truncus arteriosus repair at high- versus low-volume centers.<sup>121</sup> Costs were lower at high-volume centers attributed largely to lower median days of postoperative ventilation, ICU stay, and inotropic agent use, and overall length of stay.<sup>113</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 CCDs in 2019, representing 2305.2 per 100 000 live births (95% UI, 1772.9–3039.2).<sup>7</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>8</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 RV, 0.106; and truncus arteriosus, 0.078 (among others reviewed).<sup>122</sup>
- CCDs were responsible for 261 247 deaths globally in 2017 (95% CI, 216 567–308), which is a 30% decline from 1990.<sup>8</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>8</sup>
- The GBD Study 2020 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 2020). In 2020:
  - The prevalence of CCDs 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 CCDs worldwide.
  - Age-standardized mortality rates of CCDs 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 CCDs 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 8.2 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>122</sup>
- According to a systematic review and meta-analysis of CCD data from China, birth prevalence of CCDs 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>123</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>124</sup>
- Between 1977 and 2015, a Danish study of 15 900 patients with simple CCDs (ASD, VSD, patent ductus arteriosus) found increasing incidence per 100 000 (ASD in adults, 8.8 [95% CI, 7.1–10.5] to 31.8 [95% CI, 29.2–34.5]; ASD in children, 26.6 [95% CI, 20.9–32.3] to 150.8 [95% CI, 126.5–175.0]; VSD in children, 72.1 [95% CI, 60.3–83.9] to 115.4 [95% CI, 109.1–121.6], and patent ductus arteriosus in children, 49.2 [95% CI, 39.8–58.5] to 102.2 [95% CI, 86.7–117.6]).<sup>125</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>126</sup>
- Estimated prevalence of CCDs in China is 11.5 per 1000 (95% CI, 10.2–13.0).<sup>127</sup>
- Estimated (pooled) prevalence of ASD among CCDs in East Africa is 10.36% (95% CI, 8.05–12.68;  $P=89.5\%$ ;  $P<0.001$ ).<sup>128</sup>
  - Estimated (pooled) prevalence of VSD among CCDs in East Africa is 29.92% (95% CI, 26.12%–33.72%;  $P=89.2\%$ ;  $P<0.001$ ), in Ethiopia is 36.04% (95% CI, 29.36%–42.72%), in Djibouti is 37% (95% CI, 18.79%–55.21%), and in Sudan is 32.59% (95% CI, 26.67%–38.59%).<sup>128</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, ex-

tremity 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>129</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>130,131</sup>

### **Prevalence**

- KD is the most common cause of acquired HD in children in the United States and other high-income countries.<sup>132</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 126 780 005 total hospitalizations. The incidence of KD was estimated at 6.35 per 100 000.<sup>133</sup>
- The incidence was estimated 20.8 per 100 000 US children <5 years of age in 2006.<sup>134</sup> This was calculated from 2 databases and limited by reliance on weighted hospitalization data from 38 states.
- Male children have a 1.5-fold higher incidence of KD than female children.<sup>134</sup>
- Although KD can occur into adolescence (and rarely adulthood), 76.8% of US children with KD are <5 years of age.<sup>134</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>134</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>135</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>135</sup>
- There are seasonal variations in KD that may track other respiratory and enteric viruses<sup>136</sup>; KD is more common during the winter and early spring months, except in Hawaii, where no clear seasonal trend is seen.<sup>134,135</sup>
- Incidence of KD may have decreased during SARS-CoV-2 mitigation policies (social distancing and masks), with 1 center reporting a 67% decline

( $P=0.01$ ) comparing April to December 2020 with the same months in the past 8 years<sup>137</sup> and another study in Korea reporting only 60% of predicted cases (incidence 18.8 per 100 000) after standard precautions were implemented compared with the predicted mean incidence (32.2 per 100 000) based on >50 000 cases between 2010 and 2020.<sup>138</sup>

- KD rarely recurs. Recurrences constitute 2% to 4% of total KD cases in both the United States and Japan,<sup>139</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>140,141</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>134</sup>

### Genetics/Family History/Risk Factors

- 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>132</sup>
- GWASs have identified loci in *FCGR2A*, *FAM167-BLK*, *CD40*, *IHGV3-66*, HLA class II region, *NAALADL2*, and *ZFHX3* to be associated with KD.<sup>142–146</sup> Recently, a novel loci (intergenic variant rs6017006) has been identified to be associated with coronary artery aneurysm in patients of European descent with KD.<sup>147</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>130,146,148</sup>
- Advanced maternal age ( $\geq 35$  years; OR, 1.18 [95% CI, 1.07–1.30],  $P<0.001$ ), maternal ankylosing spondylitis (OR, 2.01 [95% CI, 1.17–4.43];  $P=0.01$ ), and Sjögren syndrome (OR, 1.75 [95% CI, 1.03–2.95];  $P=0.04$ ) may be perinatal factors associated with increased risk of KD.<sup>149</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>132</sup> Aspirin is routinely used for its anti-inflammatory and antiplatelet effects, but it

does not reduce the incidence of coronary artery aneurysms.<sup>150</sup>

- 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>151</sup>
- Resistance to IVIG, defined as recurrent or persistent fever  $\geq 36$  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>132</sup> A multicenter comparative effectiveness trial including 30 US hospitals and 103 patients (4 weeks to 17 years of age) showed that infliximab compared with a second dose of IVIG resulted in shorter fever duration (1.5 days [SD, 1.4 days] versus 2.5 days [SD, 2.5 days]) and shorter hospitalization (3.2 days [SD, 2.1 days] versus 4.5 days [SD, 2.5 days]). No difference was found in coronary artery outcomes.<sup>152</sup>
- Cyclophosphamide may arrest further coronary artery dilation in those with severe and progressive coronary artery enlargement after KD.<sup>153</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>154,155</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>132,156</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  $\geq 2.5$ ), and 1% develop giant aneurysms (Z score  $\geq 10$  or  $>8$  mm).<sup>132</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  $\geq 2.5$  in 30% of patients with KD up to 12 weeks from fever onset, including medium ( $Z$  score  $\geq 5$ – $<10$ ) and giant aneurysms in  $\approx 6\%$  and  $\approx 3\%$  of patients with KD, respectively.<sup>157</sup>

- Risk factors for coronary artery abnormalities include younger age, male sex, late treatment, and failure to respond to initial IVIG with defervescence.<sup>157–161</sup>
- Noncoronary cardiac findings, in particular in very young children (<6 months), may also increase risk for more severe KD with coronary artery aneurysms.<sup>161</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>162</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>163–165</sup> Mortality is related to thrombosis or rupture of rapidly expanding aneurysms or, less commonly, shock or macrophage activation syndrome with multiorgan failure.<sup>132,165,166</sup>
- Prognosis is predicted largely by coronary artery size 1 month from illness onset. In a Taiwanese study of 1073 patients with 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 a 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>167</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>154,168</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>169</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]).
- In 2020, US mortality attributable to KD was 5 patients for underlying mortality and 11 patients for all-cause mortality (unpublished NHLBI tabulation using CDC WONDER<sup>81</sup>).

## Health Care Use

- In 2019, there were 4000 principal and 5000 all-listed diagnoses hospital discharges for KD (HCUP,<sup>170</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>165,171,172</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 males and 1.2 per 100 females for 2007 to 2010.<sup>173</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>172</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>141,174–178</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>165,172,175,178</sup>

## Multisystem Inflammatory Syndrome in Children

MIS-C is a clinical syndrome characterized by fever, inflammation, and multiorgan dysfunction that most commonly manifests late in the course of SARS-CoV-2 infection.<sup>179</sup> MIS-C has overlapping signs and symptoms of KD and toxic shock syndrome. Case definitions of MIS-C by the CDC and WHO require fever, elevated makers of inflammation, evidence of recent SARS-CoV2 infection or exposure, multisystem organ involvement, and exclusion of alternate diagnoses. The first case reports of MIS-C (which has gone by many names) came from the United States and Europe in April 2020,<sup>180</sup> with dozens of case series now reported from around the world.

- MIS-C most commonly occurs 4 to 6 weeks after a population peak of SARS-CoV2 infection.<sup>181</sup>
- Since May 2020, the CDC has been tracking reports of MIS-C. As of March 1, 2022, 7459 cases and 63 attributable deaths (0.84%) have

been reported. Median age of cases was 9 years; 58% of cases have occurred in children who are Hispanic or Latino (1846 cases) or Black (2206 cases); 98% tested positive for SARS-CoV2 (reverse transcriptase–polymerase chain reaction, serology, or antigen test); and 60% of reported patients were male.<sup>182</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>183</sup>

- Risk of MIS-C may vary with ethnicity, with apparently higher risk among those of African descent.<sup>184,185</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>186</sup> and Parker et al.<sup>12</sup>

**Table 17-2. CCDs in the United States**

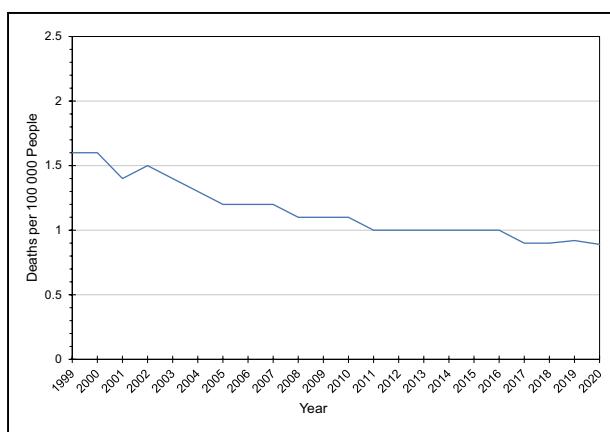
Population group	Estimated prevalence, 2010, all ages	Mortality, 2020, all ages*	Hospital discharges, 2019, all ages
Both sexes	2.4 million	2817	44 000
Males	...	1534 (54.5%)†	
Females	...	1283 (45.5%)†	
NH White males	...	933	...
NH White females	...	789	...
NH Black males	...	267	...
NH Black females	...	206	American Heart Association.
Hispanic males	...	243	...
Hispanic females	...	214	...
NH Asian or Pacific Islander males	...	68	...
NH Asian or Pacific Islander females	...	60	...
NH American Indian or Alaska Native people	...	29	...

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.

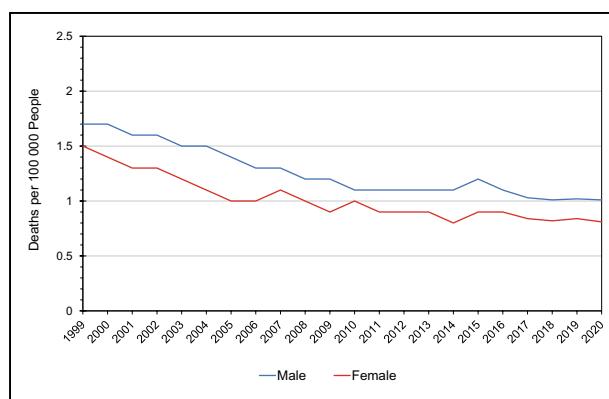
Sources: Prevalence: Gilboa et al.<sup>10</sup> Mortality (for underlying cause of CCDs): unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics System.<sup>80</sup> These data represent underlying cause of death only. Hospital discharges (with a principal diagnosis of CCD): unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2019.<sup>170</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 2020.**

CCD indicates congenital cardiovascular defect.

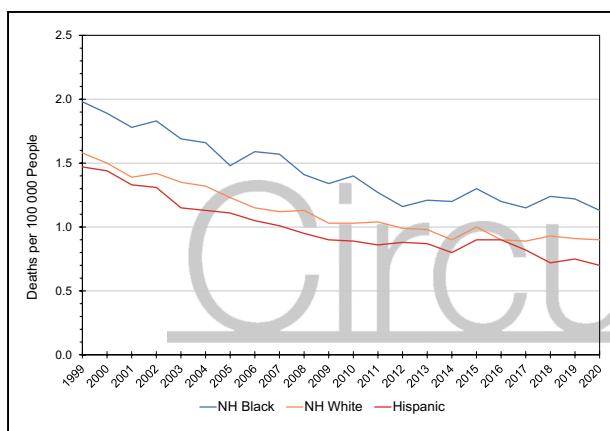
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>81</sup>



**Chart 17-3. Trends in age-adjusted death rates attributable to CCDs by sex, United States, 1999 to 2020.**

CCD indicates congenital cardiovascular defect.

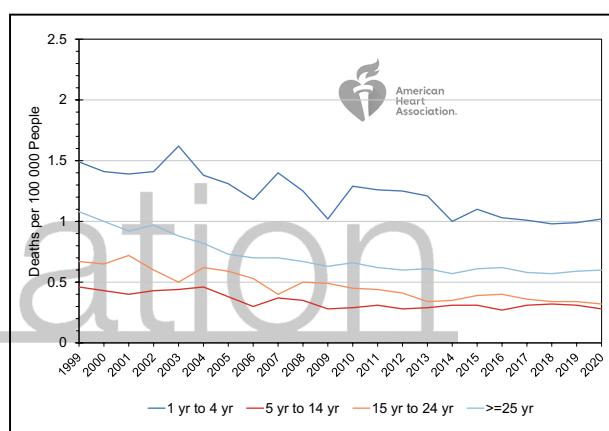
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>81</sup>



**Chart 17-2. Trends in age-adjusted death rates attributable to CCDs by race and ethnicity, United States, 1999 to 2020.**

CCD indicates congenital cardiovascular defect; and NH, non-Hispanic.

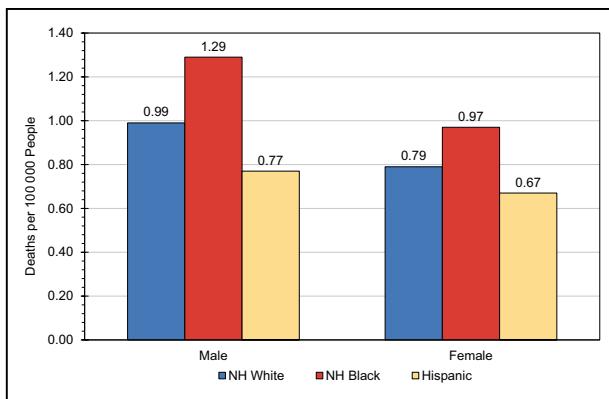
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>81</sup>



**Chart 17-4. Trends in age-specific death rates attributable to CCDs by age at death, United States, 1999 to 2020.**

CCD indicates congenital cardiovascular defect.

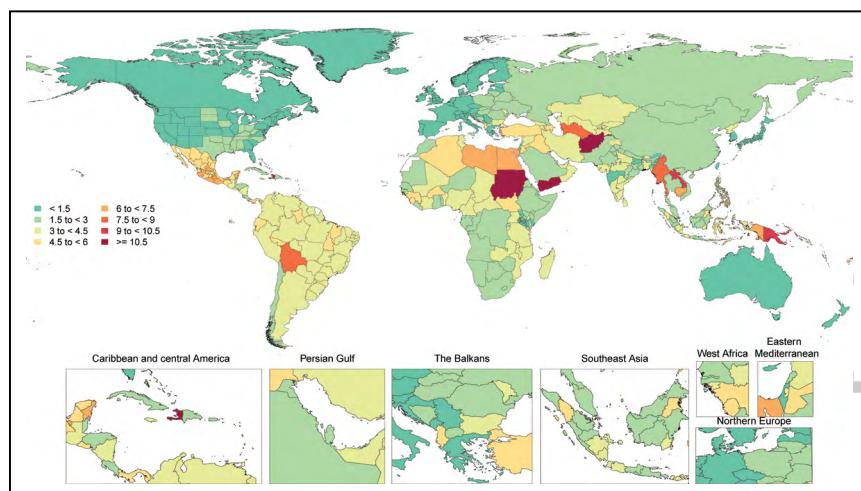
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>81</sup>



**Chart 17-5. Age-adjusted death rates attributable to CCDs by sex, race, and ethnicity, United States, 2020.**

CCD indicates congenital cardiovascular defect; and NH, non-Hispanic.

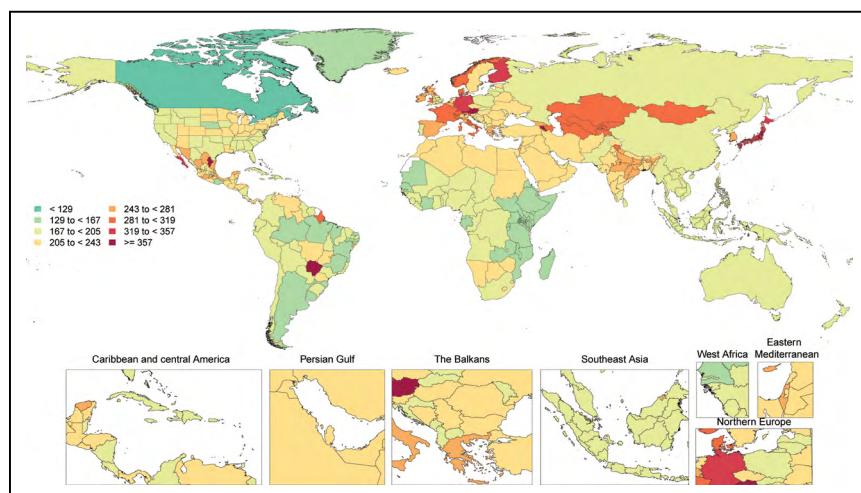
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>81</sup>



**Chart 17-6. Age-standardized global mortality rates of congenital heart anomalies per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease. Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>187</sup>



**Chart 17-7. Age-standardized global prevalence rates of congenital heart anomalies per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease. Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>187</sup>

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# Circulation

## 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)

2020, United States: Underlying cause mortality—55 749. Any-mention mortality—665 305.

2019, United States: Hospital discharges—667 000.

### Bradyarrhythmias

**ICD-9 426.0, 426.1, 427.81; ICD-10 I44.0 to I44.3, I49.5.**

2020, United States: Underlying cause mortality—1439. Any-mention mortality—9249.

2019, United States: Hospital discharges—104 000.

2016, United States: 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

- 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 studies (N=1081–10 785) conducted in different European countries.<sup>1–3</sup>

##### 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>4</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 0.6% in a large

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

sample of people (N=552 623) with hypertension and without diabetes enrolled with Veterans Health Administration hospitals.<sup>5</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>6</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>7</sup>
- An English registry study estimated the incidence of infant complete atrioventricular block as 2.1 (95% CI, 1.3–3.5) per 100 000 live births.<sup>8</sup>
- Atrioventricular block of varying degrees is reported in 8.6% of patients hospitalized with COVID-19.<sup>9</sup> The prevalence appears higher in Asia (22.7%) than in Europe (8.1%) and North America (7.0%).

#### Risk Factors

- In individuals from MESA (N=1252) without recognized CVD or CVD risk factors, PR-interval reference ranges in individuals  $\geq 65$  years were reported as 176 milliseconds (32 milliseconds) in men and 162 milliseconds (22 milliseconds) in women of White race; 178 milliseconds (31 milliseconds) in men and 160 milliseconds (19 milliseconds) in women of Black race; and 162 milliseconds (17 milliseconds) in men and 163 milliseconds (18 milliseconds) in women of Hispanic ethnicity.<sup>10</sup>
- Although a prolonged PR interval and Mobitz type I second-degree atrioventricular block can occur in healthy people, especially during sleep, presence of Mobitz II second- or third-degree atrioventricular block may indicate underlying HD, including CHD, and HF.<sup>4</sup>
- Long sinus pauses and atrioventricular block can occur during sleep apnea, which may be reversible with treatment of the condition.<sup>11,12</sup>

#### Complications

- In the FHS, PR-interval prolongation ( $>200$  milliseconds) was associated with increased risk of AF (HR, 2.06 [95% CI, 1.36–3.12]), pacemaker implantation (HR, 2.89 [95% CI, 1.83–4.57]), and all-cause mortality (HR, 1.44 [95% CI, 1.09–1.91]).<sup>13</sup> Compared with FHS participants 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.
- In a large, prospective, regional French registry of 6662 patients with STEMI presenting from 2006 to

2013, high-degree atrioventricular block was noted in 3.5% of individuals. In 64% of those with high-grade atrioventricular block, this level of conduction disease was present on admission. After multivariable adjustment, high-degree atrioventricular block on admission or occurring during the first 24 hours of hospitalization was not associated with in-hospital mortality (OR, 0.99 [95% CI, 0.60–1.66]).<sup>14</sup>

## Sinus Node Dysfunction

### Prevalence and Incidence

- Analysis of a sample of Medicare beneficiaries who underwent permanent pacemaker implantation between 1988 and 90 found that ≈50% were attributable to SND.<sup>15</sup>
- The incidence rate of SND was 0.8 per 1000 person-years of follow-up in 2 biracial US cohorts, ARIC and CHS.<sup>16</sup> The incidence increased per 5-year increment of advancing age (HR, 1.73 [95% CI, 1.47–2.05]). Investigators projected that the number of new cases of SND per year in the United States would rise from 78 000 in 2012 to 172 000 in 2060.<sup>16</sup>
- Bradycardia (including SND) has been reported in 12.8% of patients hospitalized with COVID-19 infection. The occurrence of bradycardia appears to be higher in Asia (20.5%) than in Europe (10.7%) and North or South America (13.6% and 8.0%, respectively).<sup>9</sup>
- A survey of 3846 patients hospitalized with COVID-19 infection at 2 London institutions revealed only 6 patients requiring permanent pacemaker implantation (4 implantations were indicated for Mobitz 2 or complete heart block, and 2 were for SND). All implantations were in males, whose mean age was 82.7 years.<sup>17</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>18</sup>
- Idiopathic degenerative disease is probably the most common cause of SND.<sup>19</sup>
- In the CHS and ARIC studies, factors associated with incident SND included White versus Black race (Black participants: HR, 0.59 [95% CI, 0.37–0.98]), higher mean BMI, height, prevalent hypertension, lower heart rate, right bundle-branch block, NT-proBNP, cystatin C, and history of a major cardiovascular event.<sup>16</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>20</sup> *SCN5A*,<sup>21</sup> *RYR2*,<sup>22</sup> *KCNJ3*,<sup>23</sup> and *KCNJ5*<sup>24</sup>) and variants in *ANK2*<sup>25</sup> and *TRPM4*<sup>26</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];  $P=1.5\times10^{-29}$ ).<sup>27</sup>

### Complications

#### (See Chart 18-1)

- 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>28,29</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>28</sup>
- Individuals requiring pacemakers for either SND or atrioventricular conduction block (N=2568) were randomized to receive either atrial or dual-chamber pacemakers. Those randomized to receive atrial or dual-chamber pacing had decreased development of AF (2.8%/y) compared with those randomized to single-chamber, ventricular-demand pacing (3.8%/y) over a mean 3-year follow-up.
- 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>30</sup>
- A large (N=1692157) observational study in France demonstrated a higher incidence of stroke in individuals with SND compared with those with other cardiac conditions (HR, 1.27 [95% CI, 1.19–1.35]). In contrast, the study observed that individuals with SND had a lower incidence of stroke compared with those with AF (HR, 0.77 [95% CI, 0.73–0.82]).<sup>31</sup>
- In a multicenter study from the Netherlands of 1517 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>32</sup>

- SVT, including AF, was prevalent in 53% of 2010 patients with SND.<sup>28</sup>
- An analysis conducted in the NIS reported that 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>33</sup>
- On the basis of NHDS data, the escalating rate of pacemaker implantation has been attributable to isolated SND, which increased by 102% from 1990 to 2002, whereas implantation for all other indications did not increase during this time frame (Chart 18-1).<sup>34</sup>

## SVT (Excluding AF and Atrial Flutter)

**ICD-9 427.0; ICD-10 I47.1.**

2020, United States: Underlying cause mortality—224. Any-mention mortality—2278.

2019, United States: Hospital discharges—42 000.

### Prevalence, Incidence, and Risk Factors

- 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.<sup>35</sup>
- A review of ED visits in US hospitals using NHAMCS data from 1993 to 2003 revealed that an estimated 550 000 visits (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]), were for SVT. 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>36</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>37</sup>

- SVTs other than AF or flutter have been reported in 9.7% of patients hospitalized with COVID-19 infection.<sup>9</sup> The prevalence of SVT appears higher in Asia (18.2%) than in Europe (10.3%) and North and South America (8.4% and 12.0%, respectively).

### 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>38</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 identified in the *HCN1* through *HCN4* genes.<sup>39</sup>
- Patients with ARVC can often present with ventricular arrhythmias. The Clinical Genome Resource Gene Curation Expert Panel appraised the 26 genes reportedly associated with ARVC and found that only 6 genes (*PKP2*, *DSP*, *DSG2*, *DSC2*, *JUP*, and *TMEM43*) had strong evidence and 2 genes (*DES* and *PLN*) had moderate evidence of association with ARVC.<sup>40</sup>

### Complications

- A retrospective study of individuals in a California administrative database from 2009 (N=4 806 830) 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>41</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>42</sup>
- In a Swedish study of 214 patients (51% females) with paroxysmal SVT undergoing ablation, females had a longer history of symptomatic arrhythmia ( $16.2\pm14.6$  years versus  $9.9\pm13.1$  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>43</sup>

### Types of SVT

- Atrioventricular nodal reentrant tachycardia was the most common mechanism of SVT among adults

presenting for invasive electrophysiological study and ablation (56%) in a case series of 1754 individuals from 1991 to 2003.<sup>44</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>44</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>45</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 being the predominant mechanism in older individuals (60% and 30%, respectively, among patients >80 years of age).<sup>44</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 individuals undergoing catheter ablation.<sup>44</sup>
- Multifocal atrial tachycardia is an arrhythmia that may be confused with AF and is characterized by ≥3 distinct P-wave morphologies, irregular R-R intervals, and a ventricular 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>46</sup> and adults,<sup>47</sup> with a prevalence in hospitalized adults estimated at 0.05% to 0.32%.<sup>47</sup> The average age at onset in adults is 72 years. Adults with multifocal atrial tachycardia have a high mortality rate, with estimates of ≈45%, but this is generally ascribed to the underlying condition(s).<sup>47</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>48</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>49</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>50</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>51</sup>
- A cohort study from Intermountain Healthcare with ≈8 years of follow-up reported that rates of cardiac arrest were low and similar between patients with WPW and control subjects without WPW. In follow-up, WPW was associated with a significantly higher risk of AF (HR, 1.55 [95% CI, 1.29–1.87]); 7.0% of the patients with WPW developed AF compared with 3.8% of those without WPW.<sup>52</sup>
- Asymptomatic adults with ventricular preexcitation appear to be at no increased risk of sudden death compared with the general population.<sup>53,54</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>55</sup>
- In a meta-analysis of 20 studies involving 1869 asymptomatic patients with a WPW electrocardiographic pattern followed up for 11 722 person-years, the rate of sudden death was estimated to be 1.25 (95% CI, 0.57–2.19) per 1000 person-years in a random-effects model. Risk factors for sudden death included male sex and age <18 years.<sup>56</sup>
- Several studies in asymptomatic children with ventricular preexcitation detected by screening suggest a benign prognosis.<sup>54,57</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>58</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>59</sup>

- A multicenter international survey of 1589 subjects ≤21 years of age (mean, 13 years of age) with preexcitation identified that 15% had non-persistent (intermittent) preexcitation.<sup>60</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 electrophysiological 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.**

2020, United States: Underlying cause mortality—26616. Any-mention mortality—217279.

2019, United States: Hospital discharges—488000.

### **Prevalence**

#### **See Chart 18-2**

- Prevalence of AF in the United States is estimated to increase from ≈5.2 million in 2010 to 12.1 million in 2030.<sup>61</sup>
- From the Rotterdam Study, the prevalence of AF in adults >55 years of age in the European Union 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>62</sup>
- Among Medicare beneficiaries ≥65 years of age diagnosed with AF from 1993 to 2007, the prevalence increased ≈5%/y, from 41.1 per 1000 beneficiaries to 85.5 per 1000 beneficiaries.<sup>63</sup>
- In an integrated, regional health care system, the incidence of AF increased from 4.74 (95% CI, 4.58–4.90) per 1000 person-years in 2006 to 6.82 (95% CI, 6.65–7.00) in 2018. Increases in incidence were observed in all subgroups by sex and age. The study did not report data on AF incidence by race or ethnicity.<sup>64</sup>
- Investigators from MESA identified clinically detected AF after 14.4 years of follow-up as 11.3% in NH White people, 7.8% in Hispanic people, 6.6% in NH Black people, and 9.9% in those of Chinese origin. In contrast, in these same individuals, the proportion with AF detected with 14-day electrocardiographic monitoring was 7.1% in NH White people, 6.9% in Hispanic people, 6.4% in NH Black

people, and 5.2% in those of Chinese origin (Chart 18-2).<sup>65</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>66</sup>
- In a population-based analysis conducted in South Korea, the prevalence of AF increased from 0.73% in 2006 to 1.53% in 2015 and is estimated to reach 5.35% in 2050 and 5.81% in 2060.<sup>67</sup>

### **Incidence**

- In a sample of Medicare beneficiaries, the age- and sex-standardized incidence of AF was 27.3 per 1000 person-years in 1993 and 28.3 in 2007, representing a 0.2% mean annual increase ( $P=0.02$ ).<sup>63</sup>
- An analysis of a geographically diverse US health insurance claims database estimated the incidence of AF as increasing from 1.2 million new cases in 2010 to 2.6 million in 2030.<sup>61</sup>
- In a population-based analysis conducted in South Korea, the incidence of AF between 2006 and 2015 remained flat at 1.77 new cases per 1000 person-years during this 10-year observation period.<sup>67</sup>
- The incidence of AF in American Indian people in California administrative databases was similar to that in White people and higher than in Black, Asian, and Hispanic people.<sup>68</sup>

### **Lifetime Risk and Cumulative Risk**

#### **(See Chart 18-3)**

- In the ARIC study, the lifetime risk of AF was estimated as 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>69</sup>
- In a population-based study conducted in Taiwan, 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>70</sup>
- The lifetime risk for AF in individuals of European ancestry has been estimated as ≈1 in 3.
  - In the BiomarCaRE Consortium including 4 community-based European studies, the incidence of AF began to increase after 50 years of age in males and 60 years of age in females with a cumulative incidence of ≈30% by 90 years of age.<sup>71</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% when accounting for both clinical and genetic risk.<sup>72</sup> A subsequent analysis conducted in the FHS reported that individuals with optimal cardiovascular risk

profiles had a lifetime AF risk of 23.4% (95% CI, 12.8%–34.5%), those with a borderline risk profile had a lifetime AF risk of 33.4% (95% CI, 27.9%–38.9%), and those with an elevated risk profile had a lifetime AF risk of 38.4% (95% CI, 35.5%–41.4%; Chart 18-3).<sup>73</sup>

### **Secular Trends**

- Over 50 years of observation in the FHS (1958–1967 to 1998–2007), the age-adjusted prevalence and incidence of AF approximately quadrupled (prevalence: from 2% to 10% in males, from 1% to 5% in females; incidence: from 4 to 13 per 1000 person-years in males, from 3 to 9 per 1000 person-years in females). However, when only AF that was ascertained on ECGs collected in the FHS was considered, the prevalence increased from 1.3% to 2.6% in males and from 0.8% to 1.2% in females, but the incidence did not increase (remaining at ≈2 per 1000 person-years in males and females), suggesting that enhanced surveillance may contribute to AF identification. Although the prevalence of 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 of these conditions).<sup>74</sup>
- Between 2000 and 2010 in Olmsted County, Minnesota, age- and sex-adjusted incidence rates and survival did not change.<sup>75</sup> However, over a similar time frame in the United Kingdom (2001–2013), the incidence of nonvalvular AF in people ≥45 years of age increased modestly from 5.9 (95% CI, 5.8–6.1) to 6.9 (95% CI, 6.8–7.1) per 1000 patient-years, with the largest increase observed in those >80 years of age.<sup>76</sup>
- Between 1999 and 2013, among Medicare fee-for-service beneficiaries, rates of hospitalization for AF increased ≈1%/y.<sup>77</sup> Although the median hospital length of stay, 3 days (IQR, 2.0–5.0 days), did not change, the mortality rate declined by 4%/y, and hospital readmissions at 30 days declined by 1%/y.
- Analysis of a national health insurance database in Korea from 2006 to 2015 reported that the prevalence of AF increased 2.10-fold and the incidence remained flat (1.8 per 1000 person-years). Concurrently, the 2-year risks of all-cause mortality (HR, 0.70 [95% CI, 0.68–0.93]) and ischemic stroke (HR, 0.91 [95% CI, 0.88–0.93]) after AF declined.<sup>67</sup>
- COVID-19 and 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>78</sup> An analysis of IQVIA longitudinal prescription claims, medical claims,

and institutional claims data from January 2019 to July 2020 of individuals receiving anticoagulation for AF (N=1 439 145) identified significant reductions in ED visits, inpatient admissions, and hospital admissions for ischemic stroke or bleeding at the onset of the declaration of the COVID pandemic.<sup>79</sup>

### **Risk Factors**

(See Chart 18-4)

- The highest PAF for AF was for hypertension, followed by BMI, smoking, cardiac disease, and diabetes in ARIC (Chart 18-4).

### **BP and Hypertension**

- In MESA, the PAF (percent) of AF attributable to hypertension appeared to be higher in US Chinese (46.3% [95% CI, 24.9%–76.5%]), Hispanic (43.9% [95% CI, 20.3%–60.5%]), and NH Black (33.1% [95% CI, 20.6%–53.8%]) participants than in NH White participants (22.2% [95% CI, 10.8%–32.3%]). In contrast, the PAFs for diabetes, BMI ≥30 kg/m<sup>2</sup>, and current smoking were not significant for any racial or ethnic strata.<sup>80</sup>
- Among 9 797 418 individuals enrolled in the Korean National Health Insurance Service and followed up from 2009 to 2017, a graded association between hypertension and AF was identified. In reference to nonhypertension, the HR was 1.15 for prehypertension, 1.39 for hypertension without medication, 1.85 for hypertension treated <5 years, and 2.34 for hypertension treated ≥5 years. Each 5-mm Hg increase in SBP and DBP was associated with an increased risk of 4.3% and 4.6%, respectively, of incident AF.<sup>81</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 obesity. Individuals with obesity had an RR of 1.51 for developing AF (95% CI, 1.35–1.68) compared with those without obesity.<sup>82</sup>
- A meta-analysis of 29 studies related anthropometric components 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>83</sup>
- In a meta-analysis of 10 studies (N=108 996), 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>84</sup>

- A genetic mendelian randomization study conducted in a consortium of 7 cohorts of European ancestry identified significant associations between both a genotype associated with obesity and a BMI GRS comprising 39 SNPs with increased risk of incident AF.<sup>85</sup>

### **Smoking**

- A meta-analysis of 29 studies identified that current smoking was associated with an RR of 1.32 (95% CI, 1.12–1.56) for AF, former smoking with an RR of 1.09 (95% CI, 1.00–1.18), and ever-smoking with an RR of 1.21 (95% CI, 1.12–1.31) compared with the referent of never having smoked. 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>86</sup>

### **Diabetes and HbA1c**

- In a meta-analysis of 8 prospective studies (N=102 006), elevated 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>87</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>88</sup>
- A machine-learning meta-analysis of 29 studies (N=8 037 756) reported similar risks of incident AF in individuals with type 1 and type 2 diabetes. In a meta-analysis, diabetes was associated with an RR of 1.11 (95% CI, 1.01–1.22) for incident AF in males and an RR of 1.38 (95% CI, 1.19–1.60) in females.<sup>89</sup>

### **Activity and Exercise**

(See Chart 18-5)

- A longitudinal study from Detroit, MI, reported a dose-response relationship between objectively assessed exercise capacity and lower risk of new-onset AF.<sup>90</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 achieved during exercise testing, respectively. Every 1-unit peak MET increase 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.
- An analysis in the Korea National Health Insurance Service (N=66 692) classified individuals by exercise status before and after AF diagnosis.

Compared with those who continued not to exercise, those who maintained exercise were significantly less likely to have ischemic stroke (HR, 0.86 [95% CI, 0.77–0.96]), HF (HR, 0.92 [95% CI, 0.88–0.96]), or mortality (HR, 0.61 [95% CI, 0.55–0.67]; Chart 18-5).<sup>91</sup>

- A meta-analysis of 9 observational studies concluded that endurance athletes had an increased risk of AF compared with referents not engaging in comparable exertional activity (OR, 2.34 [95% CI, 1.04–5.28]). The investigators reported substantial heterogeneity in the data and identified the highest risks observed among males and individuals <60 years of age.<sup>92</sup>
- A meta-analysis of 23 observational studies included 1930 725 individuals, in whom there were 45 839 cases of AF. The most physically active had an RR of 0.99 (95% CI, 0.93–1.05) compared with the least active. This association was modified by sex: The most physically active males had an increased risk (RR, 1.20 [95% CI, 1.02–1.42]) and females had a decreased risk (RR, 0.91 [95% CI, 0.84–0.99]) for AF.<sup>93</sup>

### **HD as a Risk Factor**

- Among participants in the FHS, type of HF (HFrEF or HFpEF) was not differentially associated with the incidence of AF, but prevalent AF was marginally more strongly associated ( $P=0.06$ ) with multivariable-adjusted incidence of HFpEF (HR, 2.34 [95% CI, 1.48–3.70]) than with HFrEF (HR, 1.32 [95% CI, 0.83–2.10]).<sup>94</sup>
- Individuals with congenital HD are at increased risk of AF. In an analysis in Sweden including 21 982 individuals with congenital HD and 219 816 without congenital HD, 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>95</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>96</sup> CKD,<sup>97</sup> and moderate or heavy alcohol consumption.<sup>98</sup> Concerning heavy alcohol consumption, a small study (N=100) correlated alcohol ingestion with AF as identified by mobile rhythm monitor and concluded that ingestion of a single alcoholic beverage was associated with an OR of 2.02 (95% CI, 1.38–3.17) and ingestion of ≥2 drinks with an OR of 3.58 (95% CI, 1.63–7.89) relative to the absence of alcohol use.<sup>99</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>100</sup>
- A meta-analysis of sleep quality reported associations between insomnia (N=3 studies) and increased odds of AF (OR, 1.30 [95% CI, 1.26–1.35]) and frequent awakening (N=2 studies) and AF (OR, 1.36 [95% CI, 1.13–1.63]).<sup>101</sup>
  - Air pollution:
    - A systematic review and meta-analysis of 18 studies reported short-term and long-term associations of air pollution with AF.<sup>102</sup> For every 10- $\mu\text{g}/\text{m}^3$  increase in PM2.5 and PM10 (particles with aerodynamic diameter <10  $\mu\text{m}$ ) concentration, the ORs for AF were 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 PM2.5 and 1.03 (95% CI, 1.03–1.04) for PM10. 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.
  - The association of caffeine ingestion and AF has been variable. In the Spanish PREDIMED study, ingestion of 1 to 7 cups of coffee weekly was associated with decreased AF risk (HR 0.53 [95% CI, 0.36–0.79]) compared with no or rare coffee ingestion.<sup>103</sup> However, a higher level of caffeine ingestion (>1 cup of coffee per day) was not associated with AF risk (HR, 0.79 [95% CI, 0.49–1.28]) compared with no or rare coffee ingestion.
  - 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 multivariable adjustment (HR, 1.13 [95% CI, 1.02–1.24]).<sup>104</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  $\geq 16$  on 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>105</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>106</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>107</sup>
  - AF frequently occurs secondary to other comorbidities.
    - Among 11239 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 did not vary significantly over the observation period.<sup>108</sup>
    - A meta-analysis of 13 studies (N=52959) reported that new-onset AF has been observed in 10.9% (95% CI, 7.22%–15.33%) of patients undergoing noncardiac general surgery.<sup>109</sup>
    - A meta-analysis of 13 studies (N=225841) determined that new-onset AF during sepsis was associated with  $\approx 2$ -fold increase in in-hospital mortality (OR, 2.09 [95% CI, 1.53–2.86]), postdischarge mortality (OR, 2.44 [95% CI, 1.81–3.29]), and stroke (OR, 1.88 [95% CI, 1.13–3.14]). The incidence of AF varied with severity of sepsis, from 1.9% in mild sepsis to 46% in septic shock.<sup>110</sup>
    - AF is a common occurrence in hospitalized patients with COVID-19. A meta-analysis of 14 studies (N=17435) reported an incident atrial arrhythmia (AF, atrial flutter, or atrial tachycardia) in 8.2% (95% CI, 5.5%–11.3%) of patients hospitalized with COVID-19.<sup>111</sup> An international registry of patients hospitalized with COVID-19 reported that AF was the most common arrhythmia in COVID cases, occurring in 509 (61.5%) of 827 events.<sup>9</sup>
  - Reports suggest that cancer and cancer medications are associated with increased risk of AF. For example, a meta-analysis of 8 studies (N=2580) reported that ibrutinib was associated with AF (RR, 4.69 [95% CI, 2.17–7.64]).<sup>112</sup> A meta-analysis of 6 studies (N=533514) 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>113</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 and Health Equity

- Study of social determinants and AF remains limited.<sup>114</sup>
- In an analysis of a large regional health care system, individuals (N=28858) living in intermediate-poverty neighborhoods (as defined by census tract-level variables) had higher adjusted odds of 5-year incident AF (OR, 1.23 [95% CI, 1.01–1.48]) compared with those residing in lower-poverty neighborhoods.<sup>115</sup>
- An analysis of an administrative claims study of individuals with prevalent AF (N=336736) identified

that those with household income <\$40 000/y had increased risks for HF (HR 1.17, [95% CI, 1.05–1.30]) and MI (HR, 1.18 [95% CI, 0.98–1.41]) compared with those with household income ≥\$100 000/y.<sup>116</sup>

- In an analysis in the community-based ARIC study, AF incidence decreased with progressively increased categories of income and education.<sup>69</sup> The risk of AF in White males with annual income ≥\$50 000 was an RR of 0.76 (95% CI, 0.65–0.88) and in White females 0.70 (95% CI, 0.59–0.83) compared with those with annual income <\$25 000. Income was not associated with AF risk in Black males; in Black females with annual income ≥\$25 000, the risk was an RR of 0.73 (95% CI, 0.56–0.96) compared with those with annual income <\$25 000. Similar estimates were observed with educational attainment.
- In a 5% sample of Medicare beneficiaries, NH Black individuals were significantly less likely to receive oral anticoagulation (OR, 0.84 [95% CI, 0.78–0.91]) than NH White individuals. There was no difference between Hispanic individuals (OR, 0.92 [95% CI, 0.83–1.01]) and NH White individuals. Among initiators of oral anticoagulation, DOAC use was low (35.8% NH White individuals, 29.3% NH Black individuals, 40.0% Hispanic individuals). NH Black individuals were less likely to initiate DOACs than NH White individuals (OR, 0.75 [95% CI, 0.66–0.85]); in contrast, the odds of DOAC initiation did not differ between Hispanic and NH White individuals (OR, 1.02 [95% CI, 0.88–1.18]).<sup>117</sup>
- In a limited-sized cohort (N=339) followed up for a median of 2.6 years (range, 0–3.4 years), individuals in the lowest income category (<\$19 999/y) had 2.0-fold greater hospitalization risk (OR, 2.11 [95% CI, 1.08–4.09]) compared with those in the highest income category (≥\$100 000/y).<sup>118</sup>

### Risk Prediction of AF

- Life's Simple 7:
  - In the REGARDS study, better CVH, as classified by Life's Simple 7, was associated with 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>119</sup>
  - The ARIC study observed that cohort participants 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>120</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>121</sup>

- A similar analysis in the MESA cohort reported a 27% lower risk of AF over a median follow-up of 11.2 years (IQR, 10.6–11.7 years) 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>122</sup>
- ARIC,<sup>123</sup> FHS,<sup>124</sup> and WHS<sup>125</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).
- A CHARGE-AF risk prediction model for AF has been validated in a US multiethnic patient cohort,<sup>126</sup> in MESA,<sup>127</sup> in a UK cohort (EPIC Norfolk),<sup>128</sup> in a post-CABG cohort,<sup>129</sup> and in a large nationwide primary care database in the Netherlands.<sup>130</sup>
- A study evaluating electronic health records in a uniform health care system (N=2 252 219) used machine-learning models to predict 6-month incident AF.<sup>131</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>132</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 an RR of 2.88 (95%

CI, 1.79–4.64;  $P<0.001$ ) for thromboembolism, which was higher with longer duration ( $\geq 5$  minutes: RR, 3.86; <1 minute: RR, 1.77).<sup>133</sup>

- A meta-analysis reported that high-atrial-rate episodes detected by implanted cardiac devices were associated with  $\approx 2$ -fold increased thromboembolic stroke risk (RR, 2.13 [95% CI, 1.53–2.95]) in studies excluding patients with prior AF or atrial tachyarrhythmias (n=7 studies including 4961 participants) and across all studies (N=10 including 37 266 participants; RR, 1.92 [95% CI, 1.44–2.55]).<sup>134</sup>

### **Community Screening for Undiagnosed AF**

(See Chart 18-6)

- 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>135</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>136</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 698 900 were undiagnosed, including 535 400 (95% CI, 331 900–804 400) in individuals  $\geq 65$  years of age and 163 500 (95% CI, 17 700–400 000) in individuals 18 to 64 years of age.<sup>137</sup>
- A multicenter, open-label, randomized trial of individuals  $\geq 75$  years of age with hypertension compared a 2-week continuous electrocardiographic patch coupled with an automated home BP machine with oscillometric AF screening capability and usual care over a 6-month period.<sup>138</sup> AF was detected in 23 of 434 (5.3%) in the screening group compared with 2 of 422 (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 (18 of 434 [4.1%] versus 4 of 422 [0.9%]; risk difference, 3.2% [95% CI, 1.1%–5.3%]).<sup>138</sup>
- A multicenter clinical trial randomized individuals with at least 1 stroke risk factor and without prevalent AF in a 1:3 ratio to receive long-term rhythm monitoring with an implanted loop recorder (n=1501) or usual care (n=4503).<sup>140</sup> Over a median follow-up of 64.5 months (IQR, 59.3–69.8 months), those randomized to monitoring were 3-fold more likely to be diagnosed with AF (HR, 3.17 [95% CI, 2.81–3.59]).

- A multicenter, parallel-group RCT conducted in Sweden evaluated the effect of intermittent ECGs for 14 days as an intervention for AF detection on a composite outcome of stroke, systemic embolism, bleeding, and mortality compared with usual care. After a median follow-up of 6.9 years (IQR, 6.5–7.2 years), there were significantly fewer primary end point events in the intervention group (n=13 979; 5.45 events per 100 years [95% CI, 5.52–5.61]) than in the control group (n=13 996; 5.68 events per 100 years [95% CI, 5.52–5.85]). The intervention was associated with an  $\approx 4\%$  reduced risk for the composite outcome (HR, 0.96 [95% CI, 0.92–1.00]).<sup>141</sup>
- 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>142</sup>
  - The US Preventive Services Task Force has concluded that evidence for screening for AF in individuals  $\geq 50$  years of age remains lacking.<sup>143</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% (95% CI, 1.13%–1.82%) in those  $\geq 65$  years of age and 0.41% in individuals  $< 65$  years of age. The study included low-, middle-, and 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>144</sup>
  - Another systematic review included 25 published studies from 2000 to 2015 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% [95% CI, 1.4%–2.3%] versus 1.1% [95% CI, 0.6%–1.6%]) and with multiple (2.1% [95% CI, 1.5%–2.8%]) versus single-time-point (1.2% [95% CI, 0.8%–1.6%]) rhythm assessments.<sup>145</sup>
  - Wearable, commercially available technology:

- 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>146</sup>
- To date, no studies have demonstrated that AF screening reduces mortality or incidence of thromboembolic complications. The minimum duration of AF episodes required to increase risk for stroke is unknown. However, longer episode duration is associated with increased thromboembolic risk (Chart 18-6); the threshold varies depending on the presence of other stroke risk factors.<sup>147</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>148,149</sup>
- A recent prospective observational cohort study has noted that among individuals with early-onset AF (age <66 years), the prevalence of disease-associated pathogenic/likely pathogenic variants in cardiomyopathy and arrhythmia-associated genes was 10.1%.<sup>150</sup> The prevalence of the pathogenic/likely pathogenic variants was highest among patients with an AF diagnosed before 30 years of age ( $\approx 17\%$ ) and was lowest among those diagnosed with AF after 60 years of age ( $\approx 7\%$ ).<sup>150</sup>
- A prospectively enrolled 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 [95% CI, 1.06–6.91]), Hispanic (OR, 9.25 [95% CI, 2.37–36.34]), and European (OR, 2.51 [95% CI, 1.29–4.87]) descent.<sup>151</sup>
- A Taiwanese population-based study (>23 million people) 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 (76.6%) environmental factors.<sup>152</sup>
- A study conducted in CHS and ARIC suggested that genetic markers of European ancestry were associated with an increased risk of incident AF.<sup>153</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>154</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>155</sup>
- Whole-exome/genome sequencing studies have identified rare mutations in additional genes associated with AF, including *MYL4*,<sup>156</sup> and loss-of-function mutations in *SCN4B* and *KCNA5*, a conserved gene that encodes the voltage-gated Kv1.5 potassium channel.<sup>157,158</sup> Loss-of-function variants in the titin gene have been associated with early-onset AF.<sup>159,160</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 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>72</sup>
- Proteomic studies have identified proteins identified with incident AF. For example, in the ARIC study, 4668 participants were followed up for  $5.7 \pm 1.7$  years, during which 585 developed AF. After adjustment for clinical factors, NT-proBNP was associated with the risk of incident AF (HR, 1.82 [95% CI, 1.68–1.98];  $P=2.91 \times 10^{-45}$  per doubling of NT-proBNP). After further adjustment for medication use and GFR, the study identified 17 proteins significantly associated with incident AF. The study implicated matrix metalloprotease inhibition as the foremost canonical pathway in AF pathogenesis.<sup>161</sup>
- It is unclear whether genetic markers of AF could improve risk prediction for AF over models that include only clinical factors.<sup>125</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%]) and in late-onset cases (net reclassification index, 10.4% [95% CI, 4.1%–16.7%]).<sup>162</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>163</sup>

- GRSs also could identify patients at higher risk of cardioembolic stroke<sup>164</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>165</sup> and after CABG.<sup>166</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 are associated with cardiac conduction, arrhythmias, and other cardiovascular end points.<sup>167</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>168</sup> A GRS of PR interval–associated variants was found to be associated with a higher risk of atrioventricular block (OR per SE of GRS, 1.11;  $P=7\times10^{-8}$ ) and pacemaker implantation (OR, 1.06;  $P=1.5\times10^{-4}$ ) and reduced risk of AF (OR, 0.95;  $P=4.3\times10^{-8}$ ).
- In a study of 19 709 participants from ARIC, MESA, and 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 those in the highest quintile in adjusted models.<sup>169</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 (HR, 0.71 [95% CI, 0.60–0.83];  $P<0.001$ ) risk of developing AF in a median 19-year follow-up than matched referents.<sup>170</sup> A registry-based study that matched individuals with obesity and diabetes undergoing bariatric surgery to those not having surgery reported a 41% reduced risk of AF (HR, 0.59 [95% CI, 0.44–0.78]) and concomitant HF and AF (HR, 0.23 [95% CI, 0.12–0.46]) after bariatric surgery during a mean 4.5-year follow-up.<sup>171</sup>

#### **Secondary Prevention of AF: Observational Data**

- Increasingly more data support the importance of risk factor modification for secondary prevention of AF recurrence and improved symptoms.
  - In individuals who underwent catheter ablation, those who agreed to aggressive risk factor modification ( $n=61$ ) had lower symptom burden in follow-up and higher adjusted AF-free survival

than those receiving standard care ( $n=88$ ; 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 ( $0.74\pm1.3$  versus  $1.05\pm1.60$ ), cardioversions ( $0.89\pm1.50$  versus  $1.51\pm2.30$ ), and ablation procedures ( $0.60\pm0.69$  versus  $0.72\pm0.86$ ) than their counterparts who declined enrollment ( $n=147$ ; mean follow-up, 49 months). Participation in risk factor management was associated with a predicted 10-year cost savings of \$12 094 per patient.<sup>173</sup>
- Treatment of OSA has been noted to decrease risk of progression to permanent AF.<sup>174</sup> In a meta-analysis of 8 studies (N=1247), CPAP use 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>175</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.
- A study of 2 national Canadian primary care audits observed that of 11 264 individuals with AF, 84.3% were eligible for at least 1 evidence-based cardiovascular 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>176</sup>

### **Prevention: Randomized Data**

#### **Primary Prevention of AF: Randomized Data**

- In the ACCORD study (N=10 082), intensive glycemic control was not associated with reduced occurrence of incident AF ( $P=0.52$ ).<sup>177</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>178</sup> However, the studies were primarily secondary or post hoc analyses, the intervention duration was modest, and the results were 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>179</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>180</sup>
- A post hoc analysis of the PREDIMED randomized primary prevention study (N=6705) 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]) compared with the control diet. After a median follow-up of 4.7 years, there were 253 cases of AF across all 3 study arms.<sup>181</sup>

- Although heterogeneous in their findings, modest-sized short-term studies suggested that the use of statins may contribute to the prevention of AF; however, larger longer-term studies do not provide support for the concept that statins are effective in AF prevention.<sup>182</sup>

### **Secondary Prevention of AF: Randomized Data**

- An Australian multisite, open-label, controlled trial randomized 140 adults who consumed ≥10 drinks of alcohol per week with a history of AF and sinus rhythm at baseline either to abstain from alcohol or to continue their usual alcohol consumption.<sup>183</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**

- An analysis in REGARDS reported that individuals not aware of their AF diagnosis ( $n=150$ ) had a 94% higher risk of mortality in follow-up compared with individuals who were aware ( $n=2058$ ).<sup>184</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 limited health literacy. In adjusted analyses, limited health literacy was associated with a lack of awareness of AF diagnosis (literacy PR, 0.96 [95% CI, 0.94–0.98]).<sup>185</sup>

### **Treatment and Control**

#### **Anticoagulation Undertreatment**

- 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>186</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 ≥4, received an oral anticoagulant prescription.<sup>187</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>188</sup>
  - In the PINNACLE registry, females were significantly less likely to receive oral anticoagulation at all levels of CHA<sub>2</sub>DS<sub>2</sub>-VASC scores (56.7% versus 61.3%;  $P<0.001$ ).<sup>189</sup>
  - An analysis in the PINNACLE registry also reported that receipt of warfarin versus a DOAC varied significantly by type of insurance: Military-, private-, and Medicare-insured patients were more likely to receive newer anticoagulants than individuals with Medicaid or other insurance.<sup>190</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>191</sup>

#### **Racial and Ethnic Disparities in Treatment**

- In the ORBIT-AF II US-based registry study of outpatients with AF, Black individuals were less likely than their White counterparts to receive DOACs if an anticoagulant was prescribed, after adjustment for socioeconomic and clinical factors (aOR, 0.73 [95% CI, 0.55–0.95]); there were no significant differences in DOAC use for AF between groups of White and Hispanic individuals.<sup>192</sup>

#### **Role of Coordinated Care**

- A systematic review and meta-analysis identified 3 studies of coordinated systems of care that included 1383 patients.<sup>193</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];  $P=0.0002$ ) but not with cerebrovascular events or hospitalizations related to AF.

## Mortality

### 2016 ICD-9 427.3; ICD-10 I48.

(See Chart 18-7)

In 2020, AF was the underlying cause of death in 26 616 people and was listed on 217 279 US death certificates (any-mention mortality; unpublished NHLBI tabulation using NVSS<sup>194</sup>).

- The age-adjusted mortality rate attributable to AF was 6.4 per 100 000 people in 2020 (unpublished NHLBI tabulation using CDC WONDER<sup>195</sup>).
- Although there was significant between-study heterogeneity ( $P<0.001$ ), a meta-analysis of 30 studies ( $N=4\,371\,714$ ) identified that the adjusted risk of death was significantly higher in females with AF than in males (RR, 1.12 [95% CI, 1.07–1.17]).<sup>196</sup>
- An observational study of Olmsted County, Minnesota, residents with first diagnosis of AF or atrial flutter between 2000 and 2010 had 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>75</sup>
- The association of AF with mortality in the FHS 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 ( $P_{\text{trend}}=0.70$ ).<sup>197</sup>
- From 2006 to 2015, all-cause mortality events decreased in individuals diagnosed with AF ( $N=679\,416$ ) in the Korean National Insurance Service (Chart 18-7).<sup>67</sup> The 2-year risk of all-cause mortality decreased by 30% for those individuals diagnosed in 2013 relative to those diagnosed in 2006 (HR, 0.70 [95% CI, 0.68–0.72]).
- AF is also associated with increased mortality in subgroups of individuals, including the following:
  - Individuals with other cardiovascular conditions and procedures, including HCM,<sup>198,199</sup> MI,<sup>200</sup> pre-CABG,<sup>201</sup> post-CABG<sup>200,202,203</sup> (both short term<sup>202</sup> and long term<sup>202,203</sup>), post-transcatheter aortic valve implantation,<sup>204</sup> PAD,<sup>205</sup> and stroke.<sup>206</sup>
  - Individuals with AF have increased mortality with concomitant HF<sup>207</sup> including HFpEF<sup>208</sup> and HFrEF.<sup>208</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];  $P_{\text{interaction}}<0.001$ ).<sup>209</sup>

– AF is also associated with an increased risk of death in individuals with other conditions, including diabetes,<sup>177,210</sup> sepsis,<sup>211</sup> and critical illness in the ICU<sup>212</sup>; in individuals after primary PCI<sup>213</sup>; and in individuals  $\geq 80$  years of age with hypertension.<sup>214</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>215</sup> In contrast, in the 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>216</sup>
- In a US-based study, there was substantial variation in mortality with AF in US counties from 1980 to 2014.<sup>217</sup> Investigators estimated that there were  $\approx 22\,700$  (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  $>90$ th percentile were clustered in Oregon; California; Utah; Idaho; northeastern Montana; areas east of Kansas City, MO; and southwest West Virginia.<sup>217</sup>
- In a study using the NIS for the period of 2010 to 2015 ( $N=3\,264\,258$ ), adjusted in-hospital mortality in the setting of AF was higher (4.8% versus 4.3%;  $P=0.02$ ) among Medicaid beneficiaries than among individuals with private insurance. Medicaid recipients were significantly less likely to be discharged to home (55.3%) than those with private insurance (61.3%) and were noted to have longer median length of stay (5 days [IQR, 3–9 days]) compared with those with private insurance (4 days [IQR, 2–8 days]).<sup>218</sup>
- Investigators conducted multivariable cross-sectional analyses of the NIS between 2012 and 2014 ( $N=248\,731$ ) and observed that patients admitted to rural hospitals ( $n=29\,785$ ) had a 17% higher risk of death than those admitted to urban hospitals (OR, 1.17 [95% CI, 1.04–1.32]).<sup>219</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>220</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 over a median follow-up of 3.5 years (IQR, 1.5–5.5 years). The results were similar in models that additionally adjusted for anticoagulant and statin treatment (HR, 1.39 [95% CI, 1.05–1.83]).<sup>221</sup> In another study from the same group, unmarried and divorced males and males with lower educational attainment with AF had a higher risk of mortality than their married and better-educated male counterparts.<sup>222</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>223</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 emboli 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, those experiencing systemic emboli were more likely to be female (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>224</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 9.3%/y.<sup>225</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 (~3- to 5-fold increased risk) has not varied substantively with advancing age,

the proportion of strokes attributable to AF has increased significantly. In the FHS, AF accounted for ≈1.5% of strokes in individuals 50 to 59 years of age and ≈23.5% in those 80 to 89 years of age.<sup>226</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>215</sup> The increased risk persisted in analyses adjusted for anticoagulant therapy status.<sup>215</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 ≥65 years of age.<sup>227</sup>
- In an analysis of individuals with AF receiving care in a multihospital health system, Black individuals with AF were more likely to be younger and female and to have more cardiovascular risk factors than White individuals with AF. 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>228</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>229</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>196</sup>

### Cognition and Dementia

- A meta-analysis of 11 prospective studies including 112 876 participants with normal baseline cognition and without acute stroke reported an adjusted 34% (HR, 1.34 [95% CI, 1.24–1.44]) higher incidence of dementia in individuals with AF compared with those without AF.<sup>230</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>231</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>232</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.

- In the REGARDS study, participants with self-reported or ECG-ascertained AF had significantly lower scores on cognitive testing compared with those without (eg, Montreal Cognitive Assessment, Word List Learning, and Delayed Recall tasks). Over 8.1 mean years of follow-up, declines in Word List Learning scores were steeper in those with AF compared with those without.<sup>233</sup> None of the other cognitive measures showed a significant decline in those with and without AF.
- An administrative study in the United Kingdom examined oral anticoagulation and risk of dementia and cognitive impairment in individuals with AF. DOAC users were significantly less likely to receive a diagnosis of dementia (HR, 0.84 [95% CI, 0.73–0.98]) or MCI (HR, 0.74 [95% CI, 0.65–0.84]) than those treated with a vitamin K antagonist over 501 days (IQR, 199–978 days) of follow-up observation.<sup>234</sup>

### 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>235</sup> and diminished quality of life.<sup>236</sup>
- Females with AF have consistently been demonstrated to have lower quality of life with AF than males. In the ORBIT-AF Registry, females had significantly lower AF-specific quality of life scores (mean, 80; IQR, 62–92) compared with males (mean, 83; IQR, 69–94).<sup>237</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>238</sup>

### Heart Failure

- AF and HF share many antecedent risk factors, and  $\approx 40\%$  of people with either AF or HF will develop the other condition.<sup>94,207</sup>

- In the community, estimates of the incidence of HF in individuals with AF ranged from 3.3<sup>207</sup> to 5.8<sup>239</sup> per 100 person-years of follow-up. In Olmsted County, Minnesota, in individuals with AF, the incidence of HFpEF was 3.3 per 100 person-years of follow-up (95% CI, 3.0–3.7), which was more common than HFrEF (2.1 [95% CI, 1.9–2.4]).<sup>239</sup>
- A study of Medicare beneficiaries (N=39 710) examined the relationship between AF burden and new-onset HF, HF hospitalization, and mortality in those with newly implanted cardiac devices and prevalent AF. A 10% increase in burden of AF at 1 year after device implantation was associated with new HF (HR, 1.09 [95% CI, 1.06–1.12]) and mortality (HR, 1.05 [95% CI, 1.01–1.10]). Among those with prevalent HF, a 10% increased AF burden was associated with HF hospitalization (HR, 1.05 [95% CI, 1.04–1.06]) and mortality (HR, 1.06 [95% CI, 1.05–1.08]).<sup>240</sup>
- Among older adults with incident AF in Medicare (N=230 940), the 5-year rates of events were 13.7% for HF, 7.1% for stroke, 1.2% for MI, and 48.8% for mortality.<sup>241</sup> Higher rates of death and CVD after new-onset AF were associated with older age and higher mean CHADS<sub>2</sub> score.
- 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 (95% CI, 8.72–18.68) versus 1.99 (95% CI, 1.70–2.33) 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 (95% CI, 2.69–9.02) versus 0.85 (95% CI, 0.67–1.08) with and without AF with a multivariable-aHR of AF of 4.80 (95% CI, 1.30–17.70).<sup>242</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>243</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>243</sup>
- Both REGARDS<sup>244</sup> and the ARIC study<sup>245</sup> observed that the risk of MI after AF was higher in females than in males.
- For individuals with AF in REGARDS,<sup>244</sup> CHS,<sup>246</sup> and ARIC,<sup>216</sup> a higher risk of MI was observed in Black than White people.
- In ARIC, AF as a time-varying independent variable was associated with a 63% increased risk of MI (HR, 1.63 [95% CI, 1.32–2.02]). In further analysis,

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>245</sup>

#### Chronic Kidney Disease

- In a health plan registry of people with CKD ( $N=206\,229$ ), new-onset AF ( $n=16\,463$ ) was associated with an adjusted 1.67-fold (95% CI, 1.46–1.91) increased risk of developing ESRD compared with no AF (74 versus 64 per 1000 person-years of follow-up).<sup>247</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>248</sup>
- In a meta-analysis of 27 studies including 8401 individuals with AF and 67 608 controls without AF, AF was associated with a doubling in risk of sudden death (pooled RR, 2.04 [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>249</sup>

#### AF Type and Complications

- A meta-analysis of 12 studies ( $N=99\,996$ ) 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>250</sup>
- In the Canadian Registry of Atrial Fibrillation, 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>251</sup>

#### Atrial Flutter Versus AF

- Using a 5% sample of Medicare beneficiaries from 2008 to 2014, investigators identified 18 900 ischemic strokes among 318 138 individuals with AF and 14 953 with atrial flutter. The study reported the annual stroke rate to

be 2.02% (95% CI, 1.99%–2.05%) in individuals with AF and 1.38% (95% CI, 1.22%–1.57%) in those with atrial flutter. After adjustment for demographics and vascular risk factors, the risk of stroke was significantly lower in individuals with atrial flutter than in those with AF (HR, 0.69 [95% CI, 0.61–0.79]).<sup>252</sup>

- A national Taiwanese study compared the prognoses of 175 420 individuals with AF and 6239 individuals with atrial flutter. Using propensity scoring, the study observed that compared with individuals with atrial flutter, those with AF had significantly higher incidences of ischemic stroke (1.63-fold [95% CI, 1.42–1.87]), HF hospitalization (1.70-fold [95% CI, 1.46–1.97]), and all-cause mortality (1.08-fold [95% CI, 1.03–1.13]).<sup>253</sup>

#### Hospitalizations and Ambulatory Care Visits

- According to HCUP data,<sup>254</sup> in 2019, there were 488 000 hospital discharges with AF and atrial flutter as the principal diagnosis (unpublished NHLBI tabulation).
- There were 4 977 000 physician office visits (NAMCS, unpublished NHLBI tabulation)<sup>255</sup> in 2018 and 740 000 ED visits in 2019 for AF (HCUP,<sup>254</sup> unpublished NHLBI tabulation).
- Using cross-sectional data (2006–2014) from the HCUP's Nationwide ED 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 (SE, 0.02 day). 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>256</sup>
- A meta-analysis of 35 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>257</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>258</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, 25.0%; and ≥65 years, 75.0%.
- 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 ED 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>259</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, the analysis estimated that stroke-related health care costs were \$8184, \$12895, and \$41420 for lower-middle-, middle-, and high-income economies, respectively.<sup>259</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>77</sup>
- Costs of AF have been estimated for higher-income countries. In Denmark, for example, investigators estimated that the 3-year societal costs of AF were approximately €20 403 to €26 544 per person and €219 to €295 million.<sup>260</sup>

**Global Burden of AF**

(See Charts 18-8 and 18-9)

- The GBD Study 2020 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 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 15 400 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>261</sup>

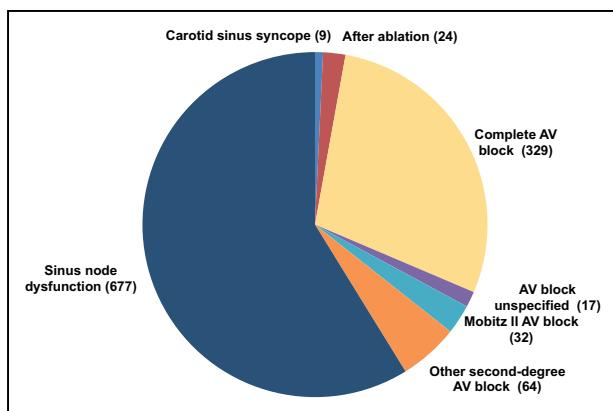
**Table 18-1. Cumulative Incidence Rate Over 5 Years After AF Diagnosis by Age, United States, Diagnosed 1999 to 2007**

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.

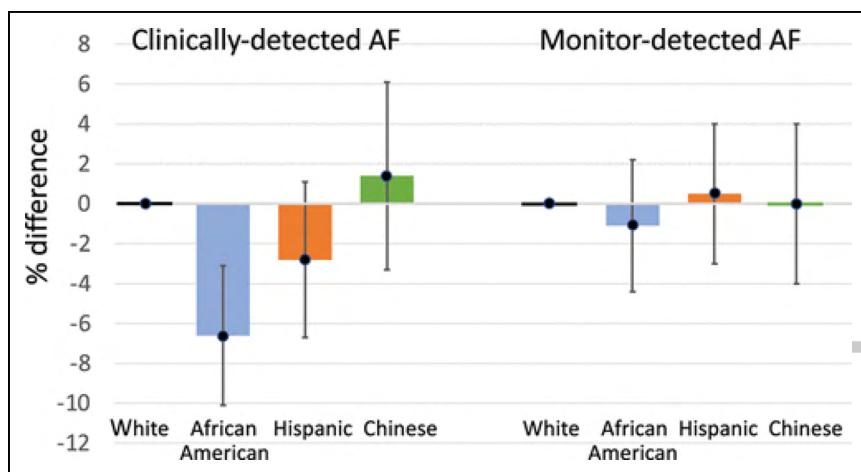
Source: Adapted from Piccini et al<sup>241</sup> with permission of the European Society of Cardiology. Copyright © 2013 The Authors.



**Chart 18-1. 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.

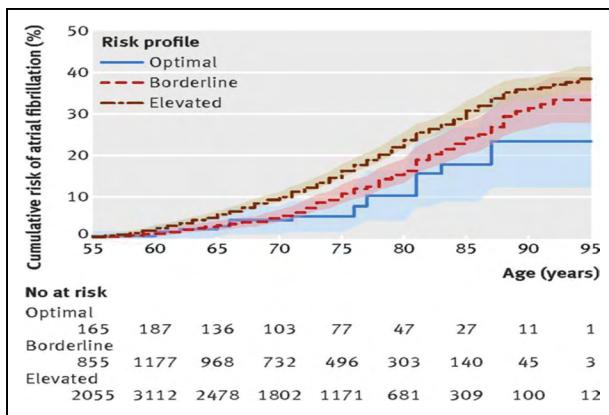
Source: Data derived from Birnie et al.<sup>34</sup>



**Chart 18-2. Adjusted percent difference in AF prevalence compared with White individuals for clinically detected AF (2000–2018) and monitor-detected AF (2016–2018) in the MESA Study.**

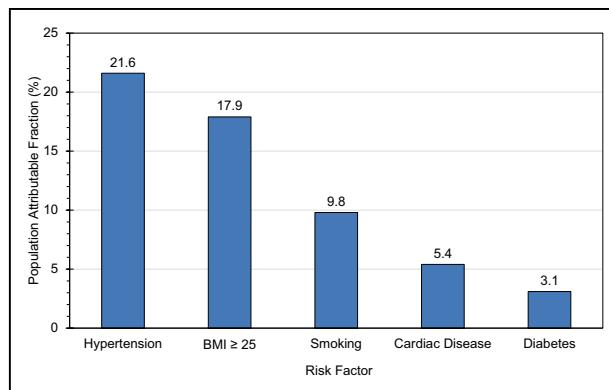
Adjusted for age, sex, height, weight, treated hypertension, current smoking, diabetes, SBP, history of HF, and history of MI; estimates for monitor-detected AF are also adjusted for monitoring duration. Vertical lines indicate 95% CI. AF indicates atrial fibrillation; HF, heart failure; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; and SBP, systolic blood pressure.

Source: Reprinted with permission from Heckbert et al.<sup>65</sup> Copyright © 2020 American Heart Association, Inc.



**Chart 18-3. 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.**

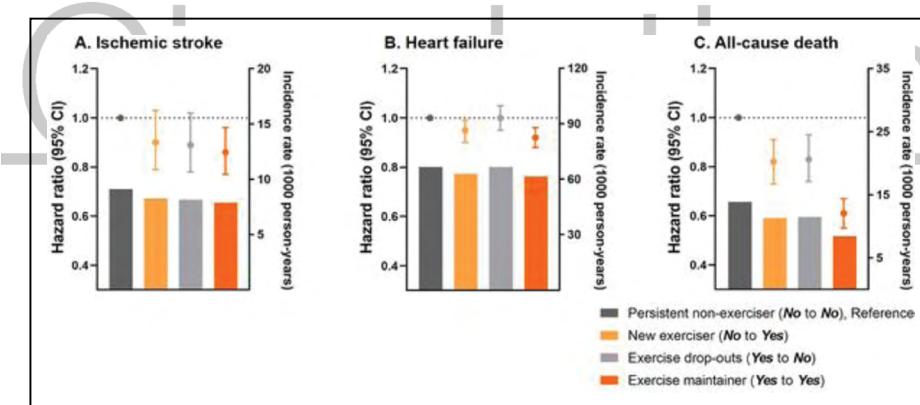
AF indicates atrial fibrillation; and FHS, Framingham Heart Study. Source: Reprinted from Staerk et al.<sup>73</sup> Copyright © 2018, The Authors. Published on behalf of the Authors by the British Medical Group. This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build on this work noncommercially, and license their derivative works on different terms, provided the original work is properly cited and the use is noncommercial. See <http://creativecommons.org/licenses/by-nc/4.0/>.



**Chart 18-4. PAF of major risk factors for AF in the ARIC study, 1987 to 2007.**

Cardiac disease includes a history of CAD or HF; smoking refers to current smoker.

AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CAD, coronary artery disease; HF, heart failure; and PAF, population attributable fraction. Source: Data derived from Huxley et al.<sup>132</sup>



**Chart 18-5. Retrospective analysis conducted in the Korean National Health Insurance Service of individuals (N=66 692) who underwent self-reported exercise assessment 2 years before and after AF diagnosis, 2010 to 2016.**

**A.** Ischemic stroke. **B.** HF. **C.** All-cause death. HRs with 95% CIs for ischemic stroke, HF, and all-cause death according to the change in exercise status.<sup>91</sup> Bars denote weighted incidence rates; dots, HRs; and whiskers, 95% CIs computed by weighted Cox proportional hazards models with inverse probability of treatment weighting.

AF indicates atrial fibrillation; HF, heart failure; and HR, hazard ratio.

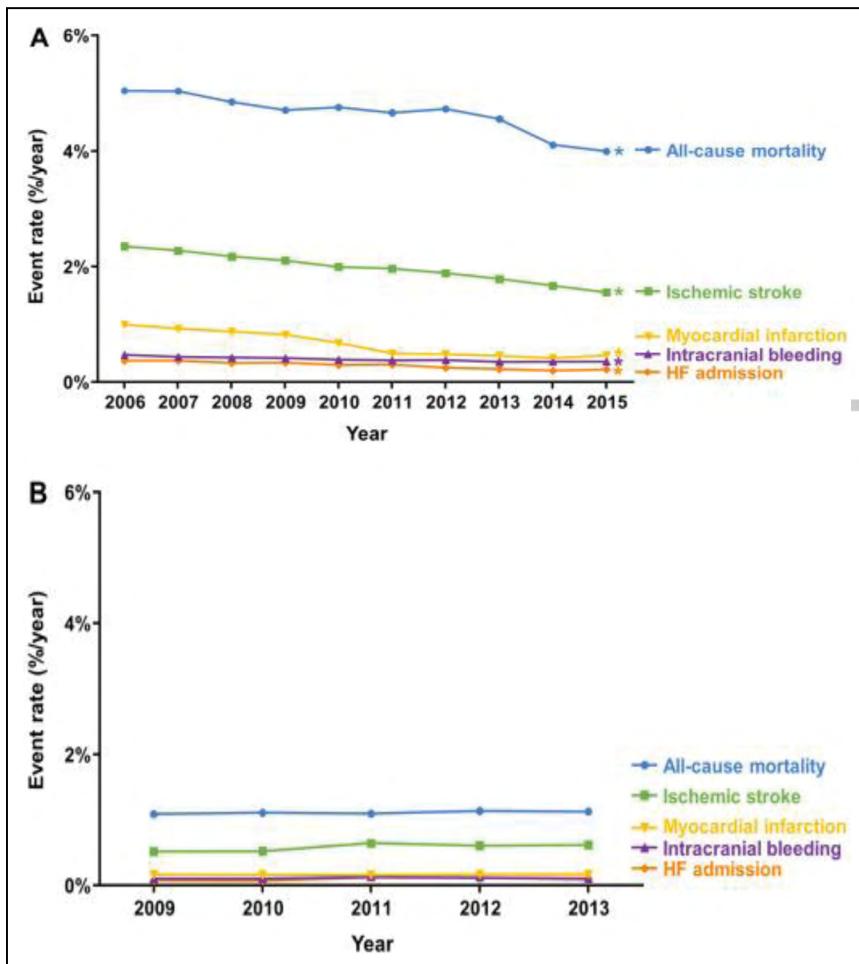
Source: Adapted from Ahn et al.<sup>91</sup> Copyright © 2021, The Authors. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits noncommercial reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

Maximum Daily AF Duration	CHA <sub>2</sub> DS <sub>2</sub> -VASc Score				
	0 n=2922 (13.4%)	1 n=2151 (9.9%)	2 n=4554 (20.9%)	3-4 n=7164 (32.9%)	≥5 n=4977 (22.9%)
No AF n=16815 (77.2%)	0.33% 40 events	0.62% 46 events	0.70% 95 events	0.83% 139 events	1.79% 157 events
AF 6 min–23.5 h n=3381 (15.5%)	0.52% 11 events	0.32% 4 events	0.62% 17 events	1.28% 42 events	2.21% 36 events
AF >23.5 h n=1572 (7.2%)	0.86% 4 events	0.50% 3 events	1.52% 19 events	1.77% 28 events	1.68% 13 events

**Chart 18-6. Risk of stroke and systemic embolism in nonanticoagulated patients (N=21768) by AF duration and CHA<sub>2</sub>DS<sub>2</sub>-VASc score from the Optum electronic health record deidentified database, 2007 to 2017.**

Stroke and systemic embolism rates over the 1% threshold are shaded red; those under the 1% threshold are shaded green. AF indicates atrial fibrillation.

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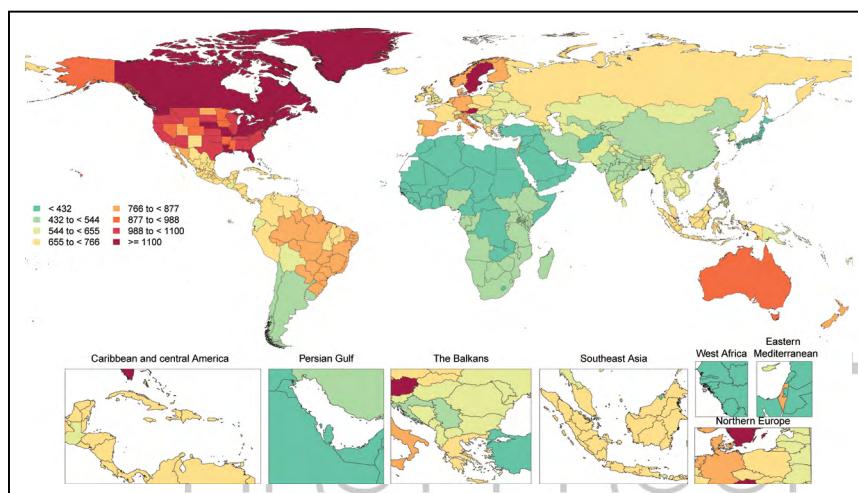
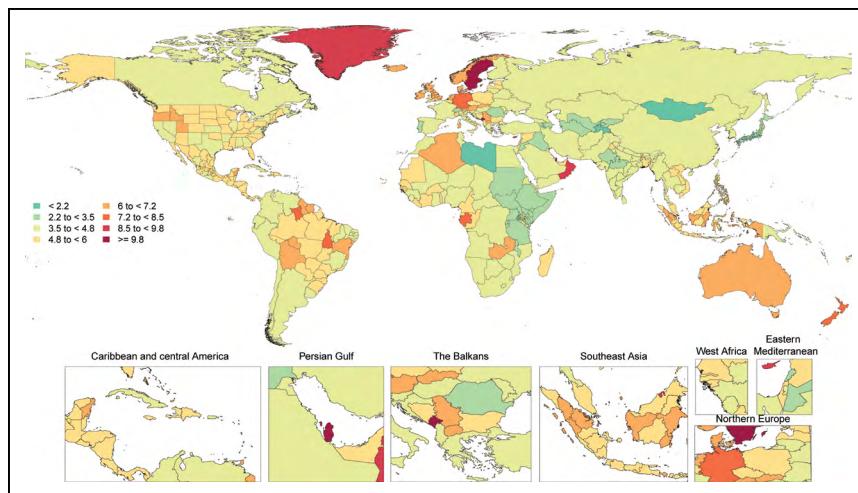


**Chart 18-7. Temporal trends of the 1-year adverse event rates from 2006 to 2015 in (A) 679 416 adults with newly diagnosed AF and (B) those without AF in the Korean National Health Insurance Service database.**

The 1-year adverse event rates (percent per year) were calculated by dividing the number of the first lifetime event that occurred in each year by the total number of patients at the start of the year who had not experienced that event previously.  $P_{trend} < 0.001$ .

AF indicates atrial fibrillation; and HF, heart failure.

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# Circulation

## 19. SUDDEN CARDIAC ARREST, VENTRICULAR ARRHYTHMIAS, AND INHERITED CHANNELOPATHIES

**See Tables 19-1 through 19-6 and Charts 19-1 through 19-5**

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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.**

2020, United States: Underlying cause mortality—19 427. Any-mention mortality—436 852.

### Tachycardia

**ICD-9 427.0, 427.1, 427.2; ICD-10 I47.1, I47.2, I47.9.**

2020, United States: Underlying cause mortality—1065. Any-mention mortality—10 041.

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 70 846 OHCAAs from 1992 to 2014, 92% of cases had medical causes. Among nonmedical cases, trauma was the most common cause.<sup>3</sup>

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

### Incidence

(See Tables 19-1 and 19-2)

- The ongoing CARES registry<sup>4</sup> estimates the incidence of EMS-treated OHCA among individuals of any age in >2200 EMS agencies in the United States. Differences in bystander intervention and survival by race, ethnicity, and sex are listed in Table 19-1.
- Incidence of EMS-treated OHCA in people of any age is 92.3 individuals per 100 000 population according to the 2021 CARES registry, with great variation between states (range, 44.2–135.5; Table 19-2).
- 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 >120 000 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%, which translates to 116 per 100 000 person-years (if everyone was followed up for 90 days; 0.19% at 30 days or 228 per 100 000 person-years).<sup>5</sup>
- Incidence of maternal cardiovascular collapse requiring CPR during childbirth was 10 in 250 719 (4.0 per 100 000 births) in a registry of births in New York.<sup>6</sup>
- Incidence of IHCA is 292 000 people each year on the basis of extrapolation of GWTG data to the total population of hospitalized patients in the United States.<sup>7,8</sup>
- Incidence of IHCA among 15 953 rapid response team calls in Australia was 159 cases in 152 individuals or 0.62 IHCAAs per 1000 multiday admissions (IQR, 0.50–1.19).<sup>9</sup>
- In the HCUP NIS for 2019<sup>10</sup>:
  - There were 28 000 hospital discharges with a primary diagnosis of cardiac arrest.
  - There were 237 000 hospital discharges with all-listed diagnoses of cardiac arrest.
  - There were 187 000 ED discharges with a principal diagnosis of cardiac arrest.

### Incidence and Response: COVID-19 Effects

The COVID-19 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>11</sup> Compared with the pre-COVID control period, individuals experiencing OHCA during COVID were older and more likely to be Asian, Black, Hispanic, or of >1 race than White. There was a higher prevalence of asystole and pulseless electric activity (ie, nonshockable

rhythms) during the COVID-19 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>12</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-19 infection was not a predictor of attempts to resuscitate.<sup>13</sup>
- In Paris, France, the incidence of OHCA doubled during the initial surge of 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>14</sup>
- Early in the COVID-19 pandemic, incidence of OHCA in the United States was higher than in 2019, primarily in communities with high COVID-19 mortality (adjusted mean difference, 38.6 [95% CI, 37.1–40.1] per million residents) and very high COVID-19 mortality (adjusted mean difference, 28.7 [95% CI, 26.7–30.6] per million residents).<sup>15</sup>
- A study of nontraumatic OHCA calls in 3 counties in southeast Michigan between January 1 and May 31 of both 2019 and 2020 showed a 60% increase in OHCA calls during the pandemic months compared with the control period.<sup>16</sup> The increase in OHCA calls slightly lagged but otherwise mirrored the rise and fall of confirmed COVID-19 cases in the counties. OHCA increased disproportionately among individuals  $\geq 85$  years of age, Black individuals, and residents of nursing facilities. In 2020, patients with OHCA were 53% less likely to receive an advanced airway device compared with 2019 (397 patients [21.4%] in 2020 versus 529 [45.5%] in 2019;  $P < 0.001$ ). Of the calls received, the proportion that were for individuals who died in the field increased by 42% (1400 patients [75.5%] in 2020 versus 619 [53.3%] in 2019;  $P < 0.001$ ). A similar significant increase in OHCA and dead-on-arrival EMS responses was observed in Los Angeles, CA, in 2020 starting around the time of California's stay-at-home order compared with 2018 and 2019 ( $P < 0.001$ ).<sup>17</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>18</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>19</sup>

- In a Swiss study, a significant contribution to the increase in OHCA was attributable to delay in seeking care for AMI.<sup>20</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>21</sup> A similar delay in ambulance response times was also noted in Taiwan.<sup>22</sup>
- The French National OHCA registry reported significant declines in frequency of performance of basic life support and advanced life support during COVID.<sup>23</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.<sup>24</sup> Among the 48 individuals who survived to hospital discharge, 58.3% had normal or mildly impaired neurological status, whereas 41.7% had moderate to severe neurological dysfunction.
- In a large US registry, rates of sustained return of spontaneous circulation after OHCA were, on average, 28% lower during the first wave of the pandemic (March 16 through April 2020) compared with the corresponding period in 2019 (23.0% versus 29.8%; adjusted rate ratio, 0.82 [95% CI, 0.78–0.87];  $P < 0.001$ ).<sup>15</sup> The decline in sustained return of spontaneous circulation paralleled the concurrent rate of COVID-19 mortality in the community, ranging from 11% to 15% in communities with very low or low rates of COVID-19 mortality to 21% to 33% in communities with high or very high rates of COVID mortality.<sup>15</sup>



## OHCA: Adults

### (See Table 19-3)

- In Saskatoon, Saskatchewan, a retrospective survey of 372 adult OHCAs 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>25</sup>
- In 2021, location of OHCA in adults was most often a home or residence (73.4%), followed by public settings (16.3%) and nursing homes (10.3%; Table 19-3). 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 16.6% of EMS-treated adult OHCAs in 2021 (Table 19-3).
  - Of 4729 patients with STEMI in Los Angeles County, California, from 2011 to 2014, 422 (9%) had OHCA.<sup>26</sup>
  - Of 851 line-of-duty firefighter fatalities with adjudicated cause of death, 319 (37%) were cardiac in origin.<sup>27</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>28</sup>
  - MI with OHCA or cardiac arrest in the ED occurred in 9682 (3.8%) of 252 882 patients from 224 hospitals in the NCDR ACTION Registry (2594 or 1.6% of patients with NSTEMI and 7088 or 7.5% of patients with STEMI).<sup>29</sup>

## IHCA: Adults

(See Table 19-3)

- Incidence of IHCA was 4.0 per 1000 hospitalizations (range, 1.4–11.8 per 1000 hospitalizations) on the basis of 2205 hospitalizations at 101 Veterans Health Administration hospitals between 2008 and 2012.<sup>30</sup>
- Incidence of IHCA was 1.7 per 1000 hospital admissions on the basis of 18 069 patients with IHCA in the Swedish Register of CPR.<sup>31</sup>
- IHCA within the first 24 hours after admission for STEMI occurred in 7.8% (136) of 1754 patients in the ARGEN-IAM-ST. Features associated with IHCA were older age and cardiogenic shock.<sup>32</sup>
- IHCA incidence was 320 (1.50%) of 21 337 patients with ACS admitted to 3 hospitals in China from 2012 to 2016.<sup>33</sup>
- According to 2021 GWTG data, location of adult IHCA was the ICU, operating room, or ED in 60.9% and noncritical care areas in 39.2% among 45 815 events at 357 hospitals (Table 19-3).
- Initial recorded cardiac rhythm was VF or VT in 12.9% of adult IHCAs in 2021 GWTG data (GWTG—Resuscitation, unpublished data, 2021; Table 19-3).

- Intraoperative cardiac arrest in adults occurred with an incidence of 5.7 per 10 000 hospital admissions in which there was an operating room procedure in a 2016 survey of the NIS.<sup>34</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>35–38</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>39</sup>

## Pathology of SCA/SCD

(See Chart 19-1)

- 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>40</sup> The second study was a community-based survey of out-of-hospital SCD.<sup>41</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 19-1). 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 electric activity, the autopsy was likely to result in a classification of nonsudden arrhythmic death.

## OHCA: Children

(See Table 19-3)

- In 2021, location of EMS-treated OHCA was home for 82.7% of children in the CARES data. Location was a public place for 16.7% of the children (Table 19-3).<sup>4</sup>
- Annual incidence of pediatric OHCA was 8.7 per 100 000 population in Western Australia from 2011 to 2014.<sup>42</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>43</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>44</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>45</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>46</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>47</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>48</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>44</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>49</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>50</sup>
- Preparticipation screening of 5169 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>51</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 19-3)

- Of 1639 events of IHCA in children (30 days–18 years of age) at 125 hospitals, 71.6% occurred in the ICU, operating room, or ED and 28.0% in noncritical care areas per 2021 GWTG data (Table 19-3).
- 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>52</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>53</sup>
- Initial recorded cardiac arrest rhythm was VF or VT in 8.0% of 1639 pediatric events at 125 hospitals in GWTG—Resuscitation in 2021 (Table 19-3).
- 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>54</sup>

## Lifetime Risk and Cumulative Incidence

(See Table 19-4 and Chart 19-2)

- SCD appeared among the multiple causes of death on 13.0% of death certificates in 2020 (436 852 of 2 854 838; Table 19-4). Because some people survive SCA, the lifetime risk of cardiac arrest is even higher.
- In 2020, infants had a higher incidence of SCD (10.9 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 30 to 34 years of age (11.2 per 100 000; Chart 19-2).
- 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>55</sup>

## Secular Trends

### (See Charts 19-3 and 19-4)

- 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>56</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, from 14.1 (1997–2000) to 8.7 (2011–2014) per 100 000 population. The incidence was even lower among children <1 year of age.<sup>42</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>57</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>58</sup> This reduction in SCD was associated with more frequent use of β-blockers (85% versus 71%), mineralocorticoid antagonists (64% versus 44%), implantable cardioverter defibrillators (19% versus 2%), and resynchronization therapy (7.2% versus 4.8%).
- Age-adjusted death rates for any mention of SCD declined from 137.7 per 100 000 population in 1999 to 91.2 per 100 000 population by 2019 and increased to 106.0 in 2020 (Chart 19-3).
- Crude incidence of OHCA increased significantly from 64.75 to 76.10 per 100 000 from 2002 to 2014 in a registry of 30 560 patients from Queensland, Australia.<sup>59</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 39.8% between 2000 and 2021 in GWTG data (Chart 19-4).
- 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>60</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%).

- A multicenter observational study of 7433 hospitalized pediatric patients who received CPR from 2000 to 2018 found significant increases in survival, from 19% in 2000 to 38% in 2018.<sup>61</sup> The improvement in survival plateaued after 2010.

## Risk Factors

### (See Chart 19-5)

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 19-5).<sup>62</sup>

- Among patients with DCM considered to be 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>63</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).
- A substudy of the DANISH trial of patients with nonischemic systolic HF (EF ≤35%) demonstrated an association of nonsustained VT and frequent ventricular premature depolarizations with total and cardiovascular mortality but no relation to SCD.<sup>64</sup>
- 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>65</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>65</sup>
- Incidence of OHCA increased with daily atmospheric levels of particulate matter in 249 372

OHCAs in Japan from 2014 to 2015 (OR, 1.016 [95% CI, 1.009–1.023] per 10- $\mu\text{g}/\text{m}^3$  increase in PM2.5).<sup>66</sup> Similar findings were reported recently from Israel and Italy.<sup>67,68</sup>

- Among 5869 autopsied individuals 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>69</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>70</sup>

### Age

(See Chart 19-2)

- In 2020, mortality rates for any mention of SCD decreased with increasing age category (<1, 1–4, and 5–9 years of age) in those 0 to 9 years of age and increased for those  $\geq$ 10 years of age with each 5-year age category through 84 years of age (Chart 19-2).

### 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>71</sup>
- In a registry that included 40 159 OHCAs from 2009 to 2012 in Singapore, Japan, the Republic of Korea, Malaysia, Thailand, Taiwan, and the United Arab Emirates, females represented 40% of individuals experiencing an OHCA.<sup>72</sup> Females were older, more often presented in a nonshockable rhythm, and more often received layperson CPR. There was no difference between sexes in survival of the event or survival to hospital discharge after adjustment for measured confounding factors.
- In an EMS-based registry of 3862 OHCAs from 2013 to 2015 that includes 90% of the population of New Zealand, OHCA was more common in males (69%) than females (31%).<sup>73</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.
- In a prospective postmortem study in San Francisco County, all incident presumed SCDs in people 18

to 90 years of age were autopsied through active surveillance of consecutive out-of-hospital deaths between February 1, 2011, to March 1, 2014.<sup>74</sup> Among 525 autopsied presumed SCDs in San Francisco County, after adjustment for age and race, females had more noncardiac causes of presumed SCD, including pulmonary emboli (8% versus 2%) and neurological causes (10% versus 3%; both  $P < 0.01$ ). Males had 3-fold higher rates of autopsy-proven sudden arrhythmic deaths (defined as cases in which no extracardiac cause of death or HF was noted on autopsy) compared with females, whereas more females had primary electric disease (4% versus 2%;  $P = 0.02$ ) and nonischemic causes (53% versus 39%;  $P < 0.01$ ).

- In a prospective multicenter international registry of 2407 patients admitted to ICUs after OHCA from 2012 to 2017, females were less likely to survive to hospital discharge, but the difference was attenuated after adjustment for differences in clinical characteristics (30.1% versus 42.7%; aOR, 0.85 [95% CI, 0.67–1.08]).<sup>75</sup> Females were less likely to have a good neurological outcome at discharge from the index hospitalization (21.4% versus 34.0%; aOR, 0.74 [95% CI, 0.57–0.96]) and at 6 months after arrest (16.7% versus 29.4%; aOR, 0.73 [95% CI, 0.54–0.98]). The use of neuroimaging and other neurophysiological testing did not differ by sex. Females were more likely to undergo withdrawal of lifesaving therapy (55.6% versus 42.8%; aOR, 1.35 [95% CI, 1.09–1.66]).

### Race

- In the ARIC study, 215 of 3832 (5.61%) Black and 332 of 11 237 (2.95%) White participants experienced SCD during 27.4 years of follow-up.<sup>76</sup> The sex-adjusted HR for SCD comparing Black with White participants was 2.12 (95% CI, 1.79–2.51), and the fully aHR was 1.38 (95% CI, 1.11–1.71).
- In a prospective postmortem study in San Francisco County, all incident presumed SCDs in individuals 18 to 90 years of age were autopsied through active surveillance of consecutive out-of-hospital deaths between February 1, 2011, and March 1, 2014.<sup>74</sup> Among 525 autopsied presumed SCDs in San Francisco County, sudden arrhythmic death was defined as deaths for which no extracardiac cause or acute HF was noted on autopsy. After adjustment for age, Black females had higher incidence of sudden arrhythmic death than White females (IRR, 2.55 [95% CI, 1.38–4.71];  $P < 0.01$ ), Asian males had a lower incidence than White males (IRR, 0.51 [95% CI, 0.36–0.73];  $P < 0.01$ ), and Hispanic males had a lower incidence than White males (IRR, 0.51 [95% CI, 0.31–0.85];  $P < 0.01$ ). Among autopsy-proven sudden arrhythmic deaths, MI with nonobstructive

coronary arteries was more common in Asian individuals than in White individuals (7% versus 1%;  $P<0.05$ ).

#### **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>77</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>55</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>78</sup>
- In a cohort of 1937360 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>79</sup>
- In a cohort of 1937360 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>80</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>81</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 a higher risk of incident SCD/SCA or VF/VT (RR, 2.04 [95% CI, 1.77–2.35]).<sup>82</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>83</sup>
- Risk of SCD in the general population ≥45 years of age 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>84</sup>
- A logistical 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>84</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>85</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>86</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>87</sup>
- In a meta-analysis that included 17 studies with 118 954 subjects, presence of depression or depressive symptoms was associated with increased risk of SCD (HR, 1.62 [95% CI, 1.37–1.92]), specifically for VT/VF (HR, 1.47 [95% CI, 1.23–1.76]).<sup>88</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 ≥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, ≈0.5).<sup>89</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>90</sup>

- Early warning score systems using both clinical criteria and vital signs identified hospitalized patients with a higher risk of IHCA<sup>91</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>92</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>93</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 ≥40 years of age, including Brugada syndrome in 0.13%, QTc <340 milliseconds in 0.18%, and QTc ≥480 milliseconds in 0.42%.<sup>94</sup>
- Among 12241 ARIC study participants, of whom 346 participants 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>95</sup>
- Among 20 177 participants 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 electric heterogeneity measured on a standard 12-lead ECG at baseline and during follow-up demonstrated an independent predictor of risk for SCD.<sup>96</sup>
- In a cohort of 4176 individuals 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 controls.<sup>97</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>98–100</sup>
- Screening of 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>101</sup>

- Multiple studies have attempted to quantify the yield of genetic screening in probands and their family members:
  - 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>102</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 presumptive diagnosis in 25% of families: Brugada syndrome in 11%, LQTS in 7.8%, DCM in 3.1%, and HCM in 3.1%.<sup>103</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>104</sup>

- Prevalence of genetic HD is reported to decline with increasing age among survivors of SCA according to a report on 180 patients from a genetic heart rhythm clinic from 1999 to 2017.<sup>105</sup> Among 127 adults, diagnoses included idiopathic VF (44.1%), arrhythmogenic bafflelet 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%).

### **Genome-Wide Association Studies**

- GWASs on cases of arrhythmic death attempt to identify previously unidentified common 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 variations may not portend a significant risk factor for SCD.<sup>106</sup> However, the oligogenic nature of genetic determinants of SCA requires further evaluation.
- Although SCA GWASs are limited, investigations have been conducted using multiple electrocardiographic traits as a phenotype (ie, QRS, QT duration), which have identified novel genetic variants associated with these traits that are also associated with cardiac conduction, arrhythmias, and other cardiovascular end points.<sup>107</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>108</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>109,110</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>111</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>112,113</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>114</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>115</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>116</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>117</sup>
- Genetic testing for LQTS among 281 families had a diagnostic yield for genetic variants of 47%.<sup>118</sup> Nearly a third of acquired LQTS patients are reported to carry pathogenic congenital LQTS variants.<sup>119</sup>
- However, some studies have called into question whether previously identified LQTS genes are truly causative.<sup>120,121</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 (*CALM1*, *CALM2*, *CALM3*, *TRDN*) having definitive evidence for association with disease onset in childhood. That group has found that *KCNE1* and *KCNE2*, which are commonly clinically tested, had limited or disputed evidence for typical LQTS but showed strong evidence for association with acquired LQTS. Several induced pluripotent stem cell–cardiomyocytes models are now being used to assess the significance of novel variants and to understand mechanisms of action of modifier genes.<sup>122</sup>

- GWASs have identified additional rare and common variants in genes associated with QT interval,<sup>120</sup> suggesting that individuals with long QT who are variant negative could have a polygenic inheritance.
- Drug-induced LQTS was a concern among patients with COVID-19 during the first wave because of the use of medications such as chloroquine, hydroxychloroquine, azithromycin, lopinavir, and ritonavir, which had QT-prolonging effects.<sup>123</sup> With subsequent studies proving their lack of efficacy, these drugs are no longer used in the management of COVID-19.
- 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. No patient developed TdP.<sup>124</sup>
- 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.<sup>123</sup> 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.
- 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.<sup>125</sup> 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.

- 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>126</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.<sup>127</sup> Patients treated with QT-prolonging agents had significantly longer QTc, but the increase in QTc was not associated with mortality independently.
- 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>128</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>129</sup>
- Prevalence of a QTc interval <320 milliseconds in a population of 41 767 young, predominantly male Swiss conscripts was 0.02%,<sup>130</sup> which was identical to the prevalence in a Portugal sudden death registry.<sup>131</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>132</sup> Short QT intervals were associated with male sex and Afro-Caribbean ethnicity.
- Prevalence of QT interval ≤340 milliseconds in 99 380 unique patients ≤21 years of age at Cincinnati Children's Hospital between 1993 and 2013 was 0.05%.<sup>133</sup> Of these children, 15 of 45 (33%) were symptomatic.

### 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>134</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<sub>1</sub> and V<sub>2</sub>), either at rest or with provocative testing, and susceptibility to ventricular arrhythmias and SCD.<sup>135</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>136</sup> Prevalence was higher in males (0.9%) than in females (0.1%).<sup>137</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>138</sup>
- In a multicenter retrospective study of 770 patients with Brugada syndrome, 177 (23%) were female.<sup>139</sup> At initial presentation, 85% were asymptomatic. Females were less likely to have a type 1 electrocardiographic pattern (31% versus 55%), but females were more likely to have a family history of SCD (49.7% versus 29.8%). Genetic testing was positive in 19% of females versus 13.5% of males ( $P=0.06$ ). During mean follow-up of 122 months 2.8% of females versus 7.1% of males ( $P=0.04$ ) experienced appropriate implantable cardioverter defibrillator therapy or SCD. Two factors independently predicted arrhythmic events: a positive genetic test (OR, 18.71 [95% CI, 1.82–192.53]) and AF (OR, 21.12 [95% CI, 1.27–350.85]).
- Family history of SCD has not been helpful in risk prediction of patients with Brugada syndrome. However, a meta-analysis of 22 studies involving 3386 patients found that history of SCD in family members <40 years of age doubled the risk for a major arrhythmic event.<sup>140</sup>

### Genetics

- Brugada syndrome is considered primarily a monogenic mendelian disease with autosomal dominant inheritance and incomplete phenotypic penetrance. However, other forms of inheritance (X-linked) have also been suggested.<sup>141</sup>
- 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>142</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>143</sup> and may be implicated in Brugada syndrome.<sup>144</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>145</sup>

## Catecholaminergic Polymorphic VT

### Prevalence and Incidence

- CPVT is a familial condition characterized by adrenergically induced polymorphic 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). Most patients present in childhood or adolescence. Variants in genes encoding *RYR2* (*CPVT1*) are found in the majority of patients and result in an autosomal dominant pattern of inheritance.<sup>146</sup> Variants in genes encoding *CASQ2* (*CPVT2*) are found in a small minority and result in an autosomal recessive pattern of inheritance. Other less common variants have also been described in *TRDN* and *TECRL* (autosomal recessive), as well as *CALM1*, *CALM2*, and *CALM3* (autosomal dominant).
- Analysis of 171 probands with CPVT who were <19 years of age and 65 adult relatives described clinical presentations and prevalence of genotypes.<sup>147</sup> The presenting symptom was cardiac arrest for 28% of cases and syncope/seizure in 58%. Genetic testing of 194 individuals identified variants in *RYR2* (60%), *CASQ2* (5%), 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>148</sup>
- Incidence of SCA in children with ≥2 CPVT gene variants was 11 of 15 (73%).<sup>149</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 attributable to VT.<sup>150</sup>

- Twelve ARVC loci have been described (*ARVC1*–*ARVC12*).<sup>151</sup>
- Clinical Genomics Resource reappraisal of 26 candidate ARVC genes found 6 to have strong definitive evidence and 2 to have moderate evidence supporting their role in ARVC.<sup>152</sup>
- Although the original descriptions localized the disease to the RV, more recent work has demonstrated that LV involvement may occur early in the course of the disease.<sup>153</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>154</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>155</sup>
- ARVC is an important cause of SCA in young people, especially during athletic competitions, and SCA may be the initial manifestation of the disease.<sup>153</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>156</sup>
- Hospitalizations related to arrhythmias among patients with HCM increased 10.5% from 7784 in 2003 to 8380 in 2014 in the NIS.<sup>157</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>158</sup>

## Early Repolarization Syndrome

### Prevalence and Incidence

- There had been no single electrocardiographic definition or set of criteria for ERP until recently. 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 epidemiological assessments of ERP or early repolarization syndrome.<sup>159</sup> The problem with older definitions of ERP is the high prevalence of this electrocardiographic finding in the general population. Currently, the existence of the electrocardiographic pattern of early repolarization in asymptomatic people is called ERP, whereas early repolarization in patients with arrhythmic syncope or cardiac arrest is called early repolarization syndrome.<sup>160</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>159</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>161</sup>
- Among 11 956 residents of rural Liaoning Province, China, who were ≥35 years of age, 1.3% had ERP, with a higher prevalence in males (2.6%) than females (0.2%).<sup>162</sup>
- In an Italian public health screening project, 24% of 13 016 students 16 to 19 years of age had at least 1 of the following electrocardiographic abnormalities: ventricular ectopic beats, atrioventricular block, Brugada-like electrocardiographic pattern, left anterior/posterior fascicular block, LVH/RV hypertrophy, long/short QT interval, left atrial enlargement, right atrial enlargement, short PQ interval, and ventricular preexcitation WPW syndrome.<sup>163</sup>

### Complications

- Early repolarization had been considered a benign normal electrocardiographic variant until reports linked early repolarization in the inferior and lateral leads with idiopathic VF.<sup>164</sup>
- The consensus panel<sup>160</sup> and others have identified certain electrocardiographic characteristics associated with increased risk for VF: ERP in the inferior and lateral ECG leads and J waves associated with horizontal or downsloping ST segments (as opposed to rapidly ascending ST segments).<sup>165</sup>
- 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>161</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>166</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>167</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>168–170</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, LV or RV dysfunction, and age at surgical repair.<sup>171</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>172</sup>
- A review of the NIS from 2012 to 2014 identified 46 289 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>173</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>174</sup>
- Prevalence of sustained VT in patients with LV aneurysm after MI is reported at 10%.<sup>175</sup>
- Incidence of late (>48 hours) monomorphic VT after AMI in the GISSI-3 database was 1% by 6 weeks.<sup>176</sup> 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>177</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>178</sup>

## Polymorphic VT/VF

### Prevalence and Incidence

- In the setting of AMI, the prevalence of polymorphic VT was 4.4%.<sup>179</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>174</sup>

### Complications

- In the setting of AMI, polymorphic VT is associated with increased mortality (17.8%).<sup>179</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>180</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>181</sup>

## Awareness and Treatment

- 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>182</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>183</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>184</sup>; 68% of citizens in Victoria, Australia<sup>185</sup>; 61.1% of laypeople in the United Kingdom<sup>186</sup>; and 49% of people in the Republic of Korea,<sup>187</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>188</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>186,187,189</sup> A total of 58% of Philadelphia respondents,<sup>189</sup> but only 2.1% of UK respondents,<sup>186</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>190</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>191</sup>
- Laypeople in the United States initiated CPR in 40.2% of OHCA in CARES 2021 data.<sup>4</sup>
- Layperson CPR rates in Asian countries range from 10.5% to 40.9%.<sup>192</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>193</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>194</sup> or in predominantly Hispanic neighborhoods (OR, 0.62 [95% CI, 0.44–0.89]) than in high-income White neighborhoods.<sup>195</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>196</sup>

## Mortality

### (See Tables 19-2 and 19-4 and Chart 19-2)

- In 2020, primary-cause SCD mortality was 19 427, and any-mention SCD mortality in the United States was 436 852 (Table 19-4). The any-mention age-adjusted annual rate was 106.0 (95% CI, 105.6–106.3) SCDs per 100 000 population.<sup>197</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>198</sup>
- Survival to hospital discharge after EMS-treated OHCA was 9.1% in the 2021 CARES registry, with variation between states reporting data (range, 4.6%–14.6%; Table 19-2).
  - Of 1 452 808 death certificates from 1999 to 2015 for US residents 1 to 34 years of age, 31 492 listed SCD (2%) as the cause of death, for an SCD rate of 1.32 per 100 000 individuals.<sup>199</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 19-2.

### OHCA: Adults

(See Tables 19-3 and 19-5)

- Survival to hospital discharge after EMS-treated OHCA was 9.1% and survival to hospital discharge with good functional status was 7.1% on the basis of 143 018 adult cases in CARES for 2021 (Table 19-3).<sup>4</sup>
- Survival to hospital admission after EMS-treated nontraumatic OHCA in 2021 was 24.6% for all presentations, with higher survival rates in public places (36.8%) and lower survival rates in homes/residences (23.4%) and nursing homes (14.1%) in the 2021 CARES registry (Table 19-5).
- 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>200</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>201</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>26</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>202</sup>
- 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>203,204</sup> An RCT comparing intravenous only with intravenous plus intraosseous administration of

adrenaline in OHCA found a higher yield of vascular access with the addition of intraosseous access but no improvement in return of spontaneous circulation, survival, or neurological outcome.<sup>205</sup>

- A Danish multicenter RCT comparing intravenous or intraosseous calcium with saline in OHCA showed no benefit and possible harm in patients randomized to receive calcium.<sup>206</sup>
- An observational study of 104 patients resuscitated from OHCA without obvious cause underwent a CT scan protocol including noncontrast head CT, cardiac and thoracic CT, and abdominopelvic CT within  $1.9 \pm 1.0$  hours of hospital arrival.<sup>207</sup> Presumed causes of OHCA were identified in 39%. Potentially life-threatening complications of resuscitation were identified in 13% of cases.
- 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>208</sup> However, in a Korean prospective registry of 678 patients, high-risk patients who had early coronary angiography exhibited improved neurological function at 6 months (OR, 2.36 [95% CI, 1.61–3.46]), whereas low-risk patients showed no benefit (OR, 1.64 [95% CI, 0.57–4.72]).<sup>209</sup>
- A multicenter RCT of 530 patients resuscitated from OHCA with no evidence of STEMI compared outcomes with immediate versus delayed coronary angiography.<sup>210</sup> At 30 days, mortality was 54% in the immediate angiography group versus 46% in the delayed angiography group (HR, 1.28 [95% CI, 1.00–1.63];  $P=0.06$ ). Death or severe neurological deficit occurred in 64.3% of the immediate angiography group versus 55.6% of the delayed angiography group (RR, 1.16 [95% CI, 1.00–1.34]).
- Multiple methods have been examined to predict neurological recovery and overall survival early after resuscitation from OHCA. Elevated serum levels of several biomarkers, including taurine<sup>211</sup> and neuron-specific enolase,<sup>212–214</sup> correlate with poorer outcomes.
- Guidelines recommend targeted temperature management to prevent hypoxic-ischemic brain damage in patients with coma after cardiac arrest. However, the benefit of this treatment has been questioned. An open-label RCT of 1861 comatose adults resuscitated after OHCA compared survival with targeted hypothermia for 40 hours and normothermia. Hypothermia treatment did not improve survival ( $P=0.37$ ), neurological status, or quality of life at 6 months. Significantly more patients in the hypothermia group experienced arrhythmias causing hemodynamic compromise (24% versus 17%;  $P<0.001$ ).<sup>215</sup> Several meta-analyses of multiple trials also found lack of benefit of hypothermia in individuals with OHCA.<sup>216</sup>
- Markers of systemic inflammation are commonly elevated in comatose patients resuscitated from

OHCA, and higher levels are associated with poorer outcomes. An RCT of tocilizumab, an interleukin-6 receptor antibody, in patients resuscitated from OHCA reduced circulating levels of CRP at 72 hours by 96% ( $P<0.0001$ ). Leukocyte levels were reduced by 23% at 48 hours ( $P=0.004$ ). In addition, troponin T levels were reduced by 36% at 12 hours ( $P=0.008$ ). However, mortality rates at 6 months were not significantly reduced with tocilizumab ( $P=0.9$ ). In addition, multiple markers of neurological function were not altered by this agent ( $P=0.82$ ).<sup>217</sup>

- In a single-center RCT of 256 adults with a witnessed OHCA of presumed cardiac origin without return of spontaneous circulation, early intra-arrest transport, extracorporeal CPR, and invasive assessment and treatment did not significantly improve survival with neurologically favorable outcome at 180 days compared with standard resuscitation (OR, 1.63 [95% CI, 0.93–2.85]; difference, 9.5% [95% CI, -1.3% to 20.1%];  $P=0.09$ ).<sup>218</sup> However, the trial was possibly underpowered to detect a clinically relevant difference.

#### 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>45</sup>

#### IHCA: Adults

(See Table 19-3 and Chart 19-4)

- Survival to hospital discharge was 18.8% of 8619 adult patients with pulseless IHCA in GWTG 2021 data (Table 19-3 and Chart 19-4). Among survivors, 12.9% 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>219</sup>
- Unadjusted survival to 30 days after IHCA was 28.3% and survival to 1 year was 25.0% in 18069 patients from 66 hospitals between 2006 and 2015 in the Swedish register of CPR.<sup>31</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 14933 cases of IHCA from 2007 to 2014.<sup>220</sup>
- Mortality was lower among 348368 patients with IHCA managed in teaching hospitals (55.3%) than among 376035 managed in nonteaching hospitals (58.8%), even after adjustment for baseline patient and hospital characteristics (OR, 0.92 [95% CI, 0.90–0.94]).<sup>221</sup>
- A propensity-matched analysis of 2000 to 2018 data from 497 US hospitals participating in the AHA

GWTG—Resuscitation registry examined the use of epinephrine before defibrillation for treatment of IHCA with a shockable rhythm.<sup>222</sup> In this evaluation of 34820 patients, 28% received epinephrine before defibrillation, contrary to current guidelines. Use of epinephrine delayed defibrillation by 3 minutes (median). Patients treated with epinephrine had a significantly lower chance of survival to hospital discharge (25.2% versus 29.9%;  $P<0.001$ ) and were less likely to have favorable neurological outcome (18.6% versus 21.4%;  $P<0.001$ ).

- A multicenter RCT conducted in 10 Danish hospitals compared vasopressin and methylprednisolone with placebo in 501 individuals with IHCA.<sup>223</sup> The active treatment group experienced significantly higher rate of return of spontaneous circulation (42% versus 33%). However, there was no significant difference in survival at 30 days (9.7% versus 12%, respectively) or achievement of a favorable neurological outcome at 30 days (7.6% versus 7.6%, respectively).

#### IHCA: Children

(See Table 19-6)

- Survival to hospital discharge was 5.7% for 1555 children <1 year of age, 15.0% for 1087 children 1 to 12 years of age, and 15.5% for 849 children 13 to 18 years of age in CARES 2021 data (Table 19-6).
- 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>224</sup>
- In Rotterdam, shockable rhythm after 369 pediatric (median age 3.4 years) OHCA was associated with significantly higher long-term survival and favorable neurological outcome. Fourteen percent had a shockable rhythm. Of these, 39% survived to hospital discharge. After a median follow-up of 25 months, 81% of hospital survivors had a favorable neurological status.<sup>225</sup>

#### IHCA: Children

(See Table 19-3)

- Survival to hospital discharge after pulseless IHCA was 39.8% in children 0 to 18 years of age per 2021 GWTG data (GWTG—Resuscitation, unpublished data, 2021; Table 19-3).
- 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>52</sup>

#### Complications

(See Tables 19-5 and 19-6)

- Survivors of cardiac arrest experience multiple medical problems related to critical illness, including

impaired consciousness and cognitive deficits (Tables 19–5 and 19–6).

- Functional impairments are associated with reduced function, reduced quality of life, and shortened life span.<sup>226,227</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>228,229</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>230</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>231</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>232</sup>
- Of 141 individuals who survived hospitalization after SCA, 41 (72%) returned to work by 12 months.<sup>231</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>233</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>234</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>235</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>236</sup>
- Among 7321 patients with OHCA in Taiwan who survived to ICU admission, 281 (3.84%) had new-onset HF.<sup>237</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>238</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]).

- An RCT of therapeutic hypothermia after IHCA conducted in 37 children's hospitals enrolled 313 patients.<sup>239</sup> Eighty percent developed acute kidney injury; severe kidney injury was associated with significantly reduced 12-month survival with favorable neurobehavioral outcome (30% versus 53%). Therapeutic hypothermia did not reduce the incidence of acute kidney injury, nor did it exhibit a beneficial effect on mortality.

## 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>240</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>241</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>242</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 37.9 and 36.2 per 100 000 for Han and Kazakh people, respectively.<sup>243</sup> After standardization for age, the incidence in these populations was 29.4 and 51.9 per 100 000.
- Hospitals in Beijing, China, reported IHCA incidence of 17.5 events per 1000 admissions.<sup>244</sup>
- Among 353 adults after IHCA in 6 Kenyan hospitals in 2014 to 2016, 16 (4.2%) survived to hospital discharge.<sup>245</sup>

## Social Determinants of Health

- In the ARIC study, 215 of 3832 (5.61%) Black and 332 of 11 237 (2.95%) White participants experienced SCD during 27.4 years of follow-up.<sup>76</sup> The sex-adjusted HR for SCD comparing Black with White participants was 2.12 (95% CI, 1.79–2.51), and the fully aHR was 1.38 (95% CI, 1.11–1.71).
- Survival and neurological recovery after cardiac arrest are worse in White Hispanic, Black, and Asian

patients compared with White people.<sup>246</sup> In this single-center, retrospective study of patients receiving targeted temperature management after cardiac arrest, survival and neurological recovery were worse in individuals from underrepresented racial and ethnic groups (self-identified or identified by family as being Black, Asian, or White Hispanic compared with NH White). White people had a higher chance of a good outcome than people from underrepresented racial and ethnic groups (34.4% versus 21.7%;  $P=0.015$ ). The observed disparities were explained in part by delays in onset of medical care: White people were brought to medical attention more quickly, and individuals from underrepresented races and ethnicities were more likely to have anoxic brain injury on early CT scans or highly malignant electroencephalograms during the first 24 hours. People from underrepresented racial and ethnic groups were more likely to have early severe electroencephalogram/CT anoxic changes (25.0% versus 15.8%;  $P=0.03$ ). There were no statistically significant differences in the number of invasive procedures.

- A study of the NIS from 2006 through 2018 identified patients with OHCA who survived to hospital admission and IHCA.<sup>247</sup> Over the study period, the proportion of patients with SCA who were Black increased from 11.9% to 18.8%. Compared with patients of other races and ethnicities, Black people hospitalized for SCA were younger (61.1 years versus 65.9 years;  $P<0.001$ ), had a slightly higher Charlson Comorbidity Index (1.50 versus 1.47;  $P<0.001$ ), and had a greater proportion of females (49% versus 42%;  $P<0.001$ ). Black people with SCA were less likely to undergo cardiac catheterization (9.5% versus 15.0%; OR, 0.61 [95% CI, 0.59–0.63];  $P<0.001$ ) compared with patients of other races and ethnicities and were more likely to die during the hospitalization (OR, 1.09 [95% CI, 1.08–1.11];  $P<0.001$ ). This study was not designed to adequately examine the patient, health system, and structural factors responsible for these differences.
- In a large artificial intelligence-guided statistical and geographic information system analysis of a prospectively collected multicenter data set of adult patients who sequentially presented to Houston metro area hospitals from January 1, 2007, to January 1, 2016, Black people were disproportionately more likely to have OHCA and, compared with White people, were significantly more likely to have poor neurological disposition (OR, 2.21 [95% CI, 1.25–3.92];  $P=0.006$ ) and to be discharged to a facility instead of home (OR, 1.39 [95% CI, 1.05–1.85];  $P=0.023$ ).<sup>248</sup> At a zip code level, each additional \$10000 above median household income was associated with a decrease in the total number of cardiac arrests by 2.86 (95% CI, −4.26 to −1.46;  $P<0.001$ ); zip codes with a median

income above \$54 600 versus the federal poverty level (ie, \$20 650 in 2007 to \$24 300 in 2017 for a family of 4) had 14.62 fewer arrests ( $P<0.001$ ).<sup>249</sup> At an institutional level, compared with the safety-net hospital system, the university hospital serving largely commercially and Medicare-insured patients had the lowest odds of death (OR, 0.45;  $P<0.001$ ), followed by the main private hospital serving primarily commercially insured patients (OR, 0.62;  $P=0.017$ ). Geographic information system maps showed convergence of the greater density of poor neurological outcome cases and greater density of poorer Black residences, suggesting the intersectionality of risk based on race and ethnicity and low income.

- 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>250</sup>
- 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>251</sup>
- In King County, Washington, the presence of more pharmacies or medical facilities was not associated with lower rates of SCA or shorter response times; in fact, SCA was more common in census tracts with more pharmacies or other medical facilities (OR, 1.28 [95% CI, 1.03–1.59]).<sup>252</sup>
- In an analysis of 347 705 SCDs in the United States between 1999 and 2019 from the CDC WONDER, age-adjusted mortality rates were higher in rural than in urban counties.<sup>253</sup> In urban counties, rates of SCD declined from 1999 through 2013 (−0.05 [−0.09 to −0.01]) but then increased through the end of the study period (0.08 [0.03–0.12]). In rural counties, age-adjusted mortality rates attributable to SCD declined throughout the study period, but the rate of decline slowed after 2013 (−0.29 versus −0.14). Age-adjusted mortality rates for urban-dwelling males increased from 2013 onward from 4.8 to 5.7 per 100 000 population. Age-adjusted mortality rates for rural-dwelling males were unchanged from 2013 onward: 9.3 versus 9.3 per 100 000 population. Age-adjusted mortality rates for urban-dwelling females were unchanged from 2013 onward: 4.2 versus 4.8 per 100 000 population. In contrast, age-adjusted mortality for rural-dwelling females declined from 8.9 to 7.7 per 100 000 population.
- In a national database of 120 365 adult, medical OHCA 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>60</sup>

**Table 19-1. Differences in Bystander Interventions and Survival After OHCA by Race, Ethnicity, and Sex, CARES, United States, 2021**

	Nontraumatic pathogenesis survival rates	Bystander intervention rates	
	Overall survival to hospital discharge	CPR	Public AED use
Total	13 402/146 924 (9.1%)	44 673/111 171 (40.2%)	1742/17 134 (10.2%)
American Indian/Alaska Native	38/525 (7.2%)	167/426 (39.2%)	8/91 (8.8%)
Asian	328/3645 (9.0%)	1236/2893 (42.7%)	33/389 (8.5%)
Black/African American	2562/31 938 (8.0%)	7719/23 059 (33.5%)	292/3345 (8.7%)
Hispanic/Latino	1061/12 593 (8.4%)	3824/9950 (38.4%)	125/1642 (7.6%)
Native Hawaiian/Pacific Islander	76/802 (9.5%)	311/650 (47.8%)	5/88 (5.7%)
White	7261/73 319 (9.9%)	23 395/55 435 (42.2%)	989/8512 (11.6%)
Unknown	2026/23 602 (8.6%)	7879/18 387 (42.9%)	284/3005 (9.5%)
Sex			
Male	8661/91 864 (9.4%)	28 868/71 459 (40.4%)	1413/13 364 (10.6%)
Female	4736/55 012 (8.6%)	15 795/39 679 (39.8%)	329/3766 (8.7%)
Neighborhood racial composition			
≥70% White	7161/74 042 (9.7%)	24 212/56 529 (42.8%)	930/8530 (10.9%)
≥40% Black	1710/22 806 (7.5%)	5498/17 114 (32.1%)	163/2314 (7.0%)
Integrated	4485/49 902 (9.0%)	14 880/37 384 (39.8%)	596/6170 (9.7%)
Neighborhood median household income			
<\$40 000 Annually	4070/44 711 (9.1%)	12 411/33 792 (36.7%)	442/5418 (8.2%)
\$40 000–\$80 000 Annually	6111/68 619 (8.9%)	20 877/51 820 (40.3%)	732/7544 (9.7%)
>\$80 000 Annually	3138/33 001 (9.5%)	11 123/25 092 (44.3%)	442/3885 (11.4%)

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 was missing for 11 cases. Race is “unknown” for 16.1% of CARES cases in the 2021 data set because a number of communities do not collect this information.

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 19-2. Variation in EMS-Treated OHCA in Selected States, United States, 2021**

	OHCA incidence			Nontraumatic pathogenesis survival rates		Bystander intervention rates	
	EMS-treated OHCA cases reported to CARES	Percent of population reporting data	Incidence 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	146 924	48.0	92.3	9.1	29.0	40.2	10.2
Alaska	563	82.7	92.8	13.0	44.0	73.5	8.0
California	28 177	85.4	83.5	7.7	28.1	40.5	7.7
Colorado	3727	79.5	81.2	12.3	35.6	41.1	13.3
Connecticut	2370	77.1	85.3	8.0	25.6	21.7	7.1
Delaware	1308	100.0	132.1	10.6	29.0	36.1	6.1
Hawaii	1484	100.0	102.0	9.2	33.8	45.5	11.2
Michigan	9634	86.8	110.1	7.7	28.8	37.6	11.6
Minnesota	3246	81.5	69.8	11.0	33.7	37.4	10.8
Mississippi	2283	79.4	97.1	6.0	15.4	39.6	9.2
Montana	645	81.5	73.0	13.2	35.8	46.4	9.3
Nebraska	789	55.0	73.1	15.7	40.5	48.4	10.2
North Carolina	8749	84.5	99.2	10.6	25.8	41.0	9.7
Oregon	3050	89.7	80.2	12.5	31.7	55.2	9.3
Pennsylvania	8062	68.7	90.3	8.8	28.1	35.8	14.5
Utah	1539	100.0	47.0	9.4	32.9	41.0	11.2
Vermont	498	100.0	77.4	9.2	23.2	47.8	7.7
Washington	5242	96.7	70.3	12.7	36.8	52.9	10.2
Wisconsin	3429	58.5	99.4	9.8	28.7	35.1	9.5
District of Columbia	944	100.0	136.9	6.5	20.0	29.2	6.0

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; CARES, Cardiac Arrest Registry to Enhance Survival; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; and OHCA, out-of-hospital cardiac arrest.

Source: CARES from states with ≥50% population reporting data and voluntarily sharing data.<sup>4</sup>

**Table 19-3. Characteristics of and Outcomes for OHCA and IHCA, United States, 2021**

	OHCA*		IHCA		
	Adults (>18 y)	Children (1–18 y)	Infants (<1 y) <sup>†</sup>	Adults	Children (0–18 y)
Survival to hospital discharge	9.1	15.2	5.7	18.8	39.8
Good functional status at hospital discharge	7.1	13.0	5.0	...	...
VF/VT/shockable	16.6	9.6	3.0	12.9	8.0
PEA	22.3	15.2	10.9	56.0	50.6
Aystole	52.4	63.2	78.5	23.5	29.4
Unknown	...	...		7.7	12.0
Public setting	16.3	16.7	6.6	...	...
Home	73.4	82.7	93.3	...	...
Nursing home	10.3	0.6	0.1	...	...
Public AED use <sup>‡</sup>	10.2	13.0	0.0		
Arrest in ICU, operating room, or ED	...	...		60.9	71.6
Noncritical care area	...	...		39.2	28.0

Values are percentages.

AED indicates automated external defibrillator; CARES, 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 where resuscitation is attempted by a 9-1-1 responder (CPR or defibrillation). This would also include patients who received an AED shock by a bystander before the arrival of 9-1-1 responders. Analysis excludes patients with missing hospital outcome (n=305).

<sup>†</sup>Stillborn neonates and perinatal newborns born without signs of life are not CARES cases and are not entered into the registry.

<sup>‡</sup>Public AED use rate excludes 9-1-1 responder–witnessed, home/residence, nursing home, and health care facility arrests.

Source: OHCA data derived from CARES<sup>4</sup> and are based on 143 018 EMS-treated OHCA adult cases, 1922 EMS-treated OHCA pediatric cases (1–18 years of age), and 1555 EMS-treated OHCA infant cases (<1 year of age) in 2021. IHCA data are from Get With The Guidelines (unpublished AHA tabulation) 2021 and are based on 45 815 adult IHCAAs in 357 hospitals and 1639 child IHCAAs in 125 hospitals.

**Table 19-4. SCA Mortality, United States, 2020 (ICD-10 I46.0, I46.1, I46.9, I49.0)**

Population group	No. of deaths as underlying cause, 2020, all ages	No. of deaths as any-mention cause, 2020, all ages
Both sexes	19 427	436 852
Males	10 677	231 614
Females	8750	205 238
NH White males	7735	154 920
NH White females	6330	136 780
NH Black males	1967	34 365
NH Black females	1734	33 275
Hispanic males	611	28 727
Hispanic females	411	23 649
NH Asian/Pacific Islander males	289	10 821
NH Asian/Pacific Islander females	228	9587
NH American Indian/Alaska Native	84	3170

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>197</sup>

**Table 19-5. Outcomes of EMS-Treated Nontraumatic OHCA in Adults (>18 Years of Age), CARES, United States, 2021**

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 (143 018)	24.6	9.1	7.1	63.1
Home/residence (104 917)	23.4	7.8	6.0	66.8
Nursing home (14 728)	14.1	3.8	1.6	73.3
Public setting (23 371)	36.8	18.3	15.6	50.3
Unwitnessed (71 427)	15.8	4.2	3.1	73.2
Bystander witnessed (54 015)	32.3	13.3	10.6	58.8
9-1-1 Responder witnessed (17 568)	37.2	15.9	12.8	57.3
Shockable presenting rhythm (23 767)	44.5	25.9	22.5	41.9
Nonshockable presenting rhythm (119 226)	20.7	5.7	4.0	72.3
Layperson CPR† (42 980)	26.7	11.1	9.3	58.3
No layperson CPR† (64 635)	21.8	6.6	5.0	69.5

Values are percentages.

Inclusion criteria: An OHCA for which resuscitation is attempted by a 9-1-1 responder (CPR or defibrillation). This would also include patients who received an AED shock by a bystander before the arrival of 9-1-1 responders. Analysis excludes patients with missing hospital outcome (n=174).

AED indicates automated external defibrillator; CARES, 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 the hospital who died before hospital discharge.

†Excludes nursing home/health care facility events.

Source: Data from CARES.<sup>4</sup>

**Table 19-6. Outcomes of EMS-Treated Nontraumatic OHCA in Children, CARES, United States, 2021**

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 (1555)	16.8	5.7	5.0	66.4
1–12 y (1073)	38.9	15.0	12.6	61.4
13–18 y (849)	34.6	15.5	13.4	55.1

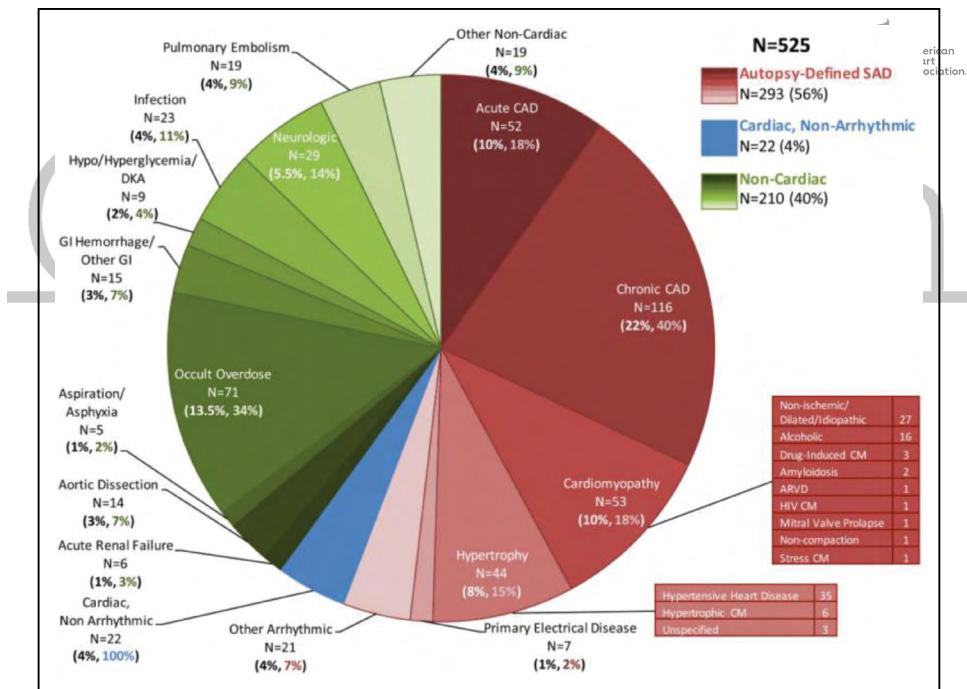
Values are percentages.

Inclusion criteria: An OHCA for which resuscitation is attempted by a 9-1-1 responder (CPR or defibrillation). This would also include patients who received an AED shock by a bystander before the arrival of 9-1-1 responders. Analysis excludes patients with missing hospital outcome (n=30). 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 the hospital who died before hospital discharge.

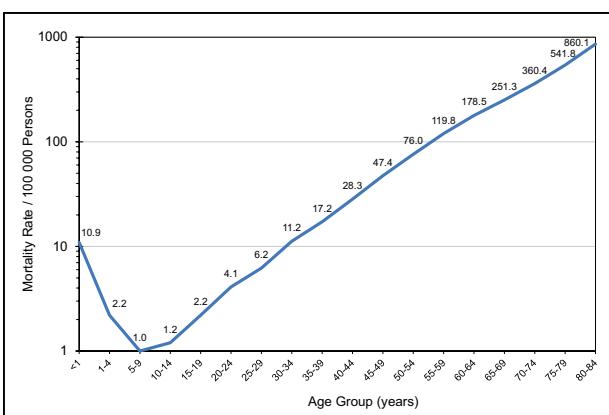
Source: Data derived from CARES.<sup>4</sup>

**Chart 19-1. 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, PE, 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 services; GI, gastrointestinal; HF, heart failure; PE, pulmonary embolism; SAD, sudden arrhythmic death; SCD, sudden cardiac death; and WHO, World Health Organization.

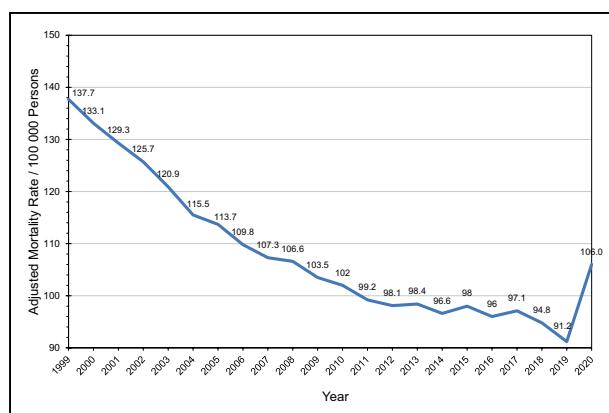
Source: Adapted with permission from Tseng et al.<sup>41</sup> Copyright © 2018 American Heart Association, Inc.



**Chart 19-2. Age-specific mortality rates for any mention of SCD by age, United States, 2020.**

SCD indicates sudden cardiac death.

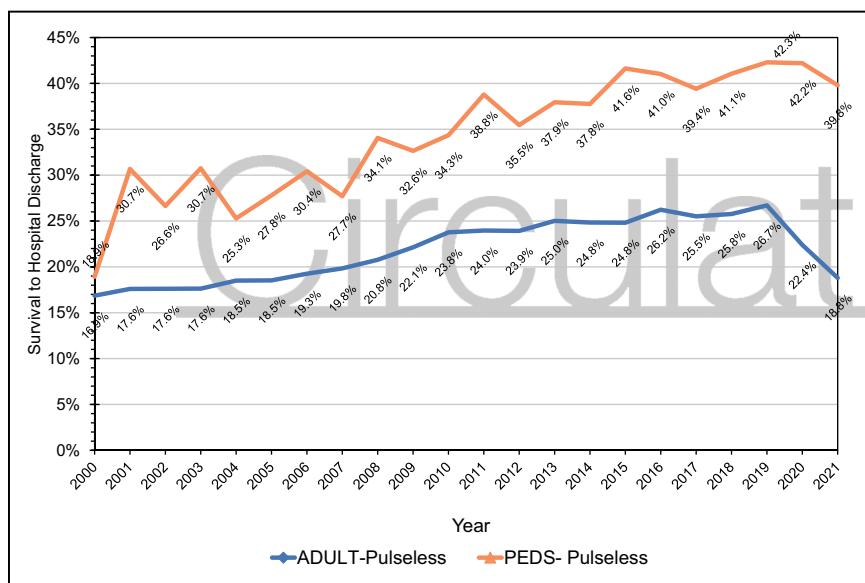
Source: Data derived from Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research database.<sup>197</sup>



**Chart 19-3. Age-adjusted mortality rates for any mention of SCD, United States, 1999 to 2020.**

SCD indicates sudden cardiac death.

Source: Data derived from Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>197</sup>

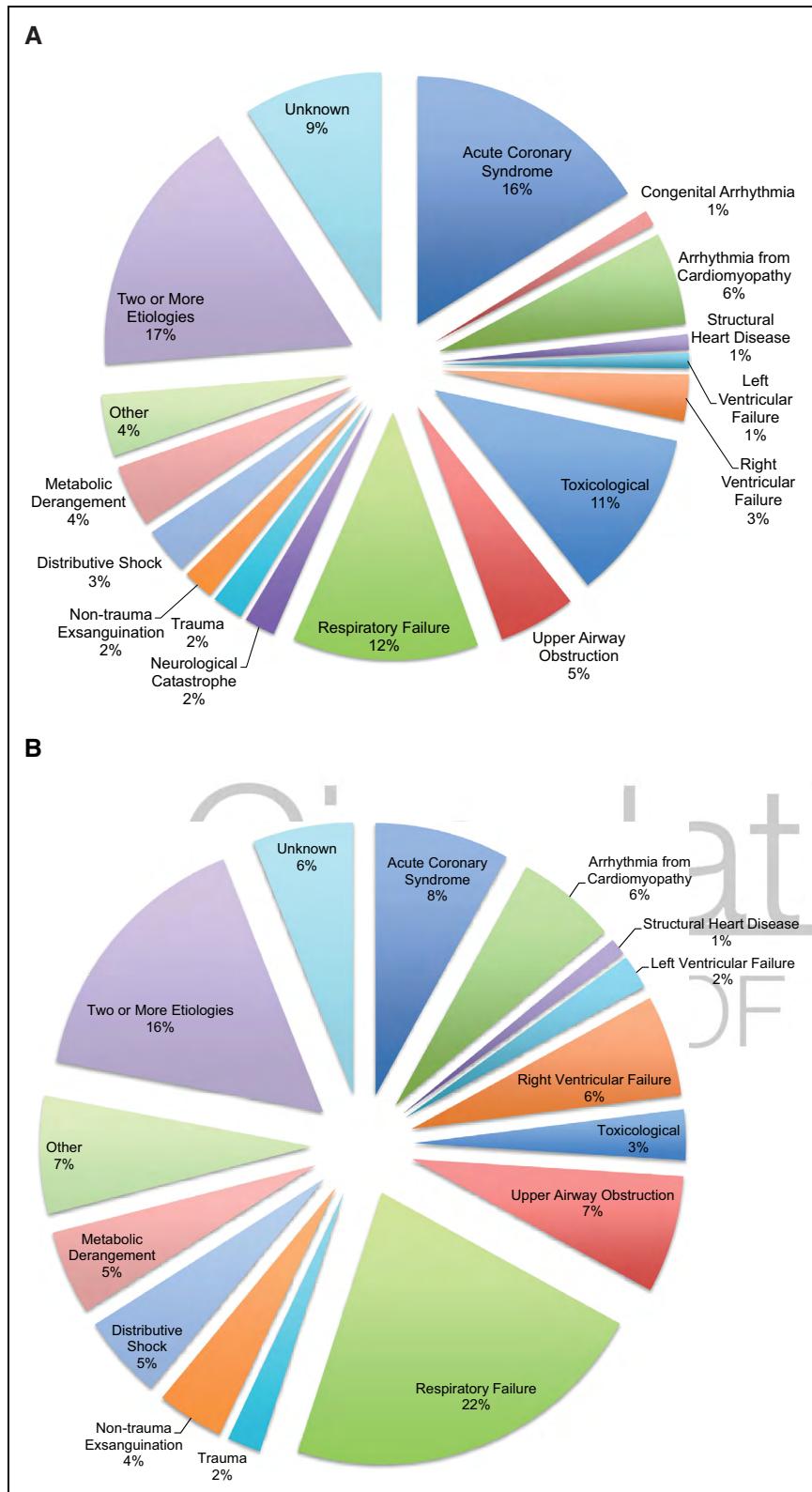


**Chart 19-4. Temporal trends in survival to hospital discharge after IHCA in adults and children in GWTG-Resuscitation from 2000 to 2021, United States.**

GWTG indicates Get With The Guidelines; IHCA, in-hospital cardiac arrest; and PEDS, pediatrics.

Source: GWTG—Resuscitation; unpublished American Heart Association data.





**Chart 19-5. 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>62</sup>

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# Circulation

## 20. SUBCLINICAL ATHEROSCLEROSIS

See Charts 20-1 through 20-4

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Multiple complementary imaging modalities allow the 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 estimation and after accounting for risk enhancers, it is reasonable to use a CAC score in the decision to withhold, postpone, or initiate statin therapy. Other professional organizations such as the National Lipid Association<sup>3</sup> also recommend the use of CAC to guide preventive strategies for ASCVD risk reduction.

### 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.

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

#### 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>4</sup>
  - 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>5</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 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>6</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>6</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>7</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>8</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, whereas HIV has been associated with noncalcified plaque but not CAC:
  - Of 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>9</sup>
  - In a meta-analysis of 42410 individuals, including 16883 with NAFLD, CAC scores were higher in those with NAFLD (OR, 1.64 [95% CI, 1.42–1.89]).<sup>10</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>11</sup>
  - In a study-level meta-analysis involving 10867 participants (6699 living with HIV, 4168 not living with HIV; mean age, 52 years; 86% male; 32% Black), the prevalence of noncalcified plaque was 49% (95% CI, 47%–52%) in individuals living with HIV versus 20% (95% CI, 17%–23%) in individuals not living with HIV (OR, 1.23 [95% CI, 1.08–1.38]).<sup>12</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>13</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)

- 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>
- In 3286 MESA participants with baseline CAC=0 by the Agatston method, a spatially weighted coronary calcium score taking into account more of the calcium density information from the CT scan predicted incident CHD events (multivariable-aHR, 1.30 per SD of natural logarithm spatially weighted coronary calcium [95% CI, 1.04–1.60];  $P=0.005$ ).<sup>17</sup>
- A meta-analysis pooling data from 3 studies examined the association of CAC with stroke in 13262 asymptomatic individuals (mean age, 60 years; 50% males) without apparent CVD.<sup>18</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 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>19</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>20</sup>

### Social Determinants and Health Equity in CAC

In addition to the differences by race and ethnicity detailed above, differences in CAC or associations with CAC have been described by factors such as sex, unemployment, and exposure to air pollution:

- In 1429 participants from the MESA study, insomnia symptoms were independently associated with an 18% higher prevalence of CAC (PR, 1.18 [95% CI, 1.04–1.33]) among females but not males (PR, 1.00 [95% CI, 0.91–1.08]).<sup>21</sup>
- In 3000 patients from rural central Appalachia, age (RR, 1.07;  $P \leq 0.0001$ ), being male (RR, 5.33;  $P \leq 0.0001$ ), having hypertension (RR, 2.37;  $P \leq 0.05$ ), and zip code-level unemployment (RR, 1.37;  $P \leq 0.05$ ) were associated with having diabetes and CAC score  $\geq 1$ .<sup>22</sup>
- 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 with greater presence of any CAC and severe CAC.<sup>23</sup> Aerodynamic diameter  $<2.5$   $\mu\text{m}$  (PM2.5) and NO<sub>2</sub> had independent associations beyond CHD risk factors and multiple pollutants, with an increase in CAC score of 27.2% (95% CI, 10.8%–46.1%) per 30  $\mu\text{g}/\text{m}^3$  PM2.5 and 24.5% (95% CI, 3.6%–49.7%) per 20  $\mu\text{g}/\text{m}^3$  NO<sub>2</sub>.
- Among 606 asymptomatic adults in Australia (51% female, 56 $\pm$ 7 years of age), exposure to higher PM2.5 was associated with greater odds of having CAC  $>100$  (OR, 1.20 [95% CI, 1.02–1.43]) and  $>400$  (OR, 1.55 [95% CI, 1.05–2.29]).<sup>24</sup> Similar associations were observed for NO<sub>2</sub>.

## Carotid IMT and Carotid Atherosclerosis

### 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.
- Stroke risk is higher with greater degrees of asymptomatic carotid stenosis (OR, 2.5 for

stenosis 80%–99% versus 50%–79% [95% CI, 1.8–3.5];  $P < 0.0001$ ) in a large meta-analysis of 11 cohort studies.<sup>25</sup>

### Risk Factors

- In a meta-analysis of 7645 individuals, carotid IMT increased from  $723 \pm 39$   $\mu\text{m}$  in participants with normal BP to  $779 \pm 45$   $\mu\text{m}$  in those with prehypertension and  $858 \pm 82$   $\mu\text{m}$  in individuals with hypertension.<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 significantly and positively associated 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>26</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<sup>29</sup> 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 males (third tertile of number of childhood oral infections versus tertiles 1 and 2: RR, 1.87 [95% CI, 1.25–2.79]).<sup>30</sup>
- Sleep patterns and duration, which are associated with CVD, are associated with subclinical atherosclerosis.<sup>31</sup> In nearly 4000 asymptomatic middle-aged individuals in the PESA study, individuals who slept  $<6$  h/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>31</sup>
- In individuals without diabetes or CVD, higher HbA1c was associated with the extent of subclinical atherosclerosis assessed by IMT and atherosclerotic plaque of the carotids, abdominal aorta, and iliofemoral arteries, as well as CAC (OR, 1.05, 1.27, 1.27, 1.36, 1.80, 1.87, and 2.47 for HbA1c 4.9%–5.0%, 5.1%–5.2%, 5.3%–5.4%, 5.5%–5.6%, 5.7%–5.8%, 5.9%–6.0%, and 6.1%–6.4%, respectively; reference, HbA1c  $\leq 4.8\%$ ;  $P < 0.001$ ).<sup>32</sup>
- Although exposure to air pollution is associated with CVD (OR, 1.10 [95% CI, 1.01–1.20] per 1  $\mu\text{g}/\text{m}^3$ ), low levels of exposure were not associated with carotid IMT after adjustment for CVD risk factors

and SES in 6103 participants in the Malmö Diet and Cancer study.<sup>33</sup>

### Social Determinants and Health Equity in Carotid IMT and Vascular Disease

- 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 ( $P<0.05$ ), and Black participants had higher common carotid and carotid bulb IMT than White participants ( $P<0.001$ ).<sup>27</sup> In MESA, Black people had the thickest carotid IMT (particularly common carotid, 0.91 mm) of all 4 ethnic groups, regardless of the presence of CAC.<sup>34</sup> Chinese participants had the lowest carotid IMT (0.83 mm), 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.
- In the biracial HANDLS study of 2270 adults, interaction analyses demonstrated a race-by-SES effect whereby individuals self-identified as Black race with high (rather than low) SES had higher carotid IMT (0.71 versus 0.67 in White individuals) and aortic stiffness than other groups, suggesting a group with greater subclinical CVD.<sup>35</sup>
- In 2903 participants of the Cardiovascular Risk in Young Finns Study of individuals initially examined in youth, in adulthood, urban-dwelling (compared with rural-dwelling) residents had lower cardiovascular risk factors and lower IMT ( $-0.01$  mm), lower vascular stiffness (PWV,  $-0.22$  m/s), and higher carotid artery compliance ( $0.07\%/10$  mmHg).<sup>36</sup>
- 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 (+7.7%, +5.3%, +4.6% for IMT<sub>max</sub>, IMT<sub>mean-max</sub>, and IMT<sub>mean</sub>, respectively; all  $P<0.0001$ ).<sup>37</sup>
- In the Cardiovascular Risk in 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 ( $P=0.002$ ).<sup>38</sup>

### Risk Prediction

No evidence or recommendation for screening asymptomatic individuals exists per the US Preventive Services Task Force.<sup>39</sup> However, several studies demonstrate the association of carotid atherosclerosis with CVD events:

- 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>40</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>41</sup> In MESA<sup>41</sup> and CHS participants,<sup>42</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>43</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>44</sup>
- Carotid plaque burden was associated with brain hypometabolism by brain <sup>18</sup>F-fluorodeoxyglucose uptake ( $B=-0.16$ ,  $P<0.001$ ) in 547 asymptomatic middle-aged participants in the PESA study.<sup>45</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 45 828 individuals<sup>46</sup> followed up for a median of 11 years demonstrated little additive value of common carotid IMT to the FRS to discriminate and reclassify incident MI and stroke (95% CI, 2.7%–4.6%).<sup>46</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>47</sup>

Advanced imaging methods may better identify risk:

- In the Biolmage 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  $\approx 2$ -fold risk for MACEs (cardiovascular death, MI, and ischemic stroke), and net reclassification improved significantly with carotid plaque burden (0.23).<sup>48</sup>
- In the Rotterdam Study of older adults, the presence of intraplaque hemorrhage (but not calcification or lipid-rich core) by high-resolution MRI demonstrated an association with incident stroke and CHD (HR, 2.42 [95% CI, 1.30–4.50] and 1.95 [95% CI, 1.20–3.14], respectively).<sup>49</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>50</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  $\geq 75$ th 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.
- 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</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>51</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>52</sup> This score was externally validated in the AWHS of similarly aged males.

## Genetics and Family History

- Subclinical atherosclerosis is heritable. With the use of Vietnam Era Twin Registry data that included 98 middle-aged male twin pairs, carotid artery IMT heritability was estimated to be 59%.<sup>53</sup> Similarly, 44% of the variation in CAC quantity was attributable to genetic factors in a study of 698 adults from 302 families.<sup>54</sup> CAC progression also is heritable, although of smaller magnitude ( $h^2=14\%$ ).<sup>55</sup>
- There is evidence for genetic control of subclinical atherosclerosis, with several loci identified that are associated with CAC and carotid artery IMT in

multiethnic and racial populations.<sup>56–60</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.

- CHARGE Consortium 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> A parallel GWAS in the UK Biobank (N=45 185) identified 7 novel loci for carotid IMT (ZNF385D, ADAMTS9, EDNRA, HAND2, MYOCD, ITCH/EDEM2/MMP24, and MRTFA).<sup>60</sup> When the CHARGE Consortium and UK Biobank data were meta-analyzed, an additional 3 novel loci were identified at APOB, FIP1L1, and LOXL4.<sup>60</sup> Positive genetic correlations with CHD, PAD, SBP, and stroke and negative genetic correlations with HDL-C using linkage disequilibrium score regression analysis were observed. These observations suggest connections between genetic susceptibility to subclinical atherosclerosis with overt CVD and CVD risk factors.
- 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>61</sup>
- The combination of GWASs 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>62</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>63</sup>
  - In a cohort of older females, a diet high in vegetables, particularly cruciferous vegetables, was associated with lower carotid IMT.<sup>64</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>65</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>66</sup>
- In the FHS, higher midlife-estimated cardiorespiratory fitness was associated with lower IMT ( $B=-0.12$  mm [SE, 0.05 mm]) and aortic stiffness measured by carotid-femoral PWV ( $B=-11.13$  ms/m [SE, 1.33 ms/m]).<sup>67</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<sub>5</sub>: The estimated NNT<sub>5</sub> for preventing 1 CVD event across dyslipidemia categories in the MESA cohort ranged from 23 to 30 in those with CAC  $\geq 100$ .<sup>68</sup> A very high NNT<sub>5</sub> 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<sub>5</sub> was as low as 36 and 50 with the presence of a very high CAC score ( $>300$ ) among those with a 10-year FRS of 0% to 6% and 6% to 10%, respectively.<sup>69</sup>
    - Similarly, CAC testing has identified individuals who might derive the highest net benefit with aspirin therapy: In MESA, among aspirin-naïve participants  $<70$  years of age who were not at high risk for bleeding ( $n=3540$ ), CAC  $\geq 100$  and CAC  $\geq 400$  identified individuals with an NNT<sub>5</sub> lower than the number needed to harm (for CAC  $\geq 100$ , NNT<sub>5</sub>=140 versus NNH<sub>5</sub>=518).<sup>70</sup> In individuals with CAC=0, the NNT<sub>5</sub> of 1190 was much higher than the NNH<sub>5</sub> of 567. Similarly, in the Dallas Heart Study, among individuals at lower bleeding risk, CAC  $\geq 100$  identified individuals who would tend to have net benefit, but only if 10-year ASCVD risk was  $\geq 5\%$ .<sup>71</sup> In individuals at higher bleeding risk, net harm from aspirin was observed regardless of CAC and ASCVD risk.
    - In a microsimulation model of 1083 individuals with a family history of premature CAD, compared with traditional risk factor-based prediction alone, use of CAC scanning was more costly (\$145) and more effective (0.0097 QALY) with an incremental cost-effective ratio of \$15014/QALY.<sup>72</sup> The incremental cost-effective ratio improved in the male,  $>60$  years of age, and  $\geq 75\%$  10-year risk subgroups, whereas CAC was not cost-effective in individuals with  $<5\%$  10-year risk or those 40 to 50 years of age.

## 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>73</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>74</sup>

### Arterial Stiffness and CVD

- Arterial stiffness defined as pulse pressure  $\geq 60$  mm Hg conferred a 27% greater odds of in-hospital mortality after multivariable adjustment for comorbidities among 12 170 patients hospitalized with SARS-CoV-2 in the SEMI-COVID-19 network in Spain.<sup>75</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>76</sup> PWV tertiles were associated with CHD (RR, 1.72 and 2.45 for second and third tertile 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>77</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, 0.7%;  $P<0.05$ ).<sup>78</sup>
- An analysis from the JHS suggested that peripheral arterial tonometry is associated with LVH.<sup>79</sup> In 440 Black participants (mean age,  $59 \pm 10$  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 to 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>80</sup>
  - In the ARIC–Neurocognitive and ARIC–PET studies, higher arterial stiffness measured by heart-carotid PWV was associated with greater

$\beta$ -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>81</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>82–86</sup>

### FMD and CVD

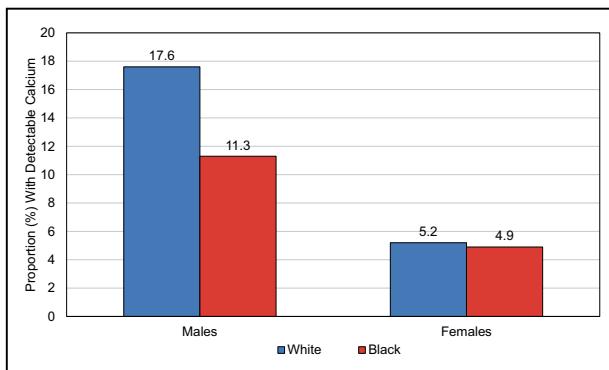
- In a meta-analysis of 13 studies involving 11 516 individuals without established CVD with a mean follow-up duration of 2 to 7.2 years and adjusted for age, sex, and risk factors, a multivariate RR of 0.93 (95% CI, 0.90–0.96) for CVD per 1% increase in brachial FMD was observed.<sup>87</sup>

### 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>88</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>89</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>90</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>91</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>92</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.

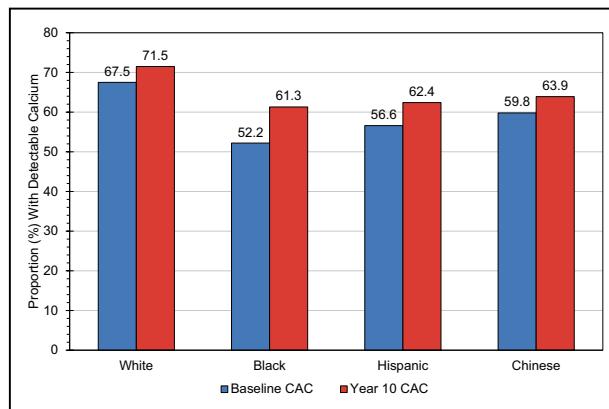


**Chart 20-1. Prevalence (percent) of detectable CAC in the CARDIA study: US adults 33 to 45 years of age (2000–2001).**

$P<0.0001$  across race-sex groups.

CAC indicates coronary artery calcification; and CARDIA, Coronary Artery Risk Development in Young Adults.

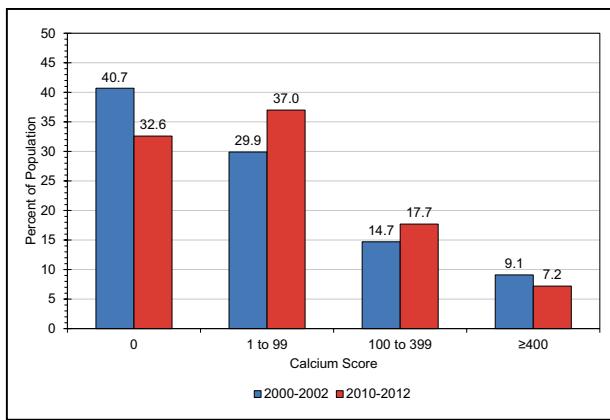
Source: Data derived from Loria et al.<sup>4</sup>



**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 CVD in MESA.**

CAC indicates coronary artery calcification; CVD, cardiovascular disease; and MESA, Multi-Ethnic Study of Atherosclerosis.

Source: Data derived from Bild et al.<sup>5,13</sup>

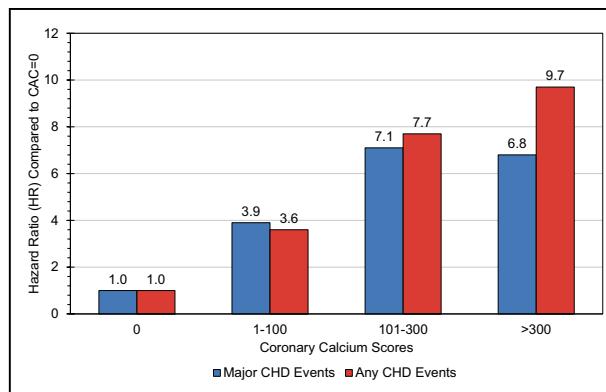


**Chart 20-3. Ten-year trends in severity of CAC in US individuals without clinical CVD in MESA, baseline examination 2000 to 2002.**

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 CT vs other).

CAC indicates coronary artery calcification; CT, computed tomography; CVD, cardiovascular disease; and MESA, Multi-Ethnic Study of Atherosclerosis.

Source: Adapted from Bild et al.<sup>13</sup> This is an open-access article, free of all copyright, and may be freely reproduced, distributed, transmitted, modified, built on, or otherwise used by anyone for any lawful purpose. The work is made available under the Creative Commons CCO public domain dedication.



**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 MI 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; MESA, Multi-Ethnic Study of Atherosclerosis; and MI, myocardial infarction.

Source: Data derived from Detrano et al.<sup>14</sup>

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# Circulation

## 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 2017 to 2020,<sup>1</sup> an estimated 20.5 million Americans ≥20 years of age have CHD (Table 21-1). The prevalence of CHD was higher for males than females in all age groups (Chart 21-1).
- According to NHANES 2017 to 2020, total CHD prevalence is 7.1% in US adults ≥20 years of age. CHD prevalence is 8.7% for males and 5.8% for females. CHD prevalence by sex and ethnicity is shown in Table 21-1.
- Based on data from the NHIS 2018, the CHD prevalence estimates are 5.7% among White people, 5.4% among Black people, 8.6% among American Indian/Alaska Native people, and 4.4% among Asian people ≥18 years of age.<sup>2</sup>
- According to data from NHANES 2017 to 2020 (unpublished NHLBI tabulation),<sup>1</sup> the overall prevalence of MI is 3.2% in US adults ≥20 years of age. Males have a higher prevalence of MI than females for all age groups (Chart 21-2). Overall MI prevalence is 4.5% for males and 2.1% for females. MI prevalence by sex and ethnicity is shown in Table 21-1.
- According to data from NHANES 2017 to 2020,<sup>1</sup> the overall prevalence of angina is 3.9% in US adults ≥20 years of age (Table 21-2).
- Data from the BRFSS 2020 survey indicate that 4.3% of respondents had been told that they had

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

had an MI. The highest age-adjusted prevalence was in Guam (6.2%) and West Virginia (6.0%), and the lowest was in the District of Columbia and Hawaii (2.3%, age adjusted; Chart 21-3).<sup>3</sup>

- In the same survey in 2020, 4.0% of respondents had been told that they had angina or CHD. The highest age-adjusted prevalence was in Arkansas (5.9%), and the lowest was in Hawaii (2.4%; 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 ≈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>

#### 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>6</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).
  - 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>7</sup>
- According to data from inpatient and ambulatory databases from 4 states (Michigan, Maryland, New York, and Florida), population trends in PCI use were examined between January 2010 and December 2017. Among a cohort of 333 819 patients (32% female; mean age, 65.7 years [SD, 12.2 years]), 1 044 698 PCIs were performed: 57.1% were elective, and 42.9% were urgent. PCI rates declined from 260.2 to 232.8 per 100 000 ( $-10.5\%$ ;  $P_{trend}<0.001$ ) between 2010 and 2017. In the same period, outpatient PCI rates increased from 33.8 to 66.7 per 100 000 (+97.1%;  $P_{trend}<0.001$ ), whereas inpatient PCI rates declined from 226.4 to 166.2 per 100 000 ( $-26.6\%$ ;  $P_{trend}<0.001$ ).<sup>8</sup>

### Admissions and Mortality Trends

- 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 in the previous year.<sup>9</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=20310), with a corresponding increase in the incidence of OHCA (see Chapter 19 [Sudden Cardiac Arrest, Ventricular Arrhythmias, and Inherited Channelopathies]).<sup>10</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]) when the 4 weeks before and after lockdown were compared.<sup>11</sup>
- In a cohort of 1533 patients admitted with AMI (STEMI and NSTEMI) in a large health system in Washington, District of Columbia, and Maryland between March 1, 2020, and June 30, 2020, 86 had confirmed COVID-19. Furthermore, 20.0% (n=17) of patients with COVID-19 underwent coronary angiography. Those with concomitant COVID-19 and AMI had higher in-hospital mortality (27.9%) than patients without COVID-19 in the same period (3.7%;  $P<0.001$ ).<sup>12</sup>
- Among 21 738 patients with type 2 MI in the National Readmission Database, in-hospital mortality and 30-day readmission for patients with type 2 MI were 9.0% and 19.1%, respectively. AF, PAD, male sex, coagulopathy, and fluid/electrolyte imbalances were associated with higher in-hospital

mortality. In addition, AF/flutter, carotid artery stenosis, diabetes, anemia, COPD, CKD, and history of MI were associated with higher odds of 30-day readmission.<sup>13</sup>

### Social Determinants of Health and Health Equity

- An NIS analysis of sex differences spanning 2004 to 2015 identified 7 026 432 hospitalizations for AMI. Compared with males, females were less likely to undergo coronary angiography (aOR, 0.92 [95% CI, 0.91–0.93]) and PCI (aOR, 0.82 [95% CI, 0.81–0.83]). Females had a higher risk of mortality (aOR, 1.03 [95% CI, 1.02–1.04]) compared with males.<sup>14</sup>
- 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>15</sup>
- 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>16</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>17</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>18</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>19</sup>
- In a retrospective cohort study of Medicare fee-for-service patients (N=453783) 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>20</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]).
  - An NHANES analysis spanning 2007 to 2016 cycles examined differences in self-reported history of CAD by limited English proficiency status in individuals reporting angina. Participants with limited English proficiency were 2.8 times more likely not to report a history of CVD compared with those without limited English proficiency (aOR, 2.77 [95% CI, 1.38–5.55]).<sup>21</sup>
  - Disparities in cardiac rehabilitation are well recognized: Individuals who are female, of Black race, of Hispanic ethnicity, of lower educational attainment, and eligible for dual Medicare/Medicaid coverage have significantly reduced attendance than referents.<sup>22,23</sup>
  - An administrative claims analysis of Medicaid, commercial insurance, and Medicare claims from 2015 to 2018 identified that patients with Medicaid were less likely to receive guideline-concordant testing for MI (aOR, 0.84 [95% CI, 0.73–0.98]) and HF (aOR, 0.59 [95% CI, 0.51–0.70]) than those with commercial insurance.<sup>24</sup>
  - A study of 2182903 Medicare beneficiaries hospitalized with MI, HF, or stroke from 2016 to 2018 compared outcomes in rural hospitals with outcomes in urban hospitals. Patients at rural hospitals were less likely to undergo cardiac catheterization (49.7% versus 63.6%;  $P<0.001$ ), PCI (42.1% versus 45.7%;  $P<0.001$ ), or CABG (9.0% versus 10.2%;  $P<0.001$ ). Mortality at 30 days was higher for patients at rural hospitals presenting with MI (aHR, 1.10 [95% CI, 1.08–1.12]), HF (aHR, 1.15 [95% CI, 1.13–1.16]), and ischemic stroke (aHR, 1.20 [95% CI, 1.18–1.22]) compared with their counterparts presenting at metropolitan hospitals.<sup>25</sup>
  - In a subset of SILVER-AMI, a community-based longitudinal study of older adults (N=1345, age  $\geq 75$

years), there was no association between neighborhood walkability scores and hospital-free survival time or physical or mental health.<sup>26</sup>

- REGARDS investigators tabulated number of social determinants of health to determine a progressive increase in fatal CHD (0 social determinants of health, 1.30; 1 social determinant of health, 1.44; 2 social determinants of health, 2.05;  $\geq 3$  social determinants of health, 2.86) and nonfatal MI (0 social determinants of health, 3.91; 1 social determinant of health, 4.33;  $\geq 2$  social determinants of health, 5.44). Compared with those with no social determinants of health, those with  $\geq 3$  social determinants of health had an aHR of 1.67 (95% CI, 1.18–2.37) for risk of fatal CHD.<sup>27</sup>
- Among 22 152 participants free of CHD at baseline in the REGARDS cohort study, there were 463 fatal incident CHD events and 932 nonfatal MIs over a median of 10.7 years (IQR, 6.6–12.7). Compared with those without social determinants of health, those with  $\geq 3$  social determinants of health had a higher risk (aHR, 1.67 [95% CI, 1.18–2.37]) of fatal incident CHD and those with  $\geq 2$  social determinants of health had a nonsignificant higher risk (aHR, 1.14 [95% CI, 0.93–1.41]) of nonfatal MI.<sup>27</sup>
- In an analysis of NIS data from January 1, 2012, through December 31, 2017, Black adults and individuals from other racial and ethnic groups with AMI were less likely to undergo coronary angiography compared with White individuals (61.9% versus 70.2% versus 73.1%) and PCI (44.6% versus 53.0% versus 58.1%;  $P<0.001$ ).<sup>28</sup>

### 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 incident rate, 6.23 [95% CI, 5.31–7.31] versus predicted incident rate, 8.02; Hosmer-Lemeshow  $\chi^2=12.43$ ;  $P=0.01$ ).<sup>29</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>30</sup>
- In 14 169 patients with ASCVD risk <5% and self-reported family history of CHD from the multicenter CAC Consortium followed up for  $\approx 12$  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>31</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>32</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 ( $\geq 1000$ ) 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>33</sup> Moreover, those with CAC  $\geq 1000$  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>34</sup>
- A precatheterization model and bedside risk score were developed and validated with data from 706 263 PCIs at 1608 sites between July 2018 and June 2019 to predict in-hospital mortality. Variables that predicted in-hospital mortality included cardiovascular instability, level of consciousness after cardiac arrest, and procedural urgency. The C indexes of the precatheterization model and bedside risk score were 0.940 and 0.923, respectively. The simplified bedside score includes age, CKD, cardiovascular instability, and the presence or absence of cardiac arrest before PCI. The total score ranges from 2 to 31 points with an overall score  $\leq 5$  corresponding to a predicted mortality rate of <0.1% and a score of  $\geq 27$  associated with mortality rate of >85%.<sup>35</sup>

- A coronary age calculator was derived with traditional risk factors and CAC score in a MESA cohort of 6727 adults and compared with chronological age, the MESA CHD Risk Score, and CAC alone. The derived coronary age with CAC was identical to the MESA CHD Risk Score in predicting 10-year risk of CHD and had the highest discrimination (AUC=0.76) compared with chronological age (AUC=0.63) and coronary age without CAC (AUC=0.70).<sup>36</sup>

## Genetics and Family History

### Family History as a Risk Factor

- Among adults  $\geq 20$  years of age, 13.8% (SE, 0.6%) reported having a parent or sibling with a heart attack or angina before 50 years of age. The racial and ethnic breakdown from NHANES 2017 to 2020 is as follows (unpublished NHLBI tabulation)<sup>1</sup>:
  - For NH White people, 14.0% (SE, 1.5%) for males and 15.7% (SE, 0.9%) for females.
  - For NH Black people, 9.7% (SE, 1.5%) for males and 14.4% (SE, 1.2%) for females.
  - For Hispanic people, 8.1% (SE, 1.1%) for males and 12.9% (SE, 1.4%) for females.
  - For NH Asian people, 6.3% (SE, 1.3%) for males and 8.4% (SE, 1.5%) for females.
- Because the incidence of HD increases with age, the prevalence of family history will vary depending on the age at which family history is assessed. The distribution of reported family history of heart attack by age of survey respondent in the US population as measured by NHANES 2017 to 2020 is as follows (unpublished NHLBI tabulation)<sup>1</sup>:
  - 20 to 39 years of age, 7.8% (SE, 1.3%) for males and 10.1% (SE, 0.8%) for females.
  - 40 to 59 years of age, 16.1% (SE, 1.7%) for males and 16.9% (SE, 1.4%) for females.
  - 60 to 79 years of age, 15.8% (SE, 2.1%) for males and 21.2% (SE, 2.6%) for females.
  - ≥80 years of age, 11.1% (SE, 2.9%) for males and 13.3% (SE, 2.1%) for females.
- Data from a longitudinal observational study (N=49 255) demonstrated an association between family history of premature angina, MI, angioplasty, or bypass surgery and increased lifetime risk by ≈50% for both HD (from 8.9% to 13.7%) and CVD mortality (from 14.1% to 21%).<sup>37</sup>

### Genetic Predictors of CHD

- CHD is heritable. From 36 years of follow-up data in 20 966 Swedish twins, the heritability of CHD mortality was 57% for males and 38% for females.<sup>38</sup> Of note, estimated heritability was greatest at younger ages of death, particularly for males. Another study of early-onset MI estimated that 56% to 63% of the phenotypic variation was attributable to genetic factors.

- The application of GWASs to large cohorts of subjects with CHD has identified consistent genetic variants associated with CHD. Although several CHD loci indicate roles for atherosclerosis and traditional CVD risk factors, other loci highlight the importance of biological process in the arterial wall.<sup>39</sup>
- The first GWAS identified a locus on chromosome 9p21.3, which is the most consistently replicated genetic marker for CHD and MI in populations of European ancestry.<sup>40</sup> The primary SNP at 9p21.3 is common; 50% of the European ancestry population is estimated to harbor 1 risk allele, and 23% harbors 2 risk alleles.<sup>41</sup>
  - A meta-analysis of 22 articles (N=35 872 cases; N=95 837 controls) identified the 10-year HD risk for a male 65 years of age with 2 9p21.3 risk alleles and no other traditional risk factors as ≈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>41</sup>
- GWASs have identified multiple loci associated with CAD implicating pathways in blood vessel morphogenesis, lipid metabolism, nitric oxide signaling, and inflammation.<sup>42</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>43</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.<sup>44</sup> These variants are associated with low plasma triglycerides and high HDL-C.
- 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*, *MRV1-CTR9*, *LRP1*, *SCARB1*, and *CETP* genes.<sup>45</sup>
- In the DiscovEHR study (N=58 335), loss-of-function variants in *ANGPTL3* (angiopoietin-like 3) were less common in patients with CAD (n=13 102) than in control subjects (n=40 430; 0.33% versus 0.45%) and were associated with 27% lower triglyceride levels, 9% lower LDL-C, and 4% lower HDL-C.<sup>46</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=5.1×10<sup>-3</sup>).<sup>47</sup>
- 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>48</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 CARDIoGRAM Consortium (OR, 0.79 [95% CI, 0.65–0.97]; P=0.016) and the CARDIoGRAMplusC4D 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>49</sup>
- Whole-genome sequencing studies 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>50</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>51</sup> Clonal hematopoiesis of indeterminate potential itself has germline genetic determinants.<sup>52</sup>

### Clinical Utility of Genetic Markers

- Studies have shown that patients with early-onset MI have a higher proportion of high polygenic GRS than of FH variants; for example, ≈2% carry a rare FH genetic variant, whereas ≈17% have a high PRS.<sup>53</sup>
- Even in individuals with high genetic risk, prevention strategies may have benefit. For example, in 4 studies across 55 685 individuals, genetic and lifestyle factors were independently associated with CHD, but even in individuals 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>54</sup>
- In the FOURIER study (N=14 298), 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, had reduced risk of major coronary events (HR, 0.69 [95% CI, 0.55–0.86];  $P=0.0012$ ).<sup>55</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>56</sup>
- Studies suggest that addition of a GRS contributes modestly to clinical risk prediction when applied in a generalizable population-based cohort. In the UK Biobank with >350 000 participants, 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>57</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>58</sup>
- A meta-analysis of PRS and CAD including 49 studies and totaling 979 286 individuals identified that a 1-SD increment increase in PRS was associated with OR of 1.67 (95% CI, 1.57–1.77) increased risk of prevalent and incident CAD. The PRS predicted incident CAD with a C statistic of 0.71.<sup>59</sup>
- GRSs derived in 1 ancestry may have limited generalizability to individuals of other ancestries.<sup>60</sup> An example is a GRS for CAD derived and validated in South Asian individuals (OR per 1 SD, 1.58 [95% CI, 1.42–1.76]).<sup>61</sup>

### Awareness, Treatment, and Control

#### Awareness of Warning Signs and Risk for HD

- 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>62</sup>
- Data from the NHIS 2017 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>63</sup> Compared with adults born in the United States, adults born in Europe, Russia, Africa, Middle East, Indian subcontinent, Asia, and Southeast Asia were likely to be aware of all 5 MI symptoms in the NHIS 2017 cycle.<sup>64</sup>

- Data from an online survey of US females ( $\geq 25$  years of age) showed that awareness related to CHD as a leading cause of death among females declined from 65% in 2009 to 44% in 2019. The decline in awareness was observed in all racial and ethnic groups and ages except females  $\geq 65$  years of age. Moreover, NH Black (OR, 0.31 [95% CI, 0.19–0.49]) and Hispanic (OR, 0.14 [95% CI, 0.07–0.28]) females and 25- to 34-year-old females (OR, 0.19 [95% CI, 0.10–0.34]) experienced the greatest 10-year decline in awareness from 2019 to 2009.<sup>65</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% (95% CI, 24%–36%) longer waiting time than White individuals.<sup>66</sup>
- The weekend effect, that is, presentation with ACS on a weekend rather than weekday, has been examined with regard to timing and use of invasive management strategies. An analysis of NIS data spanning 2000 to 2016 identified statistically different rates of coronary angiography (59.9% versus 58.8%;  $P<0.001$ ) and PCI (38.4% versus 37.6%;  $P<0.001$ ) between weekend and weekday ACS presentations, more pronounced when early coronary angiography was examined (26% versus 21%;  $P<0.001$ ).<sup>67</sup> Weekend presentation was not associated with increased risk of mortality compared with weekday presentation with ACS (OR, 1.01 [95% CI, 1.00–1.01]).
- A European registry of 6609 patients treated at 77 high-volume PCI centers determined that the COVID-19 pandemic was associated with a significant increase in door-to-balloon and total ischemia times.<sup>68</sup> 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 ( $P=0.003$ ), 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  $\leq 90$  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>69</sup>

- Rural EMS response has been longer than activation from suburban or metropolitan locations. National data from 2015 indicated that the mean response time for EMS was 14.5 minutes (9.5 minutes) in rural zip codes, 7.0 minutes (4.4 minutes) in urban zip codes, and 7.7 minutes (5.4 minutes) in suburban zip codes.<sup>70</sup>

#### *Operations and Procedures*

- In 2018, an estimated 482 000 PCIs, 202 000 CABGs, 115 000 CEA and stenting procedures, and 93 000 pacemaker and defibrillator procedures were performed for inpatients in the United States (unpublished NHLBI tabulation using HCUP<sup>71</sup>).

#### *Comparison of Outcomes: Surgery Versus*

#### *Percutaneous Intervention*

- An analysis of 30 studies determined that compared with males, females undergoing CABG and combined CABG and valve surgery had higher short-term (ie, in-hospital or within 30 days) mortality (OR, 1.40 [95% CI, 1.32–1.49];  $P=79\%$ ) and postoperative stroke (OR, 1.2 [95% CI, 1.07–1.34];  $P=90\%$ ) risks.<sup>72</sup>
- In an analysis of the BEST, PRECOMBAT, and SYNTAX trials comparing individuals with a previous MI and left main or multivessel CAD, CABG (versus PCI) was associated with a lower risk of MI (HR, 0.29 [95% CI, 0.16–0.55]) over a median follow-up of 59.8 months (IQR, 50.7–60.3 months).<sup>73</sup>
- At 10 years of follow-up in the SYNTAX trial, among 1800 trial participants, 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>74</sup>
- The ISCHEMIA trial randomized 5179 individuals with stable CAD and moderate or severe ischemia on stress testing to invasive or initial conservative treatment. Over the 4-year follow-up, there was no difference in primary end point events (defined as cardiovascular death, MI, hospitalization for unstable angina, HF, or cardiac arrest) between those randomized to the invasive (18.2 per 100 patients [95% CI, 15.8–20.9]) and conservative (19.7 per 100 patients [95% CI, 17.5–22.2]) management arms.<sup>75</sup>
- In patients (N=1905) 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 (n=948) and CABG (n=957) 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>76</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>77</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>78</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 [IQR, 7–25 minutes] versus 28 minutes [IQR, 18–39 minutes]), shorter door-to-device time (median, 40 minutes [IQR, 30–51 minutes] versus 52 minutes [IQR, 41–65 minutes]), and lower in-hospital mortality (2.8% versus 3.4%;  $P=0.01$ ).<sup>79</sup>
- In the ISCHEMIA 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 an initial conservative strategy (risk difference,  $-1.8\%$  [95% CI,  $-4.7\%$  to  $1\%$ ] at 5 years).<sup>80</sup>

#### *Secular Trends in Procedures*

- 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>81</sup>
- Between 2011 and 2014, the use of femoral access declined (from 88.8% to 74.5%), and the use of radial access increased (from 10.9% to 25.2%).<sup>82</sup>
- In a meta-analysis of 13 observational studies and 3 RCTs (N=777 841), a transradial approach for PCI was associated with a reduction in vascular complications (OR, 0.36 [95% CI, 0.30–0.43]) and stroke (OR, 0.81 [95% CI, 0.66–1.00]) compared with a transfemoral approach.<sup>83</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 between transradial approach and death was observed in the randomized trials.

- An analysis of HCUP Inpatient and State Ambulatory and Surgery and Services Databases quantified the number of patients who underwent PCI from 2010 to 2017 in Florida, Maryland, Michigan, and New York.<sup>8</sup> In these 4 states, PCI rates declined from 260.2 per 100 000 individuals in 2010 to 232.8 per 100 000 individuals in 2017 ( $-10.5\%$ ;  $P_{\text{trend}} <0.001$ ). This decline was attributed to a decrease in elective PCI across these years of  $-34.4\%$ . Rates of urgent PCI increased from 95.0 per 100 000 individuals in 2010 to 109.2 in 2017 ( $+15.0\%$ ;  $P_{\text{trend}} <0.001$ ).
- Among 216 657 adults with type 1 MI, 37 675 adults with type 2 MI, and 1521 with both type 1 and type 2 MI in the Nationwide Readmissions Database, use of coronary angiography (10.9% versus 57.3%;  $P <0.001$ ), PCI (1.7% versus 38.5%;  $P <0.001$ ), and CABG (0.4% versus 7.8%;  $P <0.001$ ) was lower among patients with type 2 MI than those with type 1 MI. Furthermore, the risks of in-hospital mortality (aOR, 0.57 [95% CI, 0.54–0.60]) and 30-day MI readmission (aOR, 0.46 [95% CI, 0.35–0.59]) were lower among those with type 2 MI than those with type 1 MI.<sup>84</sup>

### **Cardiac Rehabilitation**

- 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>23</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 to 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>22</sup>
- In a randomized trial in patients undergoing cardiac rehabilitation after ACS with PCI, patients receiving digital health 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>85</sup>

### **Mortality**

(See Table 21-1)

- On the basis of 2020 mortality data<sup>86</sup>:
  - CHD mortality was 382 820, and CHD any-mention mortality was 617 216 (Table 21-1).
  - MI mortality was 109 199. MI any-mention mortality was 158 724 (Table 21-1).
- From 2010 to 2020, the annual death rate attributable to CHD declined 19.2%, and the actual number of deaths increased 0.9% (unpublished NHLBI tabulation using CDC WONDER<sup>87</sup>).
- In 2020, CHD age-adjusted death rates per 100 000 were 128.5 for NH White males, 153.6 for NH Black males, and 102.2 for Hispanic males. For NH White females, the rate was 63.8; for NH Black females, it was 85.9; and for Hispanic females, it was 54.2 (unpublished NHLBI tabulation using CDC WONDER<sup>87</sup>).
- In 2020, 80% of CHD deaths occurred out of hospital. According to US mortality data, 307 322 CHD deaths occurred out of hospital or in hospital EDs in 2020 (unpublished NHLBI tabulation using CDC WONDER<sup>87</sup>).
- The estimated average number of YLL because of an MI death was 14.4 in 2020 (unpublished NHLBI tabulation using CDC WONDER<sup>87</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>
- In a study of Medicare beneficiaries (N=119 735) treated at 1824 hospitals, patients admitted with AMI to high-performance hospitals had longer mean years of life ranging from 0.74 year (95% CI, 0.48–1.01) to 1.14 years (95% CI, 0.84–1.44) than those treated at lower-performing hospitals.<sup>88</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>89</sup>
- An analysis of the multicenter NCDR Chest Pain–MI Registry (N=155 397 patients and 763 hospitals) 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. Furthermore, racial differences in readmission were not significant after covariate adjustment.<sup>15</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>90</sup>
- Other data indicate that the rapid increase in the population ≥65 years of age has contributed to the reduction of HD mortality. From CDC WONDER data from 2011 through 2017, a deceleration in the decline in HD mortality was observed with a <1% annualized decrease. Taking into account the increase in the growth of the population ≥65 years of age combined with the slowing of the decrease in HD mortality resulted in an increase in the absolute number of HD deaths since 2011 (50880 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>91</sup>
- An analysis of the ISCHEMIA trial (N=5179) compared 4-year mortality in trial participants classified as having mild/no ischemia, moderate ischemia, or severe ischemia. Compared with those with mild/no ischemia, 4-year mortality rates were similar in those with moderate (HR, 0.89 [95% CI, 0.61–1.30]) and severe (HR, 0.83 [95% CI, 0.57–1.21]) ischemia.<sup>92</sup> A meta-analysis of 56 studies determined that females with STEMI have higher mortality risk (OR, 1.91 [95% CI, 1.84–1.99]) than males.<sup>93</sup>

### Social Determinants and Health Equity 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%). An analysis of NCDR data from 2010 to 2015 reported that women admitted with STEMI had decreased survival to discharge compared with men (OR, 0.63 [95% CI, 0.52–0.76]).<sup>94,95</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 decreased the difference in 30-day mortality between men and women.<sup>96</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 associated with in-hospital mortality.<sup>97</sup>

- An analysis conducted in NHIS determined that 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]).<sup>98</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>99</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 (27.8% females) found that in multivariable-adjusted analyses, female sex was associated with 5-year risks 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>100</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.
- A large regional health care system conducted an analysis of 1-year mean residential-level estimates

of PM2.5 in individuals with ASCVD. A 10- $\mu\text{g}/\text{m}^3$  increase in PM2.5 exposure was associated with HR of 1.20 (95%, 1.11–1.30) increased risk of cardiovascular mortality but not stroke or MI.<sup>101</sup>

- A meta-analysis of 30 cardiac surgery studies identified that females have an increased risk of short-term mortality after CABG (aOR, 1.40 [95% CI, 1.32–1.49];  $P=79\%$ ) compared with males.<sup>72</sup>
- Sex differences in outcomes after MI are well established. In Olmsted County, Minnesota, mortality risk after premature MI (defined as 18–55 years of age in males and 18–65 years of age in females) declined by 66% in females (HR, 0.34 [95% CI, 0.17–0.68]) from 1987 through 2012. In contrast, no significant decline in mortality was observed in males.<sup>102</sup> A multicenter study in London, UK (N=26 799), determined that multivariable-adjusted sex differences in survival after STEMI over a median of 4.1 years (IQR, 2.2–5.8 years) of follow-up were significant in those >55 years of age (HR, 1.20 [95% CI, 1.09–1.41] for females compared with males).<sup>103</sup>

### 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>82</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>82</sup> In the NCDR ACTION Registry—GWTG, a measure of neighborhood SES based on census data 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 lowest 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>104</sup>
- In an analysis of the NIS, females with AMI presenting 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];  $P<0.001$ ) in a propensity-matched analysis.<sup>105</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>106</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 concomitant 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>107</sup>
- In a trial of patients presenting with STEMI (N=402), those with HF symptoms (New York Heart Association functional class  $\geq 2$ ; n=76) 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>108</sup>
- The burden of rehospitalizations for AMI is 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>109</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 ≥45 years of age, 4% of males and 7% of females.
  - At ≥45 years of age, 5% of White males, 6% of White females, 4% of Black males, and 10% of Black females.
- The median survival time (in years) after a first MI is as follows:
  - At ≥45 years of age, 8.2 for males and 5.5 for females.
  - At ≥45 years of age, 8.4 for White males, 5.6 for White females, 7.0 for Black males, and 5.5 for Black females.
- A systematic review and pooled analysis of 4 CABG trials compared sex differences in outcomes between females (n=2714) and males (n=10479). Over the 5-year follow-up, females had a significantly increased risk of major adverse cardiac and cerebrovascular events (aHR, 1.12 [95% CI, 1.04–1.21]), MI (aHR, 1.30 [95% CI, 1.11–1.52]), and repeat revascularization (aHR, 1.22 [95% CI, 1.04–1.43]) but not stroke (aHR, 1.17 [95% CI, 0.90–1.43]).<sup>110</sup>
- A meta-analysis of 56 studies of STEMI identified that compared with males, females hospitalized with STEMI are more likely to experience repeat MI (OR, 1.25 [95% CI, 1.00–1.56]), stroke (OR, 1.67 [95% CI, 1.27–2.20]), and major bleeding (OR, 1.82 [95% CI, 1.56–2.12]).<sup>93</sup>
- An analysis of the US Nationwide Readmissions Database determined that after hospitalization for AMI, females had 13% increased risk of 6-month HF hospitalization compared with males (6.4% in females versus 5.8% in males; HR, 1.13 [95% CI, 1.05–1.21]).<sup>111</sup>

## Hospital Discharges and Ambulatory Care

(See Table 21-1 and Chart 21-8)

- From 2009 to 2019, the number of inpatient discharges from short-stay hospitals with CHD as the first-listed diagnosis decreased from 1438000 to 1021000 (Table 21-1).
- From 1997 through 2019, the number of hospital discharges for CHD generally declined (Chart 21-8).
- In 2018, there were 9221000 physician office visits for CHD (unpublished NHLBI tabulation using NAMCS<sup>112</sup>). In 2019, there were 1032000 ED visits with a primary diagnosis of CHD (unpublished NHLBI tabulation using HCUP<sup>71</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>113</sup>

## Cost

- The estimated direct cost of HD in 2018 to 2019 (average annual) was \$117.0 billion (MEPS,<sup>116</sup> unpublished NHLBI tabulation).
- The estimated direct and indirect cost of HD in 2018 to 2019 (average annual) was \$239.9 billion (MEPS,<sup>116</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>117</sup>
- In 642105 Medicare beneficiaries hospitalized for AMI between 2011 and 2014, 30-day episode payments averaged \$22128 but varied 2-fold across hospitals. Median costs were \$20207 in the lowest quartile versus \$24174 in the highest quartile of hospitals.<sup>118</sup>
- In Medicare beneficiaries hospitalized with AMI, the 180-day expenditures increased from an average of \$32182 per person in 1999 to 2000 to \$36836 in 2008 and remained relatively stable thereafter, with expenditures of \$36668 in 2013 to 2014.<sup>119</sup>
- In 11969 patients with AMI from 233 US hospitals who underwent PCI from 2010 to 2013, average hospital costs were higher for patients with STEMI (\$19327) compared with patients with NSTEMI (\$18465;  $P=0.002$ ) 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 (\$6116 for hospitalizations, \$1334 for outpatient hospital stays, and \$587 for ED visits).<sup>120</sup>
- Among 26 255 patients with isolated CABG in a regional STS database between 2012 and 2019, the median hospital cost was higher among those with open CABG (\$35 011) than minimally invasive CABG surgery (\$27 906;  $P<0.001$ ) after propensity score matching. There was no significant difference in mortality or morbidity, although patients with open CABG had longer hospital stays (7 days versus 6 days;  $P=0.005$ ) than those with minimally invasive CABG surgery.<sup>121</sup>

### Global Burden

(See Table 21-3 and Charts 21-9 and 21-10)

- The GBD Study 2020 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 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>122</sup>

### Acute Coronary Syndrome

**ICD-9 410, 411; ICD-10 I20.0, I21, I22.**

- In 2019, there were 673 000 ACS principal diagnosis discharges. This estimate was derived by adding the principal diagnoses for MI (665 000) to those for unstable angina (8000; unpublished NHLBI tabulation using HCUP<sup>71</sup>).

- When all listed discharge diagnoses in 2019 were included, the corresponding number of inpatient hospital discharges was 1 266 000 unique hospitalizations for ACS. Of the total, 1 248 000 were for MI alone, and 18 000 were for unstable angina alone (HCUP<sup>71</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 unstable angina.<sup>123</sup>
- In a population-level study in Italy, the incidence rate of PCI for ACS decreased from 178 (before the COVID-19 outbreak) to 120 (after the COVID-19 outbreak) cases per 100 000 residents per year (IRR, 0.68 [95% CI, 0.65–0.70]).<sup>124</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];  $P_{\text{interaction}}<0.011$ ).
- Among 17 562 patients with ACS between 2005 and 2017 who lived beyond 30 days in a large PCI registry in Australia, 83.3% were on a  $\beta$ -blocker. Risk of overall mortality was lower among those who were on a  $\beta$ -blocker (aHR, 0.87 [95% CI, 0.78–0.97];  $P=0.014$ ) compared with those who were not. This mortality benefit was observed among patients with LVEF  $<$ 35% (aHR, 0.63 [95% CI, 0.44–0.91];  $P=0.013$ ) and 35% to 50% (aHR, 0.80 [95% CI, 0.68–0.95];  $P=0.01$ ) but not among those with LVEF  $>$ 50%.<sup>125</sup>
- In a retrospective analysis of 43 446 patients who were referred for cardiac catheterization at a medical center in Massachusetts between January 2006 and June 2017, 26 545 patients had ACS. Younger patients with ACS ( $<$ 35 years of age) were more likely to be White, obese, and a smoker and to report a family history of CAD, but they were less likely to have diabetes, hypertension, and hyperlipidemia than older patients. Younger patients with ACS also had a higher prevalence of elevated troponin, late-presentation STEMI, and cardiogenic shock than older patients. Compared with patients with ACS who were 36 to 54 years of age, those who were  $\leq$ 35 years of age had higher odds of 30-day mortality (aOR, 5.65 [95% CI, 2.49–12.82];  $P<0.001$ ).<sup>126</sup>
- A retrospective analysis of 801 195 patients with ACS in the NIS identified disparities in outcomes of patients admitted based on insurance (Medicaid, Medicare, private, and no insurance). Patients who had no insurance (aOR, 1.46 [95% CI, 1.26–1.69];  $P\leq0.01$ ) or were on Medicaid (aOR, 1.16 [95%

CI, 1.03–1.30];  $P=0.01$ ) had higher mortality than those who had private insurance.<sup>127</sup>

## 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 2017 to 2020, the prevalence of AP among adults ( $\geq 20$  years of age) was 3.9% (10.8 million adults; Table 21-2).
- On the basis of NHANES 2017 to 2020, the prevalence of AP increased with age from <1% among males and females 20 to 39 years of age to >9% among males and females  $\geq 80$  years of age (Chart 21-11).
- On the basis of data from NHANES in 2009 to 2012, an average of 3.4 million people  $\geq 40$  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>128</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>129</sup>
- Among 1612 of 4139 eligible patients diagnosed with CAD in a network consisting of 15 primary care clinics in Massachusetts, the prevalence of angina was measured with the Seattle Angina Questionnaire-7; 21.2% reported angina symptoms at least once monthly, and among those, 12.5% reported daily or weekly angina symptoms and 8.7% reported monthly angina symptoms.<sup>130</sup>

**Table 21-1. CHD in the United States**

Population group	Prevalence, CHD, 2017–2020, $\geq 20$ y of age	Prevalence, MI, 2017–2020, $\geq 20$ y of age	New and recurrent MI and fatal CHD, 2005–2014, $\geq 35$ y of age	New and recurrent MI, 2005–2014, $\geq 35$ y of age	Mortality,* CHD, 2020, all ages	Mortality,* MI, 2020, all ages	Hospital discharges: CHD, 2019, all ages
Both sexes	20 500 000 (7.1%) [95% CI, 6.1%–8.3%]	9 300 000 (3.2%) [95% CI, 2.5%–4.0%]	1 055 000	805 000	382 820	109 199  American Heart Association.	1 021 000
Males	11 700 000 (8.7%)	6 100 000 (4.5%)	610 000	470 000	227 887 (59.5%) <sup>†</sup>	65 137 (59.6%) <sup>†</sup>	
Females	8 800 000 (5.8%)	3 200 000 (2.1%)	445 000	335 000	154 933 (40.5%) <sup>†</sup>	44 062 (40.4%) <sup>†</sup>	
NH White males	9.4%	4.8%	520 000 <sup>‡</sup>	...	174 617	49 972	...
NH White females	5.9%	2.2%	370 000 <sup>‡</sup>	...	116 492	32 831	...
NH Black males	6.2%	4.0%	90 000 <sup>‡</sup>	...	26 088	7282	...
NH Black females	6.3%	2.3%	75 000 <sup>‡</sup>	...	20 595	6029	...
Hispanic males	6.8%	3.1%	...	...	17 834	5287	...
Hispanic females	6.1%	1.9%	...	...	11 789	3495	...
NH Asian males	5.2%	2.8%	...	...	7077 <sup>§</sup>	2021 <sup>§</sup>	...
NH Asian females	3.9%	0.5%	...	...	4816 <sup>§</sup>	1384 <sup>§</sup>	...
NH American Indian or Alaska Native	...	...	...	...	2158	674	...

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>131</sup> 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 AP, 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.

AP indicates angina pectoris; CHD, coronary heart disease; COVID-19, coronavirus disease 2019; ellipses (...), data not available; MI, myocardial infarction; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

\*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.

<sup>†</sup>These percentages represent the portion of total CHD and MI mortality that is for males vs females.

<sup>‡</sup>Estimates include Hispanic and NH people. Estimates for White people include other non-Black races.

<sup>§</sup>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  $\geq 20$  years of age. Age-specific percentages are extrapolated to the 2020 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 (for underlying cause of CHD): unpublished NHLBI tabulation using National Vital Statistics System.<sup>86</sup> Mortality for NH Asian people includes Pacific Islander people. Hospital discharges (with a principal diagnosis of CHD): unpublished NHLBI tabulation using Healthcare Cost and Utilization Project<sup>71</sup> (data include those inpatients discharged alive, dead, or status unknown).

**Table 21-2.** AP\* in the United States

Population group	Prevalence, 2017–2020, age ≥20 y	Hospital discharges, 2019, all ages
Both sexes	10 800 000 (3.9%) [95% CI, 3.3%–4.5%]	14 000
Males	5 600 000 (4.3%)	
Females	5 200 000 (3.6%)	
NH White males	4.7%	...
NH White females	3.5%	...
NH Black males	2.7%	...
NH Black females	4.1%	...
Hispanic males	3.6%	...
Hispanic females	4.3%	...
NH Asian or Pacific Islander males	2.7%	...
NH Asian or Pacific Islander females	2.7%	...

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>131</sup> AP includes people who either answered “yes” to the question of ever having angina or AP or being diagnosed with Rose angina (the Rose questionnaire is administered only to survey participants >40 years of age).

AP indicates angina pectoris; COVID-19, coronavirus disease 2019; ellipses (...), data not available; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

\*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.<sup>1</sup> Percentages for racial and ethnic groups are age adjusted for US adults ≥20 years of age. Estimates from NHANES 2017 to 2020 were applied to 2020 population estimates (≥20 years of age). Hospital discharges (with a principal diagnosis of AP): unpublished NHLBI tabulation using Healthcare Cost and Utilization Project<sup>71</sup>; data include those inpatients discharged alive, dead, or status unknown.

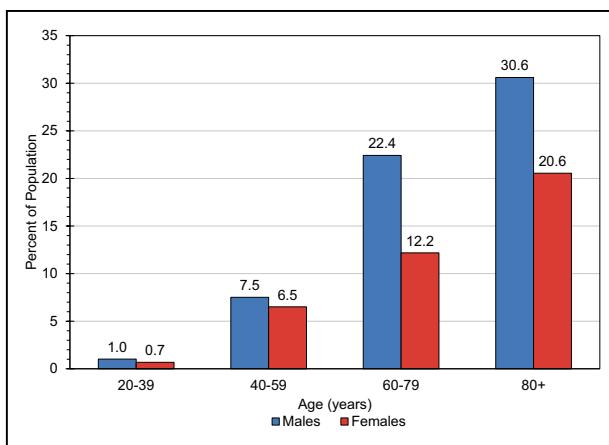
**Table 21-3.** Global Mortality and Prevalence of IHD by Sex, 2020

	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)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; IHD, ischemic heart disease, and UI, uncertainty interval.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>132</sup>

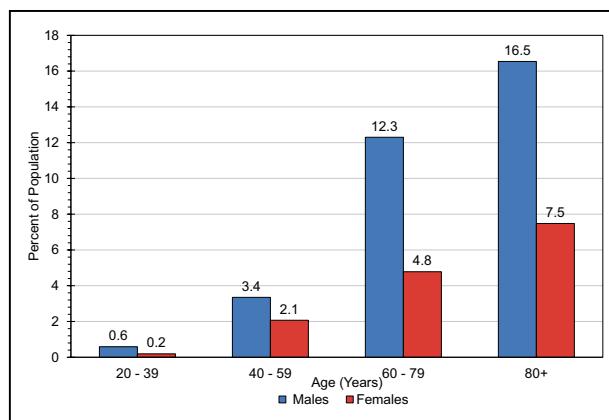


**Chart 21-1. Prevalence of CHD by age and sex, United States (NHANES, 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>131</sup>

CHD indicates coronary heart disease; COVID-19, coronavirus disease 2019; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>1</sup>



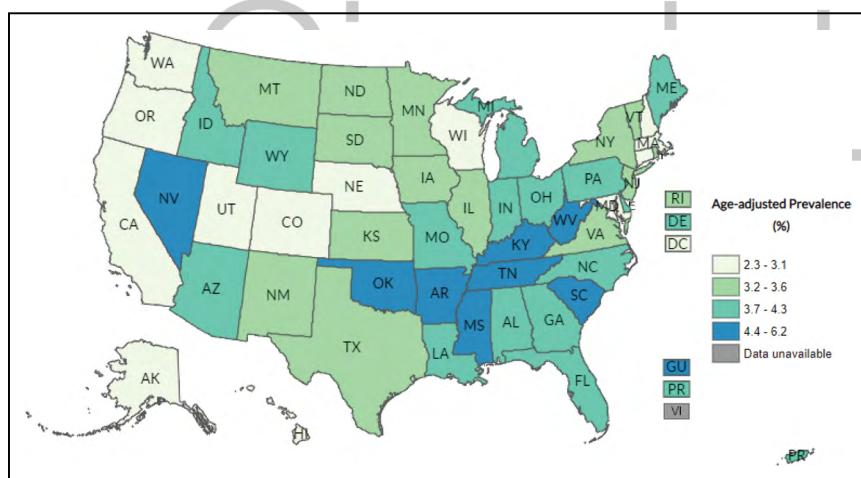
**Chart 21-2. Prevalence of MI by age and sex, United States (NHANES, 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>131</sup>

MI includes people who answered “yes” to the question of ever having had a heart attack or MI.

COVID-19 indicates coronavirus disease 2019; MI, myocardial infarction; and NHANES, National Health and Nutrition Examination Survey.

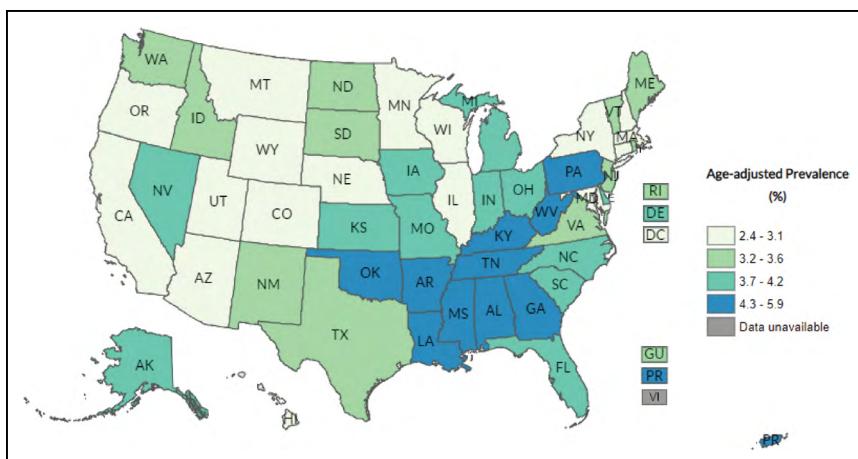
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>1</sup>



**Chart 21-3. “Ever told you had a heart attack (MI)?” Age-adjusted US prevalence by state (BRFSS prevalence and trends data, 2020).**

Original chart has been modified to remove white space between map and legend. BRFSS indicates Behavioral Risk Factor Surveillance System; and MI, myocardial infarction.

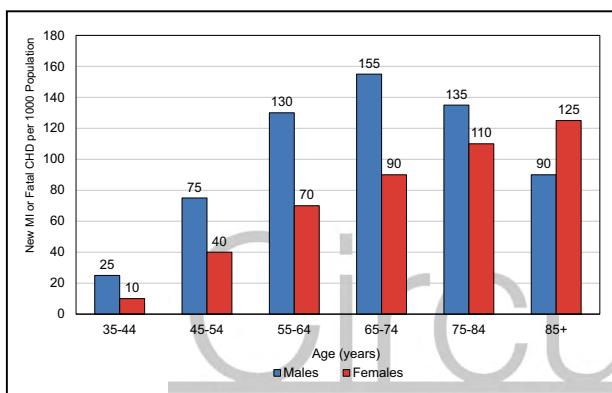
Source: BRFSS prevalence and trends data.<sup>3</sup>



**Chart 21-4. "Ever told you had angina or CHD?" Age-adjusted US prevalence by state (BRFSS prevalence and trends data, 2020).**

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>

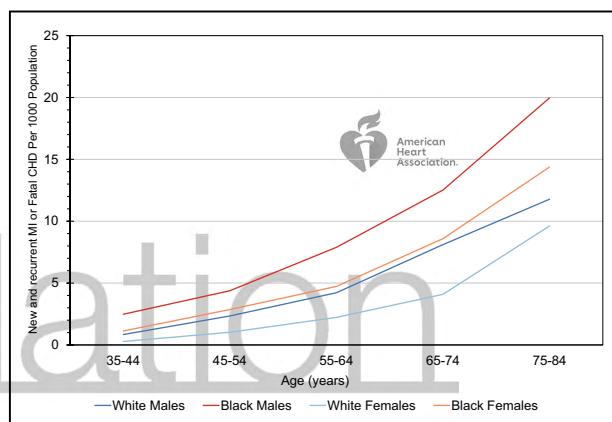


**Chart 21-5. Annual number of US adults per 1000 having diagnosed heart attack or fatal CHD by age and sex (ARIC Surveillance, 2005–2014 and CHS).**

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.

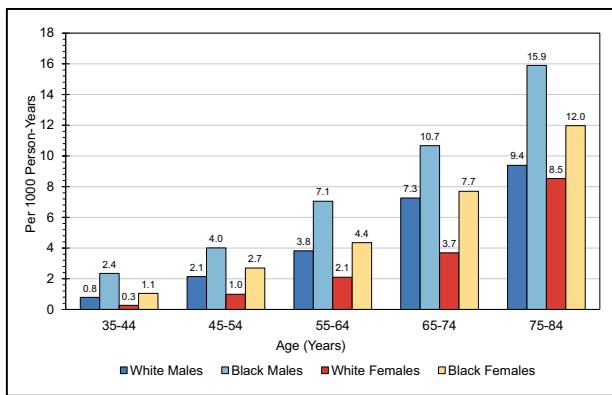
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using ARIC<sup>4</sup> and CHS.<sup>133</sup>



**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.

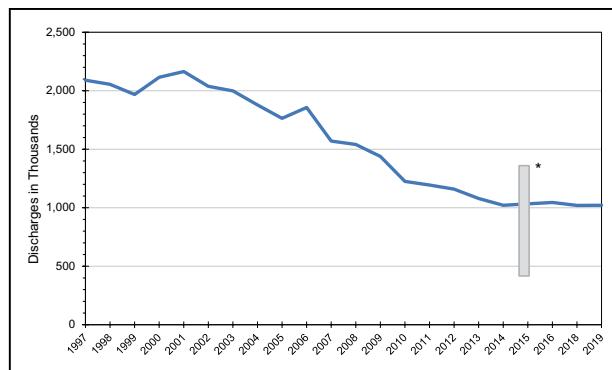
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using ARIC.<sup>4</sup>



**Chart 21-7. 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>



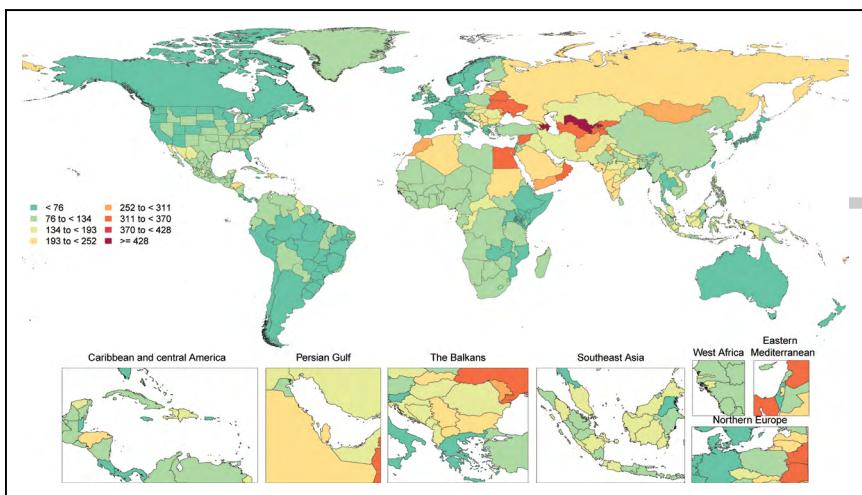
**Chart 21-8. Hospital discharges for CHD, United States (HCUP, 1997–2019).**

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 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.

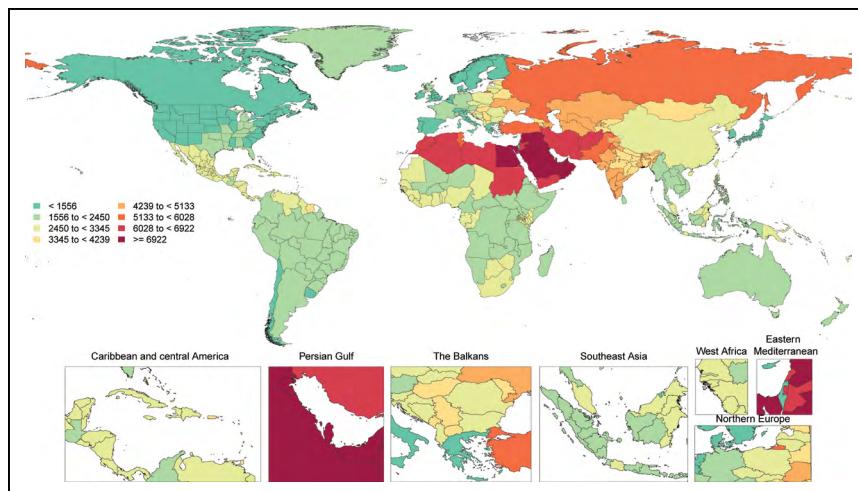
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using HCUP.<sup>71</sup>



**Chart 21-9. Age-standardized global mortality rates of IHD per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Disease; and IHD, ischemic heart disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>132</sup>

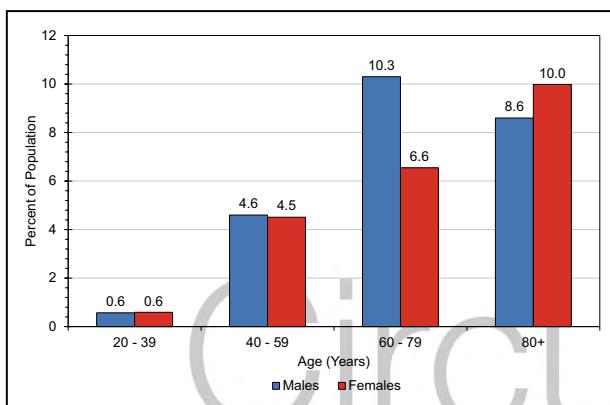


**Chart 21-10. Age-standardized global prevalence rates of IHD per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and IHD, ischemic heart disease.

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**Chart 21-11. Prevalence of AP by age and sex, United States (NHANES, 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>131</sup>

AP includes people who either answered "yes" to the question of ever having angina or AP or being diagnosed with Rose angina.

AP indicates anginal pectoris; COVID-19, coronavirus disease 2019; 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 22-3**

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### Cardiomyopathy

**ICD-9 425; ICD-10 I42.**

2020, United States: Underlying cause mortality—20 329. Any-mention mortality—45 701.

Cardiomyopathy diagnoses account for a substantial number of inpatient and outpatient encounters annually. According to HCUP 2019 data<sup>1</sup> for inpatient hospitalizations, cardiomyopathy was the principal diagnosis for 17 000, and it was included among all-listed diagnoses for 113 900.

#### Hypertrophic Cardiomyopathy

- HCM is a monogenic disorder with primarily autosomal dominant inheritance that 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>2–4</sup> A variant is identifiable in 30% to 60% of cases of familial HCM.
- Given the heterogeneous nature of the underlying genetics and incomplete penetrance, manifestation of the disease is highly variable, even in cases for which the causal variant has been identified.<sup>5</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>6</sup>
- A meta-analysis of prior GWASs found a strong correlation between common genetic variants associated with several LV traits, including increased LV mass, mean LV wall thickness, and radial strain, and HCM.<sup>7</sup> Two-sample mendelian randomization suggests a causal link between increased LV contractility and risk of developing HCM.

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

- 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). 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. Compared with males, females with HCM were at lower risk for ventricular arrhythmia (HR, 0.69 [95% CI, 0.51–0.94];  $P<0.05$ ) and AF (HR, 0.72 [95% CI, 0.60–0.87];  $P<0.001$ ) but higher risk for HF (HR, 1.28 [95% CI, 1.07–1.52];  $P<0.01$ ). There was no statistically significant difference in risk of each outcome for patients from underrepresented racial groups (all  $P>0.05$ ).<sup>8</sup>

#### Genetic Testing

- The NIH-funded Clinical Genome Resource framework identified that of the 33 speculated HCM genes, 8 genes (*MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *TPM1*, *ACTC1*, *MYL2*, and *MYL3*) have definitive evidence, 3 genes (*CSRP3*, *TNNC1*, and *JPH2*) have moderate evidence, and the remaining genes have limited to no evidence supporting an association with HCM.<sup>9</sup>
- 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>5</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>6</sup>

#### Dilated Cardiomyopathy

- Familial DCM is a common mendelian cardiomyopathy with a causal genetic variant identified in 10% to 14% of cases.<sup>2</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>10</sup> Familial DCM often displays an age-dependent penetrance.<sup>11</sup>

- Missense and truncating variants in the titin gene have been linked to autosomal dominant cardiomyopathy<sup>12</sup> and to DCM with incomplete penetrance in the general population.<sup>12</sup> Analysis of sequence data in 7855 cases with cardiomyopathy and >60 000 controls revealed the range in penetrance of putative disease variants, which further highlights the challenges in clinical interpretation of variation in mendelian disease genes.<sup>13</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>14,15</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>16,17</sup>

#### *Genetic Testing*

- Familial DCM accounts for up to 50% of cases of DCM with a prevalence of 1 in 2500, but it is likely underestimated.<sup>10</sup> Familial DCM often displays an age-dependent penetrance.<sup>11</sup> Up to 40% of cases have an identifiable genetic cause.<sup>2</sup>
- Among patients with DCM, a recent multisite nationwide cross-sectional study indicates an estimated familial prevalence of ≈30% in first-degree relatives and an estimated 19% risk of developing DCM by 80 years of age.<sup>18</sup> This study also indicates that first-degree relatives of NH Black probands (index patients with DCM) or probands diagnosed at a young age have a higher risk of DCM.<sup>18</sup> These findings suggest a potential yield of phenotypic screening of first-degree relatives of index DCM cases, especially those identified at a young age.
- In an appraisal of the 51 genes hypothesized to be associated with DCM, the recent Clinical Genome Resource framework panel noted that only 12 genes from 8 gene ontologies have definitive (*BAG3*, *DES*, *FLNC*, *LMNA*, *MYH7*, *PLN*, *RBM20*, *SCN5A*, *TNNC1*, *TNNT2*, and *TTN*) or strong (*DSP*) evidence and only 7 genes from the additional 2 ontologies (*ACTC1*, *ACTN2*, *JPH2*, *NEXN*, *TNNI3*, *TPM1*, and *VCL*) have moderate evidence supporting a robust association with DCM.<sup>19</sup> Because DCM is often the final disease manifestation of several cardiomyopathies, it shares genetic architecture with other inherited cardiomyopathies. Among the previously mentioned 19 genes linked to DCM, the

Clinical Genome Resource panel noted that 6 had a similar classification for HCM and 3 had a similar classification for ARVC.<sup>19</sup>

- Missense and truncating variants in the titin gene have been linked to autosomal dominant cardiomyopathy, as well as to DCM, with incomplete penetrance in the general population.<sup>12</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>13</sup>
- A recent GWAS has identified common genetic variants associated with HCM (16 loci identified) and DCM (13 loci identified), indicating a potential oligogenic pattern (instead of a conventionally understood monogenic pattern) for the genetic risk of HCM and DCM.<sup>7,20</sup> It is notable that 2 HCM loci (chromosome 1 near *HSPB7* and chromosome 10 near *BAG3*) have opposite directions of effect for DCM and require further evaluation in subsequent investigations.

#### *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>21</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>22–24</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>25</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>25</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>26</sup>
- Global mortality from PPCM is 9% and is lower in developed (4%) than developing (14%) countries; in addition, a high prevalence of females of

African descent was positively correlated with mortality (weight correlation coefficient, 0.29 [95% CI, 0.13–0.52]).<sup>27</sup>

- In most cases of PPCM (50%–80%), LVEF recovers to at least near-normal (≥50%) function and often within 6 months.<sup>28–31</sup> However, an initial LVEF <30%, LV end-diastolic dimension ≥6.0 cm, Black race, and initial presentation >6 weeks after delivery are associated with lower LVEF at 1 year.<sup>26</sup>

### Youth

- Since 1996, the Pediatric Cardiomyopathy Registry has collected data on children with cardiomyopathy in New England and central southwestern states.<sup>32</sup>
- Overall incidence of cardiomyopathy is 1.13 cases per 100 000 in children <18 years of age.
- 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 male (1.32) than in female (0.92) children ( $P<0.001$ ), and in New England (1.44) than in the central Southwest (0.98;  $P<0.001$ ).
- The annual incidence of HCM in children is ≈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 males (5.9 per 1 million [95% CI, 5.0–6.9]) than in females (3.4 per 1 million [95% CI, 2.8–4.2]).<sup>33</sup> Approximately 9% progress to HF and 12% to SCD over a median follow-up of 6.5 years.<sup>34</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 ≥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>35</sup>
- The annual incidence of DCM in children is ≈0.57 per 100 000 (95% CI, 0.52–0.63) with a higher incidence in males than females (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>36</sup> The 5-year incidence rate of SCD is 3% at the time of DCM diagnosis.<sup>37</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>38</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>39</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 Study 2020 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 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.**

2020, United States: Underlying cause mortality—85 855. Any-mention mortality—415 922.

2019, United States: Hospital discharges—1 297 000

### Prevalence

(See Table 22-2 and Chart 22-3)

- On the basis of data from NHANES 2017 to 2020, ≈6.7 million Americans ≥20 years of age had HF (Table 22-2), which is increased from ≈6.0 million according to NHANES 2015 to 2018 (NHLBI unpublished tabulation using NHANES<sup>40</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 ≥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>41</sup>

### Incidence

(See Table 22-2)

- According to ARIC Community Surveillance data, the incidence of HF in people ≥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>42</sup>

#### *Secular Trends*

- 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 HFrEF ( $-45\%$  [95% CI,  $-33\%$  to  $-55\%$ ]) than for HFpEF ( $-27.9\%$  [95% CI,  $-12.9\%$  to  $-40.3\%$ ]).<sup>43</sup> In the FHS, secular trends across 2 decades (1990–1999 and 2000–2009) showed similar incidence of overall HF but declining incidence for HFrEF (IRR, 0.80 [95% CI, 0.69–0.93]) and increasing incidence for HFpEF (IRR, 1.53 [95% CI, 1.30–1.79]).<sup>44</sup>

#### *Race-Based Differences*

- 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>45</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>46</sup> Black individuals also had the highest proportion of incident HF not preceded by MI (75%).<sup>46</sup>

#### *Lifetime Risk*

- The lifetime risk for HF in the community ranges from 20% to 46% at 45 years of age and is higher in individuals with higher BP and BMI as described in pooled data from the Chicago Heart Association Detection Project in Industry, ARIC, and the CHS.<sup>42</sup>

#### *Race and Sex Differences*

- 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.<sup>42</sup>

#### *Secular Trends*

- The lifetime risk of HF at 50 years of age increased among participants of the FHS in a comparison of two 25-year epochs (1965–1989 versus 1990–2014) from 18.9% to 22.6% in females and from 19.1% to 25.3% in males.<sup>47</sup>

#### *HF Subtypes: HFpEF, HFmrEF, and HFrEF*

- Among 4 community-based cohorts, including the CHS, FHS, PREVEND, and MESA, incidence rates by HF subtype were as follows: 34.9 HFrEF cases, 26.9 HFpEF cases, and 6.7 HFmrEF cases per 10 000 person-years. After HF onset, all-cause mortality rates were 459 events per 10 000 person-years among those with HFrEF, 394 events per 10 000 person-years in individuals with HFpEF, and 497 events per 10 000 person-years in those with HFmrEF.<sup>48</sup>
- Data from patients admitted with HF between 2005 and 2009 in the AHA GWTG-HF registry demonstrate a prevalence of 46% HFpEF, 8.2% HFmrEF, and 46% HFrEF with similar 5-year mortality across the HF subgroups in risk-adjusted survival analysis.<sup>49</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>50</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>51</sup>
- Risk factors differ by HF subtype: among 4 community-based studies (CHS, FHS, PREVEND, MESA)<sup>52</sup>:
  - Older age was more strongly associated with incident HFpEF (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).

- Age dependency of risk factors: Although the absolute risk of HF is lower among younger individuals, the PAR of modifiable risk factors is greater among young (<55 years of age) compared with older ( $\geq 75$  years).

years of age) individuals: obesity, 21% versus 13%; hypertension, 35% versus 23%; diabetes, 14% versus 7%; and smoking, 32% versus 1%.<sup>53</sup>

- Lifestyle factors also affect HF risk. Among WHI, MESA, and CHS participants, individuals with higher than twice the minimum guideline-recommended leisure-time PA had lower risk of HFpEF compared with those with no leisure-time PA (HR, 0.81 [95% CI, 0.68–0.97]), whereas no such association was observed for risk of HFrEF.<sup>54</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>55</sup>

#### Race and Sex Differences

- In 6 US longitudinal population-based cohorts, hypertension had the highest PAR among Black males and females (28% [95% CI, 19%–37%] and 26% [95% CI, 16%–34%], respectively), whereas the highest PAR among White males and females was for obesity (21% [95% CI, 15%–27%] and 18% [95% CI, 13%–23%]).<sup>56</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>57</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>58</sup>

#### Race and Sex Differences

- In ARIC, male sex and Black race were associated with lower LVEF, and Black race was associated with greater LV wall thickness, with greater subsequent risk of HF in males versus females (HR, 1.65 [95% CI, 1.07–2.53] versus HR, 0.76 [95% CI, 0.49–1.17]) and Black versus White individuals (HR, 2.36 [95% CI, 1.37–4.08] versus HR, 1.16 [95% CI, 0.89–1.51]).<sup>59</sup> These differences were driven by risk of HFrEF, whereas risk of HFpEF was similar across sex and race groups.
- 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>60</sup> Furthermore, individuals in JHS with reduced EF (<50%) and low-normal EF (≥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>61</sup>

- In the Echocardiographic Study of Latinos, almost half of middle-aged or older Hispanic individuals had some form of cardiac dysfunction (3.6% systolic, 50.3% diastolic, or both); 96% of cardiac dysfunction was subclinical or unrecognized.<sup>62</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, and 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>63</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>64–66</sup> and *CACNB4*.<sup>67</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>68</sup>
- Multiple GWASs of cardiac structure and function have highlighted the association of genetic architecture of LV phenotypes with the risk of future HF.<sup>69,70</sup>
- The genetic basis of specific cardiomyopathies is summarized in the previous cardiomyopathy section.

#### Treatment

- Mortality declines have been attributed primarily to evidence-based approaches to treat HFrEF and the implementation of treatment with neurohormonal blockade, coronary revascularization, implantable cardioverter defibrillators, and cardiac resynchronization therapies.<sup>71</sup>
- Initiation of contemporary guideline-directed medical therapy for HFrEF (quadruple therapy with ARNI,  $\beta$ -blockers, mineralocorticoid receptor antagonists, and SGLT-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 an estimated 1.4 to 6.3 additional years alive.<sup>72</sup>
- Contemporary evidence from the CHAMP-HF registry demonstrates significant gaps in use and dose of guideline-directed medical therapy for HFrEF.

Specifically, among eligible patients, 27% were not prescribed ACE inhibitors/angiotensin receptor blockers/ARNIs, 33% were not prescribed  $\beta$ -blockers, and 67% were not prescribed mineralocorticoid antagonists.<sup>73</sup>

### Mortality

- Overall 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>74</sup>
- 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>75</sup>; however, estimated 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>43</sup>

### Race and Sex Differences

- 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>45</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>76</sup>
- In 2020, the overall any-mention age-adjusted death rate for HF was 100.1 per 100 000 with variation across racial and ethnic groups. In males, the rates were 124.1 for NH White males, 145.5 for NH Black males, 54.8 for NH Asian or Pacific Islander males, 119.0 for NH American Indian or Alaska Native males, and 82.0 for Hispanic males. In females, the respective rates were 87.5 for NH White females, 102.9 for NH Black females, 37.8 for NH Asian or Pacific Islander females, 80.7 for NH American Indian or Alaska Native females, and 57.2 for Hispanic females (unpublished NHLBI tabulation using CDC WONDER<sup>77</sup>).

### Survival by HF Subtype

- Among individuals in the GWTG-HF registry with linked Medicare data and follow-up through 2014, 5-year survival was similarly poor among individuals with HFrEF compared with those with HFpEF (75.3% versus 75.7%, respectively; HR, 1.011 [95% CI, 0.975–1.049]).<sup>49</sup>

### CVD Death

#### (See Table 22-2)

- Although overall mortality appears to be decreasing, data from the CDC WONDER database show that age-adjusted rates of HF-related CVD death declined from 1999 (78.7 per 100 000 [95% CI, 78.2–79.2]) to 2012 (53.7 per 100 000 [95% CI, 53.3–54.1]) and subsequently have increased through 2017 (59.3 per 100 000 [95% CI, 58.9–59.6]).<sup>78</sup> Significant geographic variation in HF-related CVD mortality is noted with the highest increases in annual age-adjusted mortality rates after 2011 occurring in the Midwest (1.14 per 100 000 per year [95% CI, 0.75–1.53]) and South (0.96 per 100 000 per year [95% CI, 0.66–1.26]) and compared with the Northeast (0.35 per 100 000 per year [95% CI, 0.03–0.68]).<sup>79</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 2020 has HF mentioned on the death certificate (unpublished NHLBI tabulation).<sup>80</sup>
- Hospitalizations of children with advanced HF in congenital HD have increased, but overall hospital mortality has improved.<sup>81</sup>
- In 2020, HF was the underlying cause in 85 855 deaths (40 897 males and 44 958 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 48.6% higher in 2020 (85 855) than in 2010 (57 757; unpublished NHLBI tabulation using NVSS<sup>80</sup>).



### Rural-Urban Disparities

- Among Medicare fee-for-service beneficiaries, 30-day mortality was higher among patients with HF presenting to rural versus urban hospitals (HR, 1.15 [95% CI, 1.13–1.16]).<sup>82</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>83</sup>

### Health Care Use: Hospital Discharges/Ambulatory Care Visits

- In 2018, there were 3 267 000 physician office visits with a primary diagnosis of HF (NAMCS,<sup>84</sup> unpublished NHLBI tabulation). In 2019, there were 1 503 000 ED visits for HF (HCUP,<sup>1</sup> unpublished NHLBI tabulation). In 2019, there were 1 297 000 principal diagnosis hospital discharges for HF (HCUP,<sup>1</sup> unpublished NHLBI tabulation).

- 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>85</sup>
- In the NCDR PINNACLE, 1 in 6 patients with HFrEF 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; overall, the 30-day readmission rate was 56%, and the 2-year mortality rate was 22.5%.<sup>86</sup>

#### *Secular Trends*

- In the NIS, hospitalizations for HF increased from 1 060 540 in 2008 to 1 270 360 in 2018 with a greater proportion among individuals from underrepresented racial and ethnic groups (Black individuals: 18.4% in 2008, 21.2% in 2018; Hispanic individuals: 7.1% in 2008, 9.0% in 2018;  $P<0.001$  for all).<sup>87</sup>

#### *HF Subtypes*

- In the NIS, hospitalizations by HF subtype increased from 2008 to 2018 for both HFrEF ( $n=283\,193$  to  $n=679\,815$ ) and HFpEF ( $n=189\,260$  to  $n=495\,095$ ).<sup>87</sup> A greater proportion of HFrEF hospitalizations occurred in males (60.5%), and a greater proportion of HFpEF hospitalizations occurred in females (62.5%;  $P<0.001$  for difference).

#### *Race and Sex Differences*

- Data from the 2005 to 2014 ARIC Community Surveillance study have shown that HF hospitalization rates are increasing over time with the average annual percentage change ranging from 1.9% (95% CI, 0.7%–3.1%) in White females 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>88</sup> Age-adjusted 28-day and 1-year case fatality rates after first-time hospitalized HF were higher among White versus Black individuals. Specifically, 28-day age-adjusted case fatality was 12.1% (White males), 11.7% (White females), 10.2% (Black females), and 9.2% (Black males).<sup>88</sup>

#### *Noncardiovascular Hospitalizations*

- Data from Olmsted County, Minnesota, indicate among those with HF, most hospitalizations (63%) were 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>43</sup>
- In the CHARM Program, rates of cardiovascular hospitalization were higher among those with

LVEF ≤40% (23.6 [95% CI, 22.6–24.7] per 100 patient-years) versus LVEF >40% (19.3 [95% CI, 18.2–20.5] per 100 patient-years;  $P<0.001$  for difference), whereas rates of noncardiovascular hospitalization were similar (14.3 [95% CI, 13.5–15.2] versus 14.3 [95% CI, 13.3–15.3] per 100 patient-years, respectively).<sup>89</sup>

#### *Orthotopic Heart Transplantation and Mechanical Circulatory Support Device Placement in the United States*

#### *Heart Transplantation (See Chapter 27 [Medical Procedures] for additional heart transplantation data)*

- 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> Among 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.

#### *Secular Trends*

- The 2020 Annual Data Report from the Organ Procurement Transplant Network shows a 32.5% increase in new listings for adult heart transplantation from 3019 in 2009 to 4000 in 2020.<sup>91</sup> Heart transplantation rates have increased steadily since 2015 (101 per 100 wait-list years in 2020 from 61 per 100 wait-list years in 2015) with a concomitant decline in median wait time (2.7 months for candidates in 2019–2020 from a peak of 11.9 months in 2013–2014). Mortality after transplantation has declined since 2009 with 1-year survival of 90.6% among adult recipients who underwent heart transplantation in 2019. The overall impact of the new adult heart allocation policy implemented in 2018 remains to be seen.

#### *Sex Differences*

- Among 34 198 heart transplant recipients in the International Society for Heart and Lung Transplantation registry between 2004 and 2014, 23.7% were female and 76.3% were male.<sup>92</sup> When matched for recipient and donor characteristics, there was no significant difference in survival between male and female recipients ( $P=0.57$ ).

#### *Racial and Ethnic Disparities*

- Among 32 353 adult heart transplant recipients in the United Network for Organ Sharing database, the proportion of Black and Hispanic individuals listed increased from 2011 to 2020 (21.7% to 28.2% [ $P=0.003$ ] and 7.7% to 9.0% [ $P=0.002$ ], respectively).<sup>93</sup> Black individuals were less likely to undergo heart transplantation (aHR, 0.87 [95% CI, 0.84–0.90];  $P<0.001$ ) and had a higher risk

of death after transplantation (aHR, 1.14 [95% CI, 1.04–1.24];  $P=0.004$ ) compared with White individuals.

#### Geographic Variation

- Among 15 036 adult candidates for heart transplantation between 2011 and 2016 in the United States, there was significant state-level variation in outcomes, ranging from 1.0 to 7.8 deaths per 1000 wait-list person-days for wait-list mortality.<sup>94</sup> One-year risk-adjusted graft survival ranged from 87% to 92%.

#### Mechanical Circulatory Support

- INTERMACS reported outcomes on 25 551 patients undergoing primary isolated continuous-flow LVAD implantation between 2010 and 2019.<sup>95</sup> Mechanical circulatory support volumes have grown from 1558 in 2010 to 3198 in 2019 with increasing use of full magnetic levitation devices accounting for 77.7% of LVAD implantations in 2019, hybrid levitation continuous-flow devices accounting for 20.5%, and axial design accounting for 1.8%.
- Survival after primary continuous-flow LVAD implantation improved from 1-year survival of 80.5% in 2010 to 2014 to 82.3% in 2015 to 2019 ( $P<0.0001$  for difference).<sup>95</sup> When stratified by LVAD strategy, 1-year survival was 86.8% for bridge to transplantation, 83.8% for bridge to candidacy, and 80.1% for destination therapy in 2015 to 2019.
- Device strategy has changed over time, with the majority of LVADs now implanted as destination therapy (73.1%) in 2019, 18% as bridge to candidacy, and 8.9% as bridge to transplantation (listed).<sup>95</sup> In contrast, in 2009, 34.9% were implanted as destination therapy, 36.5% as bridge to candidacy, and 28.6% as bridge to transplantation. In 2019, INTERMACS profiles of LVAD recipients were as follows: 1 (critical cardiogenic shock, 17.0%), 2 (progressive decline, 32.9%), 3 (stable but inotrope dependent, 37.3%), and 4 to 7 (resting symptoms or less sick, 12.9%).
- 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>96</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 wait 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>97</sup>

#### Sex Differences

- 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>98</sup>

#### 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>41</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>41</sup>
- In a systematic review of HF-associated medical costs in the United States from 2014 to 2020, the annual median total cost was estimated at \$24 383 per patient, with HF hospitalizations accounting for the majority (\$15 879 per patient).<sup>99</sup>
- Data from the US Nationwide Readmission Database for 2 645 336 patients with primary HF admission between 2010 and 2014 show that major contributors to inpatient HF care are associated with comorbidities, invasive procedures, and readmissions.<sup>100</sup> The mean cost for patients without invasive care was \$10 995 compared with \$129 547 for receipt of circulatory support, \$251 110 for LVAD implantation, and \$293 575 for heart transplantation.
- 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>101</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 \$192 604; in the South, median length of stay was 27 days and median cost was \$198 884; and in the West, median length of stay was 29 days and median cost was \$246 292.<sup>96</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>102</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>103</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>102</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% of cases in South America, and 20% of cases in Africa. When 1-year all-cause mortality among individuals with HF was examined, geographic variation was observed with a multivariable-aHR of 3.8 (95% CI, 2.6–5.5) for Africa, 2.9 (95% CI, 1.9–4.3) for India, 2.6 (95% CI, 1.7–3.9) for Southeast Asia, 1.3 (95% CI, 0.9–1.9) for the Middle East, and 0.7 (95% CI, 0.4–1.1) for China compared with South America as the referent group.<sup>104</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)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>105</sup>

**Table 22-2. HF in the United States**

Population group	Prevalence, 2017–2020, ≥20 y of age	Incidence, 2014, ≥55 y of age	Mortality, 2020, all ages*	Hospital discharges, 2019, all ages	Cost, 2012†
Both sexes	6 700 000 (2.3%) [95% CI, 1.9%–2.8%]	1 000 000	85 855	1 297 000	\$30.7 Billion
Males	3 700 000 (2.7%)	495 000	40 897 (47.6%)‡	...	...
Females	3 000 000 (1.9%)	505 000	44 958 (52.4%)‡	...	...
NH White males	2.9%	430 000§	32 438	...	...
NH White females	1.6%	425 000§	36 179	...	...
NH Black males	3.8%	65 000§	5 173	...	...
NH Black females	3.3%	80 000§	5 409	...	...
Hispanic males	1.8%	...	2 196	...	...
Hispanic females	1.6%	...	2 294	...	...
NH Asian males	1.4%	...	824	...	...
NH Asian females	0.5%	...	893	...	...
NH American Indian or Alaska Native	...	...	346	...	...

HF includes people who answered “yes” to the question of ever having congestive HF. 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. In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>106</sup>

COVID-19 indicates coronavirus disease 2019; ellipses (...), data not available; HF, heart failure; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

\*Mortality data for underlying cause of death listed as HF on death certificates 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. For reference to all-cause mortality in setting of prevalent HF, please see chapter text in the Mortality section.

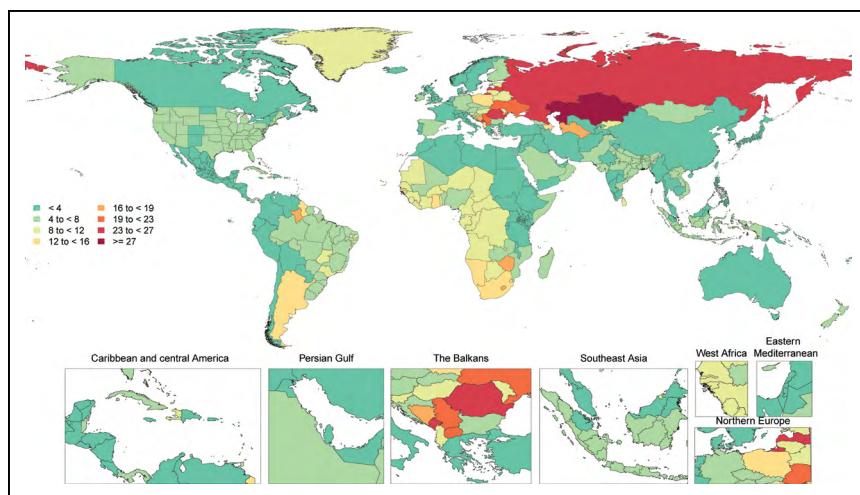
†Cost data are from Heidenreich et al.<sup>41</sup>

‡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 NHANES.<sup>40</sup> Percentages are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2020 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>107</sup> Mortality (for underlying cause of HF): Unpublished NHLBI tabulation using National Vital Statistics System.<sup>80</sup> Mortality for NH Asian people includes Pacific Islander people. Hospital discharges (with a principal diagnosis of HF): Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project (data include those inpatients discharged alive, dead, or status unknown).<sup>1</sup>

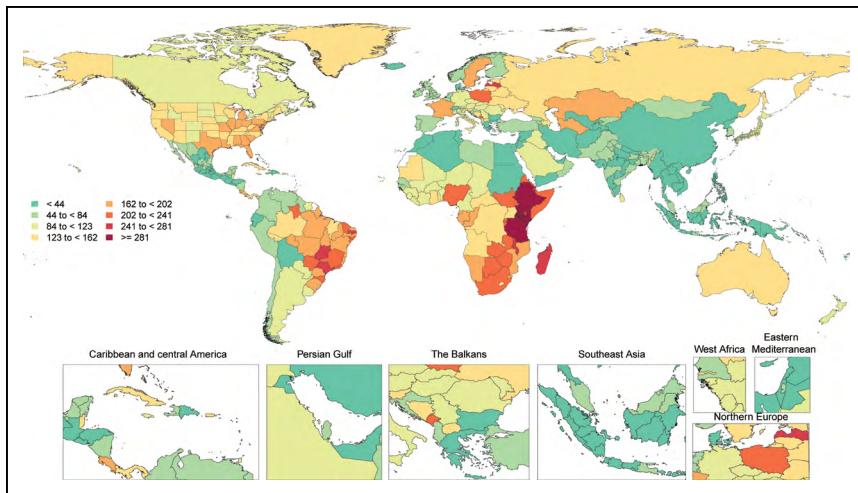


**Chart 22-1. Age-standardized global mortality rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>105</sup>

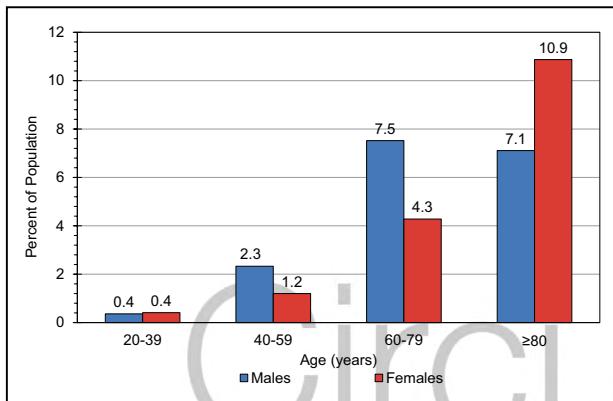


**Chart 22-2. Age-standardized global prevalence rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease.

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**Chart 22-3. Prevalence of HF among US adults ≥20 years of age by sex and age (NHANES, 2017–2020).**

HF indicates heart failure; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>40</sup>

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## 23. VALVULAR DISEASES

**See Tables 23-1 through 23-3 and Charts 23-1 through 23-6**

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Mortality and any-mention mortality in this section are for 2020 and based on unpublished NHLBI tabulations using the NVSS and CDC WONDER.<sup>1,2</sup> Mortality is the number of deaths in 2020 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> 2019; data included are for inpatients discharged alive, dead, or status unknown. Hospital discharge data for 2019 are based on *ICD-10* codes.

### Valvular HD

#### **ICD-9 424; ICD-10 I34 to I38.**

2020, United States: Underlying cause mortality—23 115. Any-mention mortality—56 219.

2019, United States: Hospital discharges—144 000.

#### **Prevalence**

- In 2500 individuals ≥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 51%.
  - 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>
- A retrospective, population-based study accessing claim records in Taiwan's National Health Insurance Research Database from 2000 to 2017, showed 1 007 078 patients with a diagnosis of valvular HD, with highest prevalence of mitral valve disease

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

(730 730 patients [72.6%]), compared with aortic (123 044 patients [12.2%]) and multiple (153 304 patients [15.2%]) valve diseases.<sup>6</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 ≥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>7</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).
- In the general population in Xinjiang, China, 14 618 participants were recruited in the CRS study.<sup>8</sup> In the total study population 35 to 101 years of age, valvular HD was observed in 1397 individuals (9.65%), with the following prevalence data: aortic valve disease, 841 (5.81%); and mitral valve disease, 769 (5.31%). Prevalence rates of valvular HD, aortic valve disease, and mitral valve disease increased strikingly with age (all  $P<0.001$ ). The prevalence rates of valvular HD in different age groups (35–44, 45–54, 55–64, 65–74, ≥75 years of age) were 3.63%, 6.53%, 13.20%, 21.6%, and 31.26% (all  $P<0.001$ ).

### Aortic Valve Disorders

#### **ICD-9 424.1; ICD-10 I35.**

2020, United States: Underlying cause mortality—15 191. Any-mention mortality—36 852.

2019, United States: Hospital discharges—109 000.

#### **Prevalence**

- Prevalence of aortic stenosis by echocardiography was 4.3% among individuals ≥70 years of age in the Icelandic AGES-Reykjavik cohort.<sup>9</sup>
- In a random sample of Swedish males from the general population born in 1943 (n=798) and followed up for 21 years, prevalence of aortic stenosis was 2.6%.<sup>10</sup>
- In younger age groups, the most prevalent cause of aortic stenosis is bicuspid aortic valve, the most common form of congenital HD:

- In the Copenhagen Baby Heart Study, which involved 25 556 newborns (51.7% male; mean age, 12 days [SD, 8 days]) in Denmark born between 2016 and 2018 who underwent transthoracic echocardiography, the prevalence of bicuspid aortic valve was 0.77% (95% CI, 0.67%–0.88%), with a male-to-female ratio of 2.1:1.
- In MESA with 6814 participants 45 to 84 years of age who did not have CVD in the United States,<sup>11</sup> 77 participants had aortic stenosis on echocardiography; the age-adjusted prevalence of aortic stenosis was highest in White (3.5% [95% CI, 2.6%–4.7%]) and Hispanic (3.7% [95% CI, 2.5%–5.6%]) participants with lower prevalence in Black (1.8% [95% CI, 1.1%–3.1%]) and Chinese (0.3% [95% CI, 0.04%–2.0%]) participants.

### 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 1989 to 1991 and 2007 to 2009.<sup>12</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>13</sup>
- In the Canadian CANHEART aortic stenosis study, the 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>14</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>15</sup>
- The pooled prevalence of all aortic stenosis in the elderly was 12.4% (95% CI, 6.6%–18.2%), and the prevalence of severe aortic stenosis was 3.4% (95% CI, 1.1%–5.7%).<sup>15</sup>
- In the Icelandic AGES-Reykjavik study alone, in both males and females, the prevalences for severe aortic stenosis, defined as an aortic valve area index of <0.6 cm<sup>2</sup>/m<sup>2</sup>, in the groups <70, 70 to 79, and ≥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 ≥70 years of age by 2040 and a tripling by 2060.<sup>9</sup>
- In a randomly selected group of male participants (N=9998) born from 1915 to 1925 in Gothenburg, Sweden, 7494 were examined and followed until a diagnosis of aortic stenosis or death (maximum follow-up time 42.8 years).<sup>16</sup> The lifetime cumulative

incidence of aortic stenosis in the middle-aged male population was 3.2%.

### Risk Factors

- In the Canadian CANHEART study, among 1.12 million individuals >65 years of age followed up for a median of 13 years, 20995 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 the development of severe aortic stenosis (all  $P<0.001$ ).<sup>14</sup>
- In the Copenhagen General Population Study, among 108 275 individuals, the risk of developing aortic stenosis was particularly high if BMI was ≥35.0 kg/m<sup>2</sup> (HR, 2.6 [95% CI, 2.0–3.5]).<sup>17</sup>
- In the Swedish General Population Study, higher BMI, obesity, cholesterol, hypertension, AF, smoking, and heredity for stroke were associated with aortic stenosis.<sup>16</sup> The HRs of being diagnosed with aortic stenosis for males with a baseline BMI of 25 to 27.5, 27.5 to 30, and >30 kg/m<sup>2</sup> were 1.99 (95% CI, 1.12–3.55), 2.98 (95% CI, 1.65–5.40), and 3.55 (95% CI, 1.84–6.87), respectively, with a BMI of 20 to 22.5 kg/m<sup>2</sup> used as a reference.

### Genetics and Family History



- Bicuspid aortic valve is thought to be highly heritable, with estimates from 47% to as high as 89%.<sup>18,19</sup> Variants in the NOTCH1, GATA4, GATA5, GATA6, EXOC4, PALMD, TEX41, FBN1, ROBO4, MYH6, and SMAD6 have been associated with bicuspid aortic valve.<sup>20–29</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>30</sup>
- First-degree relatives of patients with a bicuspid aortic valve may benefit from phenotypic screening with cardiac imaging.<sup>32,33</sup>
- A GWAS in 6942 individuals identified an SNP located in an intron of the lipoprotein(a) gene that was significantly associated with the presence of aortic calcification (OR per allele, 2.05), circulating lipoprotein(a) levels, and the development of aortic stenosis.<sup>34</sup>
- A GWAS meta-analysis of 5 115 cases and 354 072 controls identified IL6, ALPL, and NAV1 as susceptibility genes for calcific aortic valve stenosis,<sup>35</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>34,36–38</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>39</sup>

### Awareness, Treatment, and Control

#### (See Chart 23-1)

- The annual volume of TAVR has increased each year since 2011.<sup>40</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 57 626).<sup>40</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, racial disparities observed in SAVR also exist with TAVR.<sup>41</sup> Among the 70 221 patients in the STS/ACC TVT Registry who underwent TAVR between November 2011 and June 2016, 91.3% were White, 3.8% were Black, 3.4% were Hispanic, and 1.5% were of Asian/Native American/Pacific Islander race. Among the 4 racial groups, no difference was noted in the rates of in-hospital mortality, MI, stroke, major bleeding, vascular complications, or new pacemaker requirements. Among the 29 351 Medicare and Medicaid patients in this cohort, 1-year adjusted mortality rates were similar in Black and Hispanic individuals compared with White individuals but lower among patients of Asian/Native American/Pacific Islander race (aHR, 0.71 [95% CI, 0.55–0.92];  $P=0.028$ ). Black and Hispanic individuals had more HF hospitalizations compared with White individuals (aHR, 1.39 [95% CI, 1.16–1.67];  $P<0.001$ ; and aHR, 1.37 [95% CI, 1.13–1.66];  $P=0.004$ , respectively). These differences remained after further adjustment for SES.
- The 276 316 patients treated with TAVR who entered the STS/ACC TVT Registry between 2011 to 2019 demonstrated the following<sup>40</sup>:
  - Expected risk of 30-day operative mortality (STS Predicted Risk of Mortality score) decreased from 7.2% to 2.5%.<sup>40</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>40</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 was lower than 12% in 2015.<sup>40</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>42</sup> Over the same period (2011–2016), the number of SAVR procedures remained relatively stable at ≈10 000 per year, a lower number than for TAVR (Chart 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 a mortality (4.7% versus 3.9%;  $P=0.15$ ) similar to that of 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>43</sup>
- A study to determine the 5-year outcome in 18 010 patients treated by isolated TAVR or SAVR (8942 with TAVR and 9068 with SAVR) in the German Aortic Valve Registry between 2011 and 2012<sup>44</sup> showed that patients treated with TAVR were significantly older ( $80.9\pm6.1$  years versus  $68.5\pm11.1$  years;  $P<0.001$ ) and had a higher STS score ( $6.3\pm4.9$  versus  $2.6\pm3.0$ ;  $P<0.001$ ) and higher 5-year all-cause mortality (49.8% versus 16.5%;  $P<0.0001$ ). There was no significant difference in in-hospital stroke, in-hospital MI, or dialysis. With the use of propensity score-matching methods, in a total sample size of 3640 patients, there were 763 deaths (41.9%) among 1820 patients treated with TAVR compared with 552 (30.3%) among 1820 treated with SAVR during the 5-year follow-up (HR, 1.51 [95% CI, 1.35–1.68];  $P<0.0001$ ).<sup>44</sup> The patients who received TAVR had a higher rate of new pacemaker implantation compared with those who received SAVR (448 [24.6%] versus 201 [11.0%];  $P<0.0001$ , respectively).

### High-Risk Patients

- Two RCTs, PARTNER 1A and US CoreValve High Risk, using balloon-expandable and self-expanding devices, respectively, have shown that TAVR compares favorably 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>45</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>46</sup> In the 5-year follow-up of this study, there were similar midterm survival and stroke rates in high-risk patients after TAVR (55.3% all-cause mortality, 12.3% major stroke) and SAVR (55.4% all-cause mortality, 13.2% major stroke rates).<sup>47</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>48</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>49</sup> Overall, these findings demonstrate that TAVR is a noninferior alternative to SAVR in patients with severe aortic stenosis at intermediate surgical risk.<sup>49,50</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 primary composite end point (death, stroke, or rehospitalization) rate was significantly lower in the TAVR than 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>51</sup> At 2 years, the primary end point was significantly reduced after TAVR compared with SAVR (11.5% versus 17.4%; HR, 0.63 [95% CI, 0.45–0.88];  $P=0.007$ ), although TAVR valve thrombosis at 2 years was increased (2.6%; 13 events) compared with surgery (0.7%; 3 events;  $P=0.02$ ).
- Similar results were obtained in the Evolut Low Risk trial using a self-expanding valve in low-risk

patients with severe aortic stenosis.<sup>52</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>53</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  $P=0.60$ ,  $P=0\%$  at 2 years).<sup>54</sup>
- Among 96 256 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>55</sup>

#### Mortality

- According to ICD-10 data coded from 1999 to 2009, there were 146 304 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>56</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>57</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  $52\pm4\%$  in males versus  $35\pm6\%$  in females ( $P=0.01$ ).<sup>58</sup> Nevertheless, females have a significantly higher RR of death in tertiary and surgical referral cohorts, with an age-adjusted RR 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>58</sup>



The risk of death is independently associated with aortic regurgitation ( $P \leq 0.04$ ).

- In a study of 2429 patients with severe aortic stenosis, of whom 49.5% were women, the 5-year survival was lower especially in women compared with expected survival ( $62 \pm 2\%$  versus 71% for women and  $69 \pm 1\%$  versus 71% for men) and compared with 5-year survival in men despite women having longer life expectancy than men ( $66 \pm 2\%$  [expected, 75%] versus  $68 \pm 2\%$  [expected, 70%];  $P < 0.001$ ) after controlling for age.<sup>59</sup> Women also were more symptomatic ( $P = 0.004$ ) and used aortic valve replacement therapy less often (64.4% versus 69.1%;  $P = 0.018$ ).

### 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>60</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-adjusted RR 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 regurgitation (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>61</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>62</sup>
- In an observational cohort analysis of the multi-center UK TAVR registry involving a total of 8652

TAVR procedures performed from 2007 to 2015,<sup>63</sup> there were 205 in-hospital strokes (incidence, 2.4%). Factors associated with increased risk of in-hospital stroke were previous cerebrovascular disease (OR, 1.51, [95% CI, 1.05–2.17];  $P = 0.03$ ), advanced age (OR, 1.02 [95% CI, 0.10–1.04];  $P = 0.05$ ), coronary stenting at the time of TAVR (OR, 5.94 [95% CI, 2.03–17.39];  $P = 0.008$ ), and earlier year of procedure (OR, 0.93 [95% CI, 0.87–1.00];  $P = 0.04$ ); factors associated with lower risk include no prior cardiac surgery (OR, 0.62 [95% CI, 0.41–0.93];  $P = 0.01$ ) and deployment of a first-generation self-expandable transcatheter heart valve (OR, 0.72 [95% CI, 0.53–0.97];  $P = 0.03$ ). Having a stroke during hospitalization for a TAVR procedure significantly increased 30-day (OR, 5.22 [95% CI, 3.49–7.81];  $P < 0.001$ ) and 1-year (OR, 3.21 [95% CI, 2.15–4.78];  $P < 0.001$ ) mortality.

- In a study of all hospitalizations in patients  $\geq 18$  years of age who underwent TAVR in 2016 to 2017 in the Nationwide Readmission Database, a total of 54 317 unweighted hospitalizations for TAVR were identified, of which 5639 (10.4%) required permanent pacemaker implantation.<sup>64</sup> The risk of pericardial effusion was significantly greater in patients who required permanent pacemaker (2.4% versus 1.6%; aOR, 1.39 [95% CI, 1.15–1.70];  $P < 0.001$ ), and risk of cardiac tamponade nearly doubled (1.6% versus 0.8%;  $P < 0.001$ ; aOR, 1.90 [95% CI, 1.48–2.40];  $P < 0.001$ ). Pericardial complications after permanent pacemaker implantation were associated with increased in-hospital mortality, length of stay, hospital costs, and risk of 30-day readmission after TAVI ( $P < 0.01$  for all comparisons).

### Cost

- In the 3110 intermediate-risk patients with aortic stenosis 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>65</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>65</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 (difference, 4.5 and 6.3 days with XT-TAVR and SAPIEN 3

valve, respectively;  $P<0.001$  compared with SAVR for both comparisons).<sup>65</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 (difference, \$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>65</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>66</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>67</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.**

2020, United States: Underlying cause mortality—2647. Any-mention mortality—6708.

2019, United States: Hospital discharges—32 000.

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>68</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>69–71</sup>

#### Genetics and Family History

- 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>72–76</sup>
- Mitral valve prolapse may be seen in syndromes associated with connective tissue disease such as Marfan syndrome (*FBN1* gene), Loeys-Dietz syndrome (*TGFB1*, *TGFB2*, *SMAD3*, *TGFB3* genes), and Ehler-Danlos syndrome (*COL5A1*, *COL5A1*, *COL1A1*, *TNXB* genes).<sup>77–80</sup>
- Mitral valve prolapse may also be seen in patients with a specific syndrome not associated with connective tissue disease (Edward syndrome, Patau syndrome, and trisomy of chromosome 15).<sup>81,82</sup>
- Nonsyndromic mitral valve prolapse may be seen in carriers of variants in the *MMVP1*, *MMVP2*, *MMVP3*, and *FLNA* genes.<sup>71,83,84</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>85</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>85</sup>
- Among 3679 young to middle-aged Third Generation participants in the FHS with available parental data, 49 (1%) had mitral valve prolapse.<sup>86</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];  $P<0.0001$ ).
- 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>87</sup>

***Awareness, Treatment, and Control******(Charts 23-2 and 23-3)***

- The 2 main percutaneous mitral valve interventions in the United States are transcatheter edge-to-edge repair and transcatheter mitral valve replacement. Data from the STS/ACC TVT Registry between 2014 and March 31, 2020, are reported.<sup>88</sup> A total of 37 475 patients underwent a mitral transcatheter procedure, including 33 878 transcatheter edge-to-edge repairs and 3597 transcatheter mitral valve replacements. Annual procedure volumes for transcatheter edge-to-edge repair have increased from 1152 per year in 2014 to 10 460 per year in 2019 at 403 sites and for transcatheter mitral valve replacement from 84 per year to 1120 per year at 301 centers. Mortality rates have decreased for transcatheter edge-to-edge repair at 30 days (from 5.6% to –4.1%) and 1 year (from 27.4% to 22.0%). The 30-day mortality rate was 3.9%, reflective of overall improvements in outcomes over the past several years.
- 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>89</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>90</sup>
- In the United States, the commercial use of the MitraClip started in 2013, with a steadily growing number of procedures performed. In a study looking at the trend of mitral valve interventions from 2000 to 2016 performed in the United states, MitraClip procedures increased from 415 in 2013 to 4195 in 2016, an increase of ≈90%.<sup>91</sup>
- Use of MitraClip procedures has also increased in Asia, although at a slower pace (Chart 23-2), with the highest increase seen in Japan from 18 procedures in 2011 to 439 procedures in 2018.<sup>92</sup>
- 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 23-3).<sup>93–95</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 [54.6%] versus 78 of 152 [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>94</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>96</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>97</sup> In the Cardiothoracic Surgical Trials Network of 251 patients with severe ischemic MR and CAD randomized to mitral valve repair or replacement, after 2 years, the mean LV end-systolic volume index among surviving patients was  $52.6\pm27.7$  mL/m<sup>2</sup> in the repair group and  $60.6\pm39.0$  mL/m<sup>2</sup> in the replacement group with no significant between-group difference ( $Z$  score = –1.32;  $P=0.19$ ).<sup>98</sup> Two-year mortality was 19.0% in the repair group and 23.2% in the replacement group (HR in the repair group, 0.79; 95% CI, 0.46–1.35;  $P=0.39$ ). The rate of recurrence of moderate or severe MR was significantly higher with mitral valve repair (24.0 per 100 patient-years versus 15.2 per 100 patient-years;  $P=0.05$ ), leading to higher readmissions for cardiovascular causes (48.3 versus 32.2 per 100 patient-years;  $P=0.01$ ). 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>99</sup> Repairing mitral valve along with CABG yields improvement in postoperative residual MR (standard mean difference, 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>100</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).<sup>101</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>101</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>102</sup>

### Complications

- In the Olmsted County, Minnesota, population characterized by a mixed spectrum of community-dwelling and referred patients, although females were diagnosed with mitral valve prolapse more often than males (females, 54.2% [461 of 8229]; males, 45.8% [3768 of 8229];  $P<0.001$ ),<sup>103</sup> they had fewer complications compared with males (flail leaflet occurred in 2% of females versus 8% of males and severe regurgitation in 10% of females versus 23% of males; 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±1%, 70±4%, and 57±3%, respectively ( $P<0.0001$ ).<sup>104</sup>
- In a study using the Nationwide Readmission Database to identify adult patients who underwent transcatheter edge-to-edge repair from 2014 to 2018,<sup>105</sup> of the 21 323 patients identified, 1615

(7.5%) had major bleeding. Coagulopathy, ESRD, nonelective admission, weekend admission, weight loss, cancer, CKD, anemia, and female sex were identified as independent predictors of major bleeding.

- Patients with major bleeding had significantly higher rates of in-hospital mortality (aOR, 2.70 [95% CI, 1.70–4.10];  $P<0.001$ ), acute kidney injury (aOR, 3.57 [95% CI, 2.85–4.48];  $P<0.001$ ), AMI (aOR, 1.80 [95% CI, 1.37–2.36];  $P<0.001$ ), cardiogenic shock (aOR, 2.55 [95% CI, 1.82–3.57];  $P<0.001$ ), 30-day all-cause readmissions (OR, 2.12 [95% CI, 1.69–2.65];  $P<0.001$ ), and 30-day HF readmissions (OR, 1.33 [95% CI, 1.05–1.68];  $P<0.01$ ) compared with patients without major bleeding. The rates of stroke/TIA did not differ between the 2 groups (OR, 1.28 [95% CI, 0.97–1.69];  $P<0.001$ ).

### Cost

- Lifetime costs, life-years, QALYs, and incremental cost per life-year and QALYs gained were estimated for patients receiving MitraClip therapy compared with patients receiving standard of care for primary MR.<sup>106</sup> 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>107</sup>

### Global Burden

#### (See Table 23-2)

- The global burden of degenerative mitral valve disease is shown in Table 23-2.

### Pulmonary Valve Disorders

#### **ICD-9 424.3; ICD-10 I37.**

2020, United States: Underlying cause mortality—19. Any-mention mortality—67.

2019, United States: Hospital discharges—1000.

- Pulmonic valve stenosis is a relatively common congenital defect, occurring in ≈10% of children with congenital HD.<sup>108</sup> Among 44 neonates with critical pulmonic stenosis who underwent balloon

pulmonary valvuloplasty from 1990 to 2017, 15 (34.1%) needed reintervention. At a median follow-up of 8.2 years (IQR, 3.4–13.1 years), moderate or severe pulmonary regurgitation was seen in 22 children (half of the sample), 3 of whom required pulmonary valve repair/replacement.<sup>109</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>110</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>111</sup> Transcatheter pulmonic valve implantation of either a Melody or a SAPIEN valve is effective and relatively safe,<sup>111–113</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>114</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>115</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>116</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.**

2020, United States: Underlying cause mortality—49. Any-mention mortality—235.

2019, United States: Hospital discharges—1000.

- 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>117</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, 1.32 [95% CI, 1.05–1.62] for pulmonary artery systolic pressure ≤40 mmHg) and LVEF (HR, 1.54 [95% CI, 1.37–1.71] for EF ≥50%), with a similar HR for elevated pulmonary pressure and lower LVEF.<sup>117</sup>

- Patients with rapid (≤1.2 years) 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>118</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>119</sup>
- Outcomes of transcatheter tricuspid valve interventions were analyzed in 317 high-risk patients with severe tricuspid regurgitation from the international Trivalve registry.<sup>120</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).<sup>121</sup> 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.**

2020, United States: Underlying cause mortality—3876. Any-mention mortality—8410.

2019, United States: Hospital Discharges—27 000.

### **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>121</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>122</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>123–126</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>127–130</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>131</sup>
- Latent rheumatic HD appears to be half as common among youth living with HIV 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 youth living with HIV.<sup>132</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>133</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 them 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>134</sup>

### Mortality

#### (See Table 23-3)

- In the United States in 2020, mortality attributable to rheumatic fever/rheumatic HD was 3876 for all ages (2516 females and 1360 males; Table 23-3).
- Mortality attributable to rheumatic HD varies widely across the United States with the highest rates clustered in Alaska, Mississippi, Alabama, Kentucky, and Utah, where age-standardized mortality rates were estimated to be 5 to 10 per 100 000 population in 2014.<sup>135</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 23-3). Recent declines in mortality have been slowest in the South compared with other regions.<sup>135</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>133</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>136</sup>
- Prognosis after the 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>137</sup>
- The PAR of rheumatic HD for maternal mortality may approach 10% in sub-Saharan Africa.<sup>138</sup>
- In a study at 2 Gambian referral hospitals involving 255 registered patients with rheumatic HD, the case fatality rate in 2017 was estimated at 19.6%.<sup>139</sup> The median age at first presentation was 13 years (IQR, 9–18 years); 57% of patients had late-stage HF; and 84.1% had a pathological heart murmur. A history suggestive of acute rheumatic fever was reported by 48.7% of patients; only 15.8% were adequately treated, and 65.5% of those prescribed penicillin were fully adherent. As many as 46.8% of the patients had worsening of their symptoms and repeat hospitalizations. Ninety-four patients were deemed eligible for cardiac surgery. However, only 18.1% (17 of 94) underwent surgery.

### Global Burden of Rheumatic HD

#### (See Charts 23-4 through 23-6)

- The age and sex distributions of the subjects in the REMEDY study are shown in Chart 23-4. Rheumatic HD was twice as common among females, a finding consistent with prior studies across a variety of populations.<sup>133</sup>
- Mortality attributable to rheumatic HD remains exceptionally high in endemic settings. In a study from Fiji of 2619 people followed up from 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>140</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>136</sup>
- The GBD Study 2020 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 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 23-5).
- 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 23-6).

## Infective Endocarditis

**ICD-9 421.0; ICD-10 I33.0.**

2020, United States: Underlying cause mortality—1703. Any-mention mortality—3809.

2019, Mortality: Hospital discharges—13 000.

### Prevalence and Incidence

- Data from the GBD Study show that the incidence of IE has continued to rise over the past 30 years globally.<sup>141</sup> In North America, age-standardized incidence rates went from 10.11 (95% CI, 8.32–12.27) per 100 000 in 1990 to 12.54 (95% CI, 10.35–15.15) per 100 000 in 2019.
- In US commercial and Medicaid health insurance databases, the weighted incidence rate of IE was 13.8 cases per 100 000 among individuals 18 to 64 years of age with commercial insurance and 78.7 per 100 000 among those with Medicaid.<sup>142</sup> Incidence was higher in males versus females (16.9 versus 10.8 per 100 000 among those with commercial insurance; 104.6 versus 63.5 per 100 000 with Medicaid).

### 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>143</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% versus 63%;  $P<0.01$ ).<sup>144</sup>

- Data from the North Carolina Hospital Discharge Database show similar trends with rates of drug use-associated IE rising from 0.08 per 100 000 residents in 2013 to 2014 to 1.38 per 100 000 residents in 2016 to 2017.<sup>145</sup> In the final year (2016–2017), 42% of IE valve surgeries were for drug-use associated IE.
- 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>146</sup> (change in slope of *S epidermidis* 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>147</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>148</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  $1.1\pm0.4\%$  (incidence, 86.6 cases per 100 000 person-years [95% CI, 43.3–173.2]).
  - 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 or greater MR (289.5 cases per 100 000 person-years [95% CI, 108.7–771.2];  $P=0.02$  compared with less than 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>149</sup>
- Congenital HD is known to predispose to IE. In a nationwide Swedish registry case-control study, the cumulative incidence of IE was 8.5% at 87 years of age among 89 541 patients with congenital HD compared with 0.7% in matched controls, with incidence rates of 65.5 (95% CI, 62.2–68.9) and 1.8 (95% CI, 1.7–2.0) per 100 000 person-years, respectively.<sup>150</sup>
- Data from the IE After TAVI International Registry show stable rates for IE after TAVI when earlier

(2005–2013) and later (2014–2020) study periods are compared, with incidence of 6.52 (95% CI, 5.54–7.67) versus 5.45 (95% CI, 4.65–6.38) per 1000 patient-years ( $P=0.12$  for difference).<sup>151</sup> In-hospital mortality (36.4% versus 26.6%;  $P=0.016$ ) and 1-year mortality (53.5% versus 37.8%;  $P<0.001$ ) have decreased over these 2 study periods. 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>152</sup>

- In a Spanish registry of 3208 consecutive patients with IE, subjects with bicuspid AV and mitral valve prolapse had a higher incidence of viridans group streptococci IE than did a high-risk (those who met the criteria for IE antibiotic prophylaxis) 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  $P<0.01$ ).<sup>153</sup> 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.

### 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>154</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 [12.1%] versus 18 cases [9%]; between-group difference, 3.1 percentage points [95% CI, -3.4 to 9.6];  $P=0.40$ ).<sup>155</sup> After a median follow-up of 3.5 years, the primary composite end point had occurred in 38.2% of patients in the intravenous group and 26.4% in the oral antibiotic group (HR, 0.64 [95% CI, 0.45–0.91]).<sup>156</sup>

### Mortality

- According to the GBD Study 2020, the age-standardized death rate of endocarditis in 2020 was 0.93 (95% UI, 0.82–1.05) per 100 000 (data courtesy of the GBD Study 2020). 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>157</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.<sup>158</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>159</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>160</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  $49.6\pm4.9\%$ . 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>160</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>160</sup>

### Heart Valve Procedure Costs

- In 2014, for heart valve procedures<sup>161</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>161</sup>
- Among 190 563 patients with aortic valve disease in the Nationwide Readmissions Database between 2012 and 2016, the average aggregate 6-month inpatient costs starting with index admission over 6 months were as follows: for individuals who underwent SAVR, \$59 743; TAVR, \$64 395; and medical therapy, \$23 460. TAVR costs decreased over time and were similar to SAVR index admission costs by 2016.<sup>162</sup>

**Table 23-1. Global Mortality and Prevalence of Nonrheumatic Calcific Aortic Valve Disease, by Sex, 2020**

	Both sexes		Males		Females	
	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)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>163</sup>

**Table 23-2. Global Prevalence and Mortality of Nonrheumatic Degenerative Mitral Valve Disease, 2020**

	Both sexes		Males		Females	
	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)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and UI, uncertainty interval.

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**Table 23-3. Rheumatic Fever/Rheumatic HD in the United States**

Population group	Mortality, 2020: all ages*	Hospital discharges, 2019: all ages
Both sexes	3876	27000
Males	1360 (35.1%)†	
Females	2516 (64.9%)†	
NH White males	1070	...
NH White females	2011	...
NH Black males	120	...
NH Black females	214	...
Hispanic males	106	...
Hispanic females	167	...
NH Asian or Pacific Islander males	51‡	...
NH Asian or Pacific Islander females	109‡	...
NH American Indian or Alaska Native	25	...

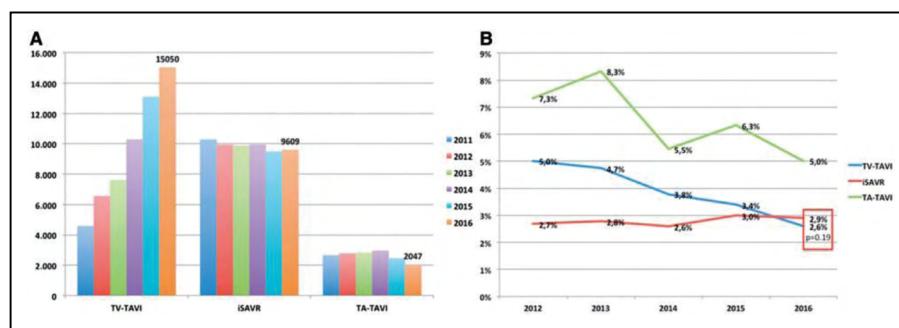
Ellipses (...) indicate data not available; HD, heart disease; and NH, non-Hispanic.

\*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.

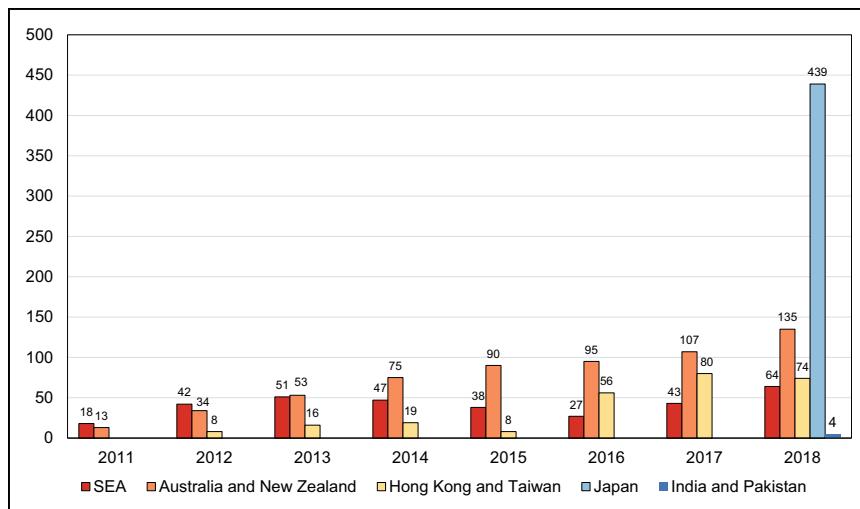
Sources: Mortality (for underlying cause of rheumatic fever/rheumatic HD): Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics<sup>1</sup>; data represent underlying cause of death only. Hospital discharges (with a principal diagnosis of rheumatic fever/rheumatic HD): Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project<sup>3</sup>; data include those inpatients discharged alive, dead, or status unknown.

**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.

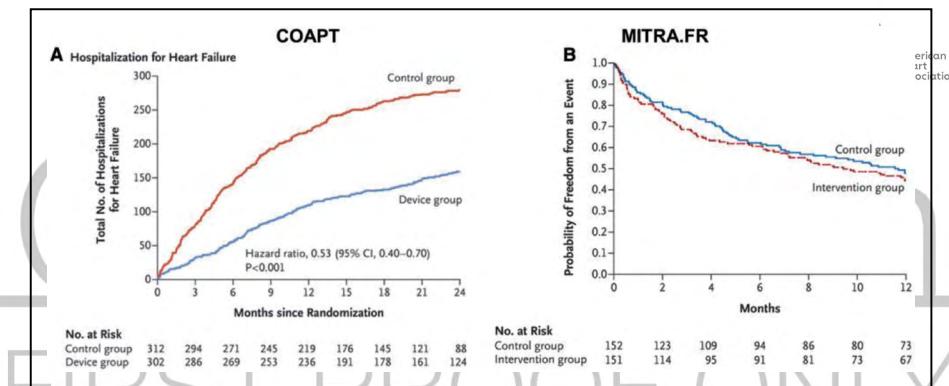
Source: Reprinted from Gaede et al.<sup>42</sup> Copyright © 2017, The Authors. Published by Oxford University Press on behalf of the European Society of Cardiology. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits noncommercial reuse, distribution, and reproduction in any medium, provided the original work is properly cited.



**Chart 23-2. 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>92</sup>



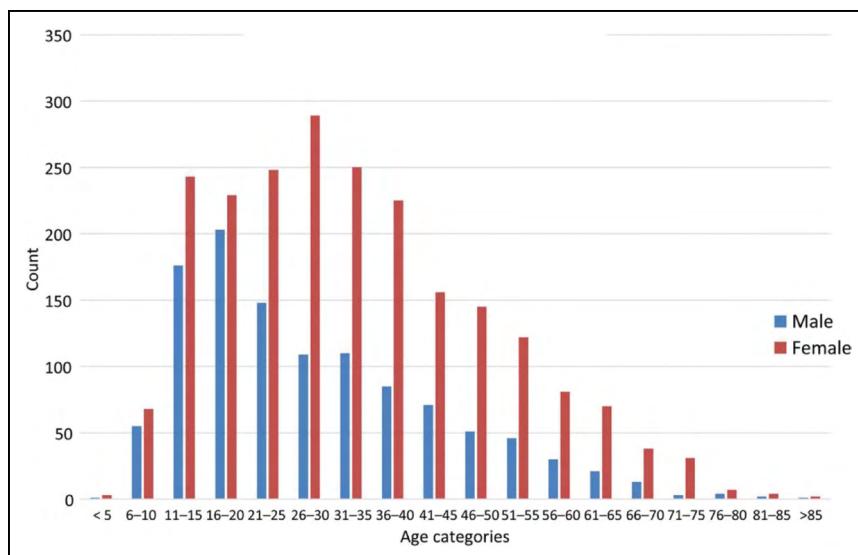
**Chart 23-3. Comparison of primary outcomes after MitraClip implantation for secondary MR in the COAPT and MITRA-FR trials.**

**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; MITRA-FR, Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation; and MR, mitral regurgitation.

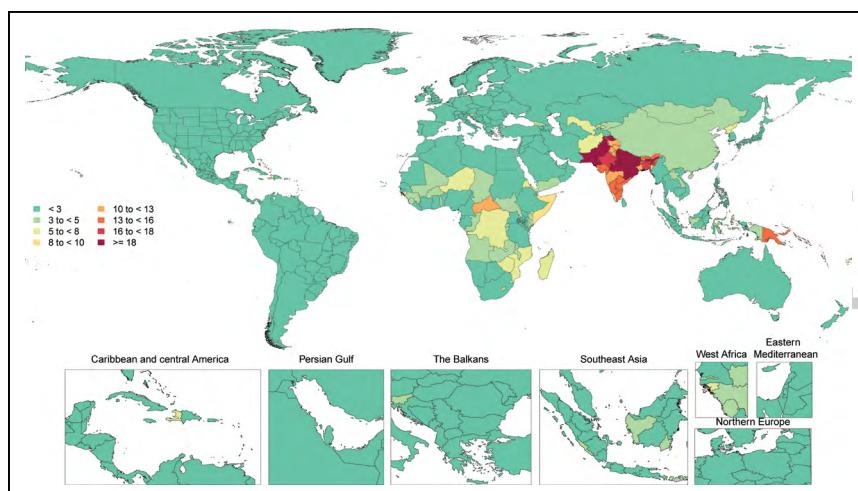
Source: **A**, Reprinted from Stone et al<sup>94</sup> with permission from the Massachusetts Medical Society. Copyright © 2018 Massachusetts Medical Society.

**B**, Reprinted from Obadia et al<sup>95</sup> with permission from the Massachusetts Medical Society. Copyright © 2018 Massachusetts Medical Society.



**Chart 23-4. Age and sex distribution of 3343 subjects with rheumatic HD participating in the REMEDY study, 2010 to 2012.**

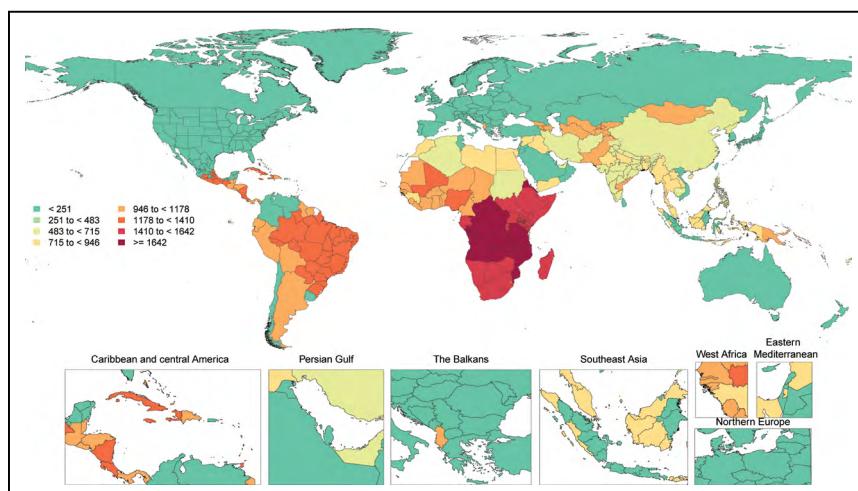
HD indicates heart disease; and REMEDY, Global Rheumatic Heart Disease Registry. Source: Reprinted from Zühlke et al<sup>133</sup> with permission of the European Society of Cardiology. Copyright © 2014, The Authors. Published by Oxford University Press on behalf of the European Society of Cardiology.



**Chart 23-5. Age-standardized global mortality rates of rheumatic HD per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Disease; and HD, heart disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>163</sup>



**Chart 23-6. Age-standardized global prevalence rates of rheumatic HD per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Disease; and HD, heart disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>163</sup>

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## 24. VENOUS THROMBOEMBOLISM (DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM), CHRONIC VENOUS INSUFFICIENCY, PULMONARY HYPERTENSION

**See Charts 24-1 and 24-2**

[Click here to return to the Table of Contents](#)

[Click here to return to the Abbreviations](#)

In this chapter, 2020 mortality data come from unpublished NHLBI tabulations using NVSS<sup>1</sup> and CDC WONDER.<sup>2</sup> Hospital discharge data, from 2019, come from unpublished NHLBI tabulations using HCUP.<sup>3</sup>

### Pulmonary Embolism

#### **ICD-9 415.1; ICD-10 I26.**

2020, United States: Underlying cause mortality—9392. Any-mention mortality—47 008.

2019, United States: Hospital discharges—189 000 (principal diagnosis), 393 000 (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.**

2020, United States: Underlying cause mortality—3695. Any-mention mortality—21 361.

2019, United States: Hospital discharges—81 000 (principal diagnosis), 643 000 (all-listed diagnoses).

### Venous Thromboembolism

#### **Incidence**

**(See Charts 24-1 and 24-2)**

- VTE includes both PE and DVT. In 2019, there were an estimated ≈393 000 cases of PE<sup>3</sup> (Chart 24-1), ≈643 000 cases of DVT<sup>3</sup> (Chart 24-2), and ≈1 036 000 total VTE cases in the United States

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

(US population was 328 million in 2019); these estimates used the all-listed diagnoses hospitalization data and assumed that 30% of DVTs were treated in an outpatient setting.

- 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%). A study using data from 73 million childbirths in the United States found a VTE incidence of 6.6 per 10 000 deliveries.<sup>5</sup>
- The MESA cohort found a higher incidence of VTE in Black participants (4.02 per 1000 person-years) than in White (2.98 per 1000 person-years), Hispanic (2.08 per 1000 person-years), and Chinese (0.79 per 1000 person-years) participants.<sup>6</sup>
- In an analysis of administrative data from 204 hospitals in Illinois involving 22 244 hospitalizations with a principal diagnosis of PE, ≈50% of patients hospitalized were <65 years of age.<sup>7</sup> In all age groups, NH Black males and females had higher rates of PE hospitalization (14.5 [95% CI, 2.0–103.2] and 16.5 [95% CI, 2.3–117.5] per 10 000 population, respectively) compared with NH White males and females (8.8 [95% CI, 1.2–62.8] and 9.3 [95% CI, 1.3–66.0] per 10 000 population, respectively). Overall, NH Black individuals were almost twice as likely to be hospitalized for PE compared with NH White individuals (rate ratio, 1.9 [95% CI, 1.5–2.3]) after adjustment for age and sex.
- In a meta-analysis comprising 3170 patients admitted for acute exacerbation of COPD, there was a high prevalence of PE and DVT in this clinical profile (pooled prevalence, 17.2% [95% CI, 13.4%–21.3%] and 7.1% [95% CI, 3.7%–11.4%], respectively).<sup>8</sup>
- Several studies with data from the 2020 COVID-19 pandemic have addressed the incidence and prevalence of VTE in different settings:
  - A study with 10 871 patients with COVID-19 admitted in New York observed an incidence of 1.09% in the initial presentation at the hospital.<sup>9</sup>
  - In hospitalized patients with COVID-19, VTE incidence was high during the COVID-19 pandemic, ranging from 14.1% (95% CI, 11.6%–16.9%) to 31% (95% CI, 24.3%–39.2%) according to several meta-analyses. PE incidence was from 8% (PE pooled incidence [95% CI, 3%–14%]) to 32% (95% CI, 25%–40%), whereas incidence of DVT was between 16.5% (DVT pooled incidence [95% CI, 11.6%–22.9%]) and 27% (95% CI, 21%–34%).<sup>10–14</sup>
  - 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>15</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 and to the VTE diagnostic protocol; a routine screening showed a much higher VTE incidence compared with centers without this approach (pooled incidence, 47.5% [95% CI, 25.3%–69.7%] versus 15.1% [95% CI, 8.35%–21.9%];  $P<0.001$ ).<sup>16</sup>

### 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>17</sup>

### Secular Trends

#### (See Charts 24-1 and 24-2)

- The HCUP NIS (Chart 24-1) shows increasing numbers of hospitalized cases for all-listed diagnoses of PE from 1996 to 2019. Focusing on all-listed diagnoses (Chart 24-2) shows that the number of hospitalized DVT cases also increased from 2005 to 2019, probably driven by an increase in VTE diagnosis that might overstate changes in VTE incidence. Improvements in VTE screening such as predictive scores, wider access to imaging tests for specific conditions,<sup>18–21</sup> and other factors (eg, outpatient management of ≈35% of DVT cases<sup>22</sup> and a smaller portion of PE cases,<sup>23,24</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>25</sup> Trends in DVT incidence were not reported. In addition, NIS data from 2000 to 2018 showed a progressive increase in incidence of DVT in vaginal deliveries (average annual percent change, 2.5% [95% CI, 1.5%–3.5%]) and in incidence of PE in both vaginal and cesarean deliveries (average annual percent change, 8.7% [95% CI, 6.0%–11.5%] and 4.9% [95% CI, 3.6%–6.2%], respectively).<sup>5</sup>

### Risk Factors

- In the GARFIELD-VTE study, 40.8% of 10 868 patients with a VTE diagnosis were considered provoked because VTE occurred subsequent to strong triggering factors or persistent risk factors such as immobilization, trauma, surgery, cancer,

or hospitalization in the preceding 3 months.<sup>26</sup> However, in the RIETE registry, ≈55% of the 97 143 patients had at least 1 provoking risk factor. The remainder are classified as unprovoked.<sup>27</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>28</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 such 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>29–34</sup>
- Data from the 2020 COVID-19 pandemic showed an increase in in-hospital VTE compared with patients without COVID-19, driven mainly by the incidence of PE (pooled PE incidence, 7.65% [95% CI, 4.05%–12.19%] versus 0.22% [95% CI, 0.03%–0.55%] in admitted patients with COVID-19 versus those without COVID-19, respectively;  $P<0.0001$ ).<sup>35</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>36</sup>
- Use of testosterone therapy was also associated with doubling of VTE risk in males with and without evidence of hypogonadism.<sup>37</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>38,39</sup> In 1 of the meta-analyses, cigarette smoking was associated with provoked but not with unprovoked VTE events.<sup>38</sup>
- Among females, VTE risk is elevated among those using estrogen-based contraceptives, hormone therapy, or infertility treatment.<sup>40</sup>
- A database analysis with ≈ 5000 US transgender participants observed in the transfeminine population (assigned male at birth) a higher incidence of VTE compared with both cisgender men (risk difference, 4.1 [95% CI, 1.6–6.7] and 16.7 [95%

CI, 6.4–27.5] for 2 and 8 years, respectively) and cisgender women (risk difference, 3.4 [95% CI, 1.1–5.6] and 13.7 [95% CI, 4.1–22.7] for 2 and 8 years, respectively).<sup>41</sup> In addition, a 2021 meta-analysis with 9180 transgender patients showed a higher risk of VTE in transfeminine compared with transmasculine people (OR, 5.29 [95% CI, 2.03–13.79]), with a high heterogeneity probably driven by duration of hormone replacement therapy.<sup>42</sup> To date, there are limited data about risk of VTE in the transmasculine population compared with cisgender men.

- 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>43</sup> An analysis in the GARFIELD-VTE study population showed that in pregnant females 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>44</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>45</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>46</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>17</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>47</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>48</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>49</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>50</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>51</sup> GWASs have identified additional common genetic variants

associated with VTE risk, including variants in *F5*, *F2*, *F11*, *FGG*, and *ZFPM2*.<sup>52</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>53</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>54,55</sup>
- A GRS comprising 297 SNPs was associated with a higher risk of incident VTE event (HR, 2.51 per 1-SD increase in GRS).<sup>55</sup> The subsequent retrospective analysis of patients with cardiometabolic disease noted that this GRS was associated with a higher risk of VTE events (47% higher risk with each 1-SD increase in GRS).<sup>56</sup>

### **Prevention**

- Elastic stockings play an important role in VTE prevention in individuals on long (>4 hours) airplane flights (OR for DVT, 0.10 [95% CI, 0.04–0.25]),<sup>57</sup> all hospitalized patients (OR for DVT, 0.35 [95% CI, 0.28–0.43]), and surgical patients (OR for DVT, 0.35 [95% CI, 0.28–0.44]; OR for PE, 0.38 [95% CI, 0.15–0.96]).<sup>58</sup>
- Pharmacological prophylaxis has shown benefit with the use of low-molecular-weight heparin in ill patients (OR for DVT, 0.59 [95% CI, 0.33–0.90]).<sup>59</sup> Furthermore, 2 meta-analyses showed benefit of low-molecular-weight heparin over unfractionated heparin in preventing DVT in patients in critical care (OR, 0.72 [95% CI, 0.46–0.98])<sup>60</sup> and patients with trauma (OR for DVT, 0.67 [95% CI, 0.50–0.88]).<sup>60</sup> DOACs are noninferior to low-molecular-weight heparin in hip fracture scenarios (pooled OR for VTE, 0.52 [95% CI, 0.25–1.11])<sup>61</sup> and are also effective in outpatients with cancer (pooled RR for VTE incidence, 0.53 [95% CI, 0.36–0.78]; pooled RR for PE incidence, 0.50 [95% CI, 0.28–0.89]).<sup>62</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>63</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>64</sup>
- Even in patients at high risk for VTE, there is no net benefit in extended thromboprophylaxis compared

with an inpatient-only strategy ( $P=0.18$  for VTE and  $P=0.43$  for bleeding).<sup>65,66</sup>

### Awareness, Treatment, and Control

- After DVT diagnosis, anticoagulants consistently reduced both VTE and DVT recurrence by 66% and 75%, respectively.<sup>67</sup> A 2021 meta-analysis observed that inferior vena cava filters reduced early (within 3 months) new PE occurrence (pooled RR, 0.17 [95% CI, 0.04–0.65]) but not recurrent PE ( $P=0.33$ ). Furthermore, inferior vena cava filter did not provide a reduction in mortality either at 3 months or at the entire follow-up ( $P=0.13$  and 0.61, respectively).<sup>68</sup>
- Systemic thrombolysis did not result in a reduction in all-cause mortality ( $P=0.56$ ), lowering the risk of PTS after 6 months (pooled RR, 0.78 [95% CI, 0.66–0.93]) and 5 years (pooled RR, 0.56 [95% CI, 0.43–0.73]) at the cost of a higher bleeding rate (RR, 2.45 [95% CI, 1.58–3.78]).<sup>69</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>70</sup>
- Although cancer is a relevant risk factor, a Cochrane meta-analysis found no evidence for additional PET/CT testing after a first unprovoked VTE because there was no benefit in any outcomes: cancer and all-cause mortality ( $P=0.25$  and  $P=0.66$ , respectively), VTE-related morbidity ( $P=0.96$ ), time to cancer diagnosis ( $P=0.88$ ), and malignancy diagnosis in the early or advanced stage ( $P=0.36$  and  $P=1.00$ , respectively).<sup>72</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>73</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>74</sup>
- In a US cohort of 14 140 patients with diagnosed VTE, Black individuals were treated less often with DOACs compared with White individuals (OR, 0.86 [95% CI, 0.77–0.97]). However, Hispanic and Asian individuals had no difference in DOAC prescription compared with White individuals ( $P=0.66$  and  $P=0.74$ , respectively).<sup>75</sup>

### Mortality

- 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>76</sup> These rates were similar to those in 1999 (5.0% and 21.5%, respectively).
- In patients with COVID-19, 3 meta-analyses observed a double risk of death after VTE (pooled

OR, 2.1 [95% CI, 1.2–3.6]).<sup>14,77,78</sup> After stratification by disease severity, the OR for mortality in the 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>79</sup>

- During pregnancy, a VTE event is associated with a higher risk of PTB (OR, 2.4 [95% CI, 1.67–3.46]) and stillbirth (OR, 5.07 [95% CI, 3.12–8.24]).<sup>80</sup> Furthermore, PE is an important contributor to maternal mortality, being responsible for ≈9% of pregnancy-associated deaths.<sup>81</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>82</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>67</sup>
  - In a French cohort including patients with no cancer, ≈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>83</sup>
- Data from NIS with >138 000 Americans with proximal DVT observed an intracranial bleeding rate of 0.2% in patients using anticoagulants and 0.7% in those receiving catheter-directed thrombolysis.<sup>84</sup> In this population, the main predictors of bleeding risk were a history of stroke (OR, 19.4 [95% CI, 8.76–42.77]), >74 years of age (OR, 2.20 [95% CI, 1.17–4.28]), and CKD (OR, 2.20 [95% CI, 1.06–4.68]). Centers with expertise were predictors for fewer complications (OR, 0.42 [95% CI, 0.21–0.84]).
- In a 2021 analysis of 65 000 elderly Medicare patients, Black individuals using both apixaban and warfarin had a higher risk of adverse events after a VTE (incidence rates per 100 person-years versus White individuals: recurrent VTE, 2.0 versus 1.4 [apixaban] and 3.3 versus 2.2 [warfarin]; major bleeding, 7.4 versus 3.5 [apixaban] and 10.1 versus 5.3 [warfarin]).<sup>85</sup> Patients with lower SES also had worse outcomes (incidence rates per 100 person-years versus high SES: recurrent VTE, 3.6 versus 2.6 [apixaban] and 3.3 versus 2.7 [warfarin]; major bleeding, 5.7 versus 3.2 [apixaban] and 7.0 versus 5.1 [warfarin]).
- 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>86</sup> and up to 70% in the long term (follow-up >5 years).<sup>69</sup> In this context, DOAC drugs appear to prevent PTS (OR, 0.46 [95% CI, 0.33–0.63]).<sup>86</sup>

- CTEPH affects ≈4% of patients with PE within 2 years of their initial PE event.<sup>87</sup> One-, 3-, and 5-year mortality in patients who did not undergo pulmonary endarterectomy was 9%, 25%, and 31%, respectively.<sup>88</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>89</sup>
- In 2018, the aggregate charges in ED and hospitalized patients accounted for almost \$10 billion. Medicare and Medicaid cover two-thirds of the total charge, whereas private insurance accounts for one-quarter of all payments.<sup>3</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>90</sup>

### Health Care Use: Hospital Discharges/Ambulatory Care Visits

- A study that examined 133 414 US patients with diagnosed DVT in the ED found that the more proximal the DVT site was, the higher the hospitalization rate was (28% distal, 54% proximal, 64% pelvic, and 78% inferior vena cava;  $P<0.0001$ ).<sup>91</sup>

### Global Burden

- The Computerized Registry of Patients With Venous Thromboembolism registry, a database from 26 countries (including 6 US centers) and 105 000 patients, found a 30-day mortality of 2.63% for distal DVT, 3.29% for proximal DVT, and 5.20% for PE.<sup>92</sup> As expected, worse prognoses involve older patients (30-day mortality in individuals >81 years of age: 5.05% for distal DVT, 5.38% for proximal DVT, and 9.22% for PE) and cancer history (30-day mortality: 6.17% for distal DVT, 7.72% for proximal DVT, and 11.31% for PE).

## Chronic Venous Insufficiency

### ICD-10 I87.2.

2020, United States: Underlying cause mortality—75. Any-mention mortality—922.

### Prevalence

- Data from the 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 prevalent predominantly in females (3:1 ratio) and in White populations (55%).<sup>93</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>94</sup>
- A study including 636 US health care workers (median age, 42 years; 93% females) found a high prevalence of CVI with presence of varicose veins in 20% of the participants.<sup>95</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>96</sup> Approximately 4% of patients with DVT experience venous stasis ulcers.<sup>97</sup>

### Incidence

- In a Spanish registry covering 5.8 million people, 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. Females presented ≈2.5-fold more CVI incidence than males (4.77 and 1.95 per 1000 person-years, respectively). Venous stasis ulcer incidence was 0.23 per 1000 person-years (95% CI, 0.21–0.24).<sup>98</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>99</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>100</sup>
- A prospective study involving 449 US patients observed a linear association between CVI severity, measured by clinical-etiiology-anatomy-pathophysiology classes and lower SES ( $P<0.003$ ). Patients with the 2 worst clinical-etiiology-anatomy-pathophysiology classes had a median annual household income of <\$40 000.<sup>101</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>96,102,103</sup>
- Using data from 762 patients with DVT, Rabinovich et al<sup>104</sup> developed a clinical prediction model for PTS. High-risk predictors were index DVT in the iliac vein, BMI of  $\geq 35 \text{ kg/m}^2$ , 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  $\geq 4$ ).
- In a meta-analysis of  $\approx 60\,000$  patients with VTE on anticoagulant therapy, the use of rivaroxaban reduced the risk of PTS by half compared with warfarin (OR, 0.52 [95% CI, 0.43–0.63]).<sup>105</sup>
- 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>106</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>107</sup>
- Although a number of genes have been implicated,<sup>108</sup> to date, no causal association has been proved.<sup>109</sup>
- GWASs in  $>400\,000$  individuals established 12 candidate loci for varicose veins in individuals with European ancestry, highlighting the SNPs in the *CASZ1*, *PIEZ01*, *PPP3R1*, *EBF1*, *STIM2*, *HFE*, *GATA2*, *NFATC2*, and *SOX9* gene regions.<sup>110</sup>

### **Awareness, Treatment, and Control**

- Several treatment options are available for patients with severe varicose veins, but evidence on the best approach is scarce. A 2021 Cochrane meta-analysis found a borderline benefit in technical success up to 5 years after endoscopic laser ablation over ultrasound-guided foam sclerotherapy (pooled OR, 6.47 [95% CI, 2.60–16.10]) and surgery (pooled OR, 2.31 [95% CI, 1.27–4.23]), in addition to the benefit of the surgery over ultrasound-guided foam sclerotherapy (pooled OR, 0.09 [95% CI, 0.03–0.30]). None of the procedures showed a solid benefit over the others when the recurrence rate was analyzed.<sup>111</sup> The success of these procedures is critically compromised according to the progressive increase in weight, especially in those with a BMI  $\geq 35 \text{ kg/m}^2$ .<sup>112</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>113</sup> Individualized therapy was noninferior to standard duration of therapy of 24 months (OR, 1.06 [95% CI, 0.78–1.44]). Multilayer bandaging was slightly more effective than compression hosiery but had higher costs without a gain in health-related quality of life ( $P=1.00$ ).<sup>114</sup>
- For treatment of leg venous ulcers, compression bandages or stockings are associated with reduced wound healing time (pooled HR, 2.17 [95% CI, 1.52–3.10]), rate of fully healed wounds (pooled RR, 1.77 [95% CI, 1.41–2.21]), and pain (pooled median difference in 10-point pain scale,  $-1.39$  [95% CI,  $-1.79$  to  $-0.98$ ]), with no adverse effects ( $P=0.97$ ).<sup>115</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>116</sup>



### **Health Care Use: Hospital Discharges/Ambulatory Care Visits**

- In 2018, varicose veins and CVI/PTS were the main diagnosis in  $>76\,000$  ED visits. The aggregate charges added up to \$450 million. Furthermore,  $\approx 13\,500$  discharges were attributed to CVI/PTS and varicose veins.<sup>3</sup>

### **Global Burden**

- An online-based survey of 16015 individuals from different nations showed a 22% prevalence of CVI, from 14% in French respondents to 37% in Russians, and fewer than half of those with CVI sought medical attention.<sup>117</sup> Among 19104 workers in Germany in a population-based study, the prevalence of CVI was similar (22.3%).<sup>118</sup>

### **Pulmonary Hypertension**

#### **ICD-10 I27.0, I27.2.**

2020, United States: Underlying cause mortality—8651. Any-mention mortality—30304.

#### **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>119</sup>
- PH incidence is somewhat higher in females than males,<sup>120</sup> and females have at least 3-fold higher

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>121</sup>

- The WHO classifies PH into 5 groups (described in the following paragraphs) 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>122</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>123</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>123</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>123</sup> Among ≈600 000 Medicare patients with acute exacerbated COPD, secondary PH diagnosis was present in 10.9%.<sup>124</sup>
  - WHO group 4 PH (CTEPH and other pulmonary obstructions): prevalence ranges from 1.0% to 8.8% among those with PE.<sup>123</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>125</sup>
  - WHO group 5 PH (multifactorial mechanisms): prevalence is 6% to 10% when it accompanies sickle cell disease and increases with advancing age; prevalence is 2.1% when it accompanies thalassemia.<sup>126</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>127</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>128</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>129</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>130</sup>
- A Japanese family study identified *BMPR2* (bone morphogenetic protein receptor type 2) as a risk factor for PAH.<sup>131</sup> In whole-exome sequencing, a Japanese cohort of patients with CTEPH were noted to carry nonsynonymous variants associated with acute PE, indicating a partial genetic overlap of CTEPH with acute PE.<sup>132</sup>
- GWASs in >11 000 individuals have identified risk loci for PAH, including *SOX17* and *HLA-DPA1/DPB1*.<sup>133</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>134</sup>



### Awareness, Treatment, and Control

- As nonpharmacological therapy, exercise-based rehabilitation programs have shown improvements in 6MWD (+47.7 m [95% CI, 33.9–61.7]) and  $\text{Vo}_2\text{peak}$  (+2.96 mL·kg<sup>-1</sup>·min<sup>-1</sup> [95% CI, 2.49–3.43]).<sup>135</sup>
- 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>136</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>137</sup>

- In symptomatic WHO group 1 patients with intermediate risk of 1-year mortality, the REPLACE investigators found a benefit of switching from other phosphodiesterase 5 inhibitors to riociguat for improvement of 2 of 6MWD, WHO functional class, and NT-proBNP (OR, 2.78 [95% CI, 1.53–5.06]) with no clinical worsening (OR, 0.10 [95% CI, 0.01–0.73]).<sup>138</sup>
- 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>139</sup> However, serious adverse events may occur in 12% to 25% of cases, including sepsis, hemorrhage, pneumothorax, and PE.
- In the CTEPH scenario, pulmonary thromboendarterectomy surgery resulted in better WHO functional class (rate in WHO functional class I/II, 82.9% versus 56% versus 48.2% in operated, operable but not operated, and inoperable, respectively;  $P<0.001$ ) and less use of oxygen ( $P<0.001$  versus inoperable cohort), diuretics ( $P<0.001$  versus inoperable cohort), and specific medications for pulmonary hypertension ( $P<0.001$  versus both others).<sup>140</sup>
- A comprehensive study of data from 132552 veterans with PH diagnosed in groups 2 and 3 found a 39% increased mortality or organ failure in those exposed to pulmonary vasodilators (HR, 1.31 [95% CI, 1.25–1.37]).<sup>141</sup>

### 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>142</sup>
- Data from the US CTEPH Registry had a 1-year mortality, stratified by pulmonary thromboendarterectomy status, of 5.6% in operated patients, 9.9% in those in whom surgery was feasible but who decided not to have the procedure, and 12.4% in inoperable patients ( $P=0.028$ ).<sup>140</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>143</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>144</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>145</sup>

- In PH group 3, patients with PH and lung disease had an increased in-hospital mortality compared with those with no PH (OR, 1.89 [95% CI, 1.73–2.07]).<sup>124</sup>
- In terms of pregnancy, a systematic review of 13 studies (4 in the United States) observed a 12% overall maternal mortality rate. Of all deaths, 61% occurred within the first 4 days of labor.<sup>146</sup> In addition, 58% of births were PTBs.
- In the United States, patients with PH admitted to the hospital have 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>119</sup>
- A retrospective analysis of 6169 US patients with PH observed a higher mortality in those living in small urban counties (HR, 1.48 [95% CI, 1.14–1.92]) and rural areas (HR, 2.01 [95% CI, 1.13–3.57]) compared with patients with PH living in metropolitan counties.<sup>147</sup>

### Costs

- Health care costs associated with PH are substantial. In inpatient scenarios, the mean cost increased progressively from \$18531 in 1993 to \$73529 in 2015.<sup>3</sup>
- In patients of WHO group 3 PH, there is an increase in hospitalization costs of \$2785 (mean difference [95% CI, \$2602–\$2967]).<sup>124</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 \$16240 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 \$14340, respectively.<sup>148</sup>

### Health Care Use: Hospital Discharges/Ambulatory Care Visits

- In 2019, there were 14 000 hospital discharges with pulmonary hypertension as the principal diagnosis (HCUP<sup>3</sup> unpublished NHLBI tabulation).
- In 2018, there were 578 000 physician office visits with pulmonary hypertension as the principal diagnosis (NAMCS,<sup>149</sup> unpublished NHLBI tabulation).

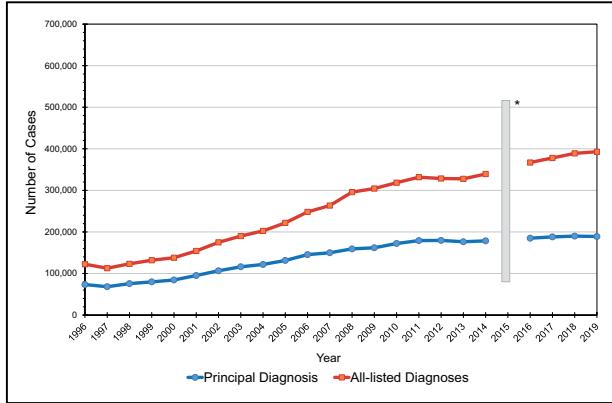
### Global Burden

- 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>123</sup>

- A meta-analysis with 5834 patients observed an overall CTEPH incidence after acute PE of 2.82% (95% CI, 2.11%–3.53%).<sup>150</sup> In this scenario, Asian

individuals showed a higher risk of CTEPH compared with Europeans (pooled incidence, 5.08% [95% CI, 2.67%–7.49%] versus 1.96% [95% CI, 1.29%–2.63%], respectively). However, in high-income countries, the 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>125</sup>

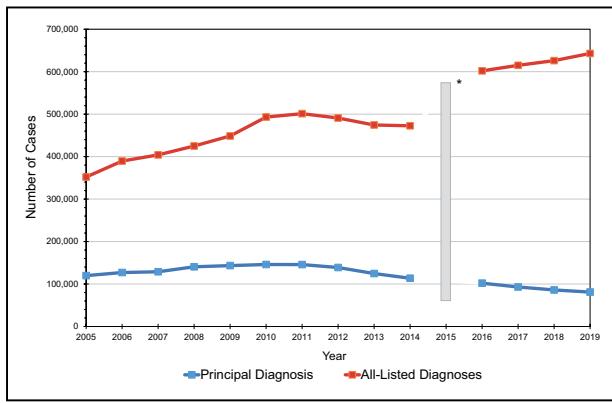


**Chart 24-1. Trends in hospitalized PE, United States, 1996 to 2019.**

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 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 24-2. Trends in hospitalized DVT, United States, 2005 to 2019.**

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>

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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

(See 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 from 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 males and females varies by age, 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 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 identified with the use

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

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 2011 and 2019, the prevalence of PAD, defined as an ABI  $\leq 0.9$ , was 5.56% with a higher prevalence in high- compared with low- to middle-income countries (7.37% versus 5.09%, respectively).<sup>9</sup>
- From 2009 to 2019, principal discharge diagnosis for PAD decreased from 144 000 to 78 000 (HCUP,<sup>10</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>11</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>12</sup>
- Between 2003 and 2011, endovascular treatment for chronic limb-threatening ischemia increased from 5.1% to 11.0%.<sup>11</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>13</sup>

### Risk Factors

- Modifiable PAD risk factors largely parallel those for atherosclerosis in other vascular beds such as CAD and include smoking, diabetes, hypertension, and atherogenic dyslipidemia.<sup>3,4,9,14</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</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>15</sup>
  - Diabetes is associated with increased risk for PAD, with ORs ranging from 1.38 to 1.89.<sup>3,9</sup>
  - Hypertension, defined as BP  $\geq 140/90$  mmHg, is associated with  $\approx 50\%$  increased odds of PAD (OR, 1.67 [95% CI, 1.50–1.86]).<sup>9</sup>
    - Each 20-mmHg 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 DBP (HR per 1-SD increase in DBP, 1.12 [95% CI, 0.97–1.30]).<sup>16</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>17,18</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>17,18</sup>
    - Further lipid subtraction 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>17–20</sup>
    - With the use of mendelian randomization, apolipoprotein B–lowering therapy was predicted to have a greater reduction in CAD risk (per 1-SD reduction: OR, 0.66 [95% CI, 0.63–0.69];  $P=4\times 10^{-73}$ ) than PAD risk (per 1-SD reduction: OR, 0.87 [95% CI, 0.84–0.91];  $P=9\times 10^{-9}$ ).<sup>21</sup>
    - Mendelian randomization also suggests a causal link between lipoprotein(a) and PAD among individuals of both European (per

1-SD increase: OR, 1.22 [95% CI, 1.11–1.34];  $P=2.97\times 10^{-5}$ ) and African (per 1-SD increase: OR, 1.16 [95% CI, 1.01–1.33];  $P=0.034$ ) ancestries.<sup>22</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>23</sup>
- MetS was associated with increased risk for incident PAD according to 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>24,25</sup>
- Other possible PAD risk factors include sedentary lifestyle, inflammation, hypertension in pregnancy, and CKD.<sup>14,24,26,27</sup>
- Mediterranean diet compared with counseling for a low-fat diet was associated with a lower risk of incident PAD according to a secondary analysis of a randomized feeding trial conducted in Spain between 2003 and 2010.<sup>28</sup>

### Social Determinants of Health and Health Equity

(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>29,30</sup>
- Lower SES is associated with greater risk for amputation (HR, 1.12 [95% CI, 1.06–1.17]).<sup>31</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>32</sup>
  - Among Medicare beneficiaries, zip codes in the top quartile of amputation rates had a larger mean proportion of Black residents than zip codes in the bottom quartile (17.5% versus 4.4%;  $P<0.001$ ).<sup>32</sup>
  - Data from the Vascular Quality Initiative suggest that individuals from underrepresented racial and ethnic groups living in rural areas have a 52% greater odds of amputation than people from underrepresented racial and ethnic groups living in urban areas (95% CI, 1.19–1.94).<sup>33</sup>



### Risk Prediction

- Models for predicting the probability of an ABI  $<0.9$  have been developed from NHANES data.<sup>3,34</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>34</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>3,35</sup>

### Subclinical/Unrecognized Disease

- Intermittent claudication, a classic PAD symptom, is present in a minority (8.7%–32%) of individuals with PAD.<sup>5,36</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>5,36</sup>
- Approximately 20% to 34% of individuals with ABI  $<0.9$  have no associated limb symptoms but still exhibit functional limitations.<sup>5,36,37</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. 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>39</sup> Chip-based genetic analyses similarly suggest that the heritability of PAD is 55%.<sup>40</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>41</sup>
  - Other common PAD-associated genetic loci include SNPs on chromosome 9 near the *CDKN2B*, *DAB21P*, and *CYBA* genes.<sup>42</sup>
- A large-scale GWAS in >31 000 cases with PAD and >211 000 controls from the Million Veteran 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>43</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>44</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>45</sup>
- Mendelian randomization has been used to examine evidence of causality for several putative PAD risk factors, including hemostatic measures, lipoproteins, smoking, and BP phenotypes. These studies reported that genetically determined increases in factor VIII, von Willebrand factor, apolipoprotein B, very low-density lipoprotein, smoking, SBP, DBP, and pulse pressure increased PAD risk.<sup>21,47,48</sup>

- One GWAS of 449 548 participants of European ancestry (12 086 PAD cases) examined evidence of SNP-by-smoking and SNP-by-type 2 diabetes interaction on PAD.<sup>40</sup> The authors report a lead variant at *CCSER1* that showed genome-wide significant evidence of association with PAD in the total population ( $P=2.5\times10^{-8}$ ) and genome-wide suggestive evidence of interaction with type 2 diabetes ( $P=5.3\times10^{-7}$ ).
- The proportion of variance that 2 traits share attributable to genetic causes (ie, genetic correlation) of PAD with CAD, BMI, HDL-C, LDL-C, triglycerides, type 2 diabetes, and SBP has been reported.<sup>40</sup> Strong genetic correlation between PAD and CAD was reported ( $r_g=0.58$ ). BMI, type 2 diabetes, LDL-C, triglycerides, and SBP also showed evidence of positive genetic correlation with PAD. HDL-C showed evidence of negative genetic correlation with PAD, suggesting that SNPs associated with higher levels of HDL-C are associated with lower PAD risk.

### **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 its 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>49</sup>
    - Of those familiar with PAD,  $\approx$ 50% were aware of smoking, diabetes, hypertension, and dyslipidemia as PAD risk factors.<sup>49</sup>
    - Approximately 25% to 28% knew that PAD is associated with increased risk of MI and stroke, with 14% awareness of amputation or death as a PAD-related complication.<sup>49</sup>
    - Income and education levels were positively associated with all knowledge domain levels.<sup>49</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 receive optimal medical therapy less frequently than patients with CAD. Data from the MarketScan and Medicare databases showed that only 33.9% of patients with PAD were prescribed statins compared with 51.7% of patients with CAD.<sup>50</sup>
  - Similarly, only 24.5% of patients with PAD in the MarketScan database achieved a target LDL-C <70 mg/dL.<sup>51</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>52</sup>
  - Optimal exercise programs for patients with PAD are summarized in a 2019 AHA scientific statement.<sup>53</sup>
  - In a 2017 Cochrane review with meta-analysis, aerobic exercise compared with usual care was associated with the following<sup>54</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,  $5.8 \pm 4.6$  minutes versus  $3.7 \pm 4.9$  minutes;  $P=0.04$ ). Results in the exercise group and stent group were superior to results in the group with optimal medical care alone ( $1.2 \pm 2.6$  minutes).<sup>55</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>56,57</sup>
  - Lipid-lowering therapy with a high-intensity statin and, in some cases, a PCSK9 inhibitor is recommended for the treatment of PAD.<sup>52,58</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>59</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>60</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>61</sup>
- The antithrombotic medication rivaroxaban, in addition to aspirin, may reduce the risk of adverse limb outcomes (eg, revascularization or amputation) among patients with PAD.<sup>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>62</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  $\geq 6.8\%$  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

(See Table 25-1 and Chart 25-4)

- In 2020, PAD was the underlying cause in 12 086 deaths. The number of any-mention deaths

attributable to PAD was 64 386 (Table 25-1; unpublished NHLBI tabulation using NVSS<sup>67</sup> and CDC WONDER).<sup>68</sup>

- In 2020, the overall any-mention age-adjusted death rate for PAD was 15.4 per 100 000 (unpublished NHLBI tabulation using CDC WONDER).<sup>68</sup>
  - Any mention-death rates were 12.8 for NH White females, 16.3 for NH Black females, 5.9 for NH Asian or Pacific Islander females, 13.9 for NH American Indian or Alaska Native females, and 10.4 for Hispanic females.
  - Any mention-death rates were 18.8 for NH White males, 25.9 for NH Black males, 8.5 for NH Asian or Pacific Islander males, 20.0 for NH American Indian or Alaska Native males, and 15.7 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  $< 0.9$ ) compared with 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 2730 742 Medicare beneficiaries  $\geq 65$  years of age with PAD using data from 2000 to 2008.<sup>73</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>74</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>75</sup>
- Mortality by 1 year after major lower-extremity amputation was estimated at 48.3% among 186 338 older Medicare patients with PAD.<sup>76</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>37</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) and, in 2019, 78 000 hospital discharges (HCUP<sup>10</sup> unpublished NHLBI tabulation) and 61 000 ED visits (HCUP<sup>10</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, the 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****Prevalence****(See Table 25-2 and Charts 25-5)**

- In 2015, an estimated 237 million people worldwide had PAD according to a systematic review of 116 studies.<sup>9</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 Study 2020 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).
  - 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****(See Table 25-2 and Chart 25-6)**

- In the GBD Study 2020, the age-standardized mortality estimated for PAD was 0.93 (95% UI, 0.80–1.00) per 100 000 individuals (Table 25-2).
  - 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>86,87</sup>
- AAA is more common in males than females, and its prevalence increases with age.<sup>88–91</sup>
  - AAA is ≈4 times more common in males than females on the basis of data from an ultrasound screening study of 125 722 veterans 50 to 79 years of age conducted between 1992 and 1997.<sup>92,93</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>94</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>95,96</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>97</sup>
- In a Swedish study of 14 229 individuals with thoracic aortic disease, the incidence of TAA or dissection was 16.3 per 100 000 per year in males and 9.1 per 100 000 per year in females in 2002. The median age at diagnosis was 71 years.<sup>98</sup>
- In 2010, the estimated annual incidence rate of AAA per 100 000 individuals was 0.83 (95% CI, 0.61–1.11) and 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>99</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>100</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>101</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>102</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>103</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>104</sup>
- Risk factors for AAA were assessed in a retrospective analysis of 3.1 million patients between 2003 and 2008.<sup>105</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  $P < 0.0001$ ).
- Data suggest that lipoprotein(a) is linked to AAA risk. In ARIC, individuals with baseline lipoprotein(a) measures in the top quartile were at greater risk of incident AAA than those in the bottom quartile (HR, 1.57 [95% CI, 1.19–2.08]).<sup>106</sup>
  - Mendelian randomization analyses also suggest a causal link between genetically determined lipoprotein(a) levels and AAA in individuals of European (per 1-SD increase: OR, 1.28 [95% CI, 1.17–1.40]) and African (per 1-SD increase: OR, 1.34 [95% CI, 1.11–1.62]) ancestries.<sup>22</sup>
- Diabetes may be associated with lower risk of aortic aneurysmal disease.<sup>103,107,108</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>

- Evidence suggests there may be a temporal relationship between fluoroquinolone use and aortic disease. A study analyzing  $> 9$  million fluoroquinolone prescriptions showed an increased risk of newly diagnosed AAA in patients  $> 35$  years of age prescribed a fluoroquinolone compared with other antibiotics (HR, 1.31 [95% CI, 1.25–1.37]).<sup>109</sup>
- In a case-crossover analysis of patients in Taiwan, fluoroquinolone use was associated with an increased risk of aortic dissection or aneurysm (OR, 2.71 [95% CI, 1.14–6.46]), and there was a greater risk with more prolonged fluoroquinolone exposure.<sup>110</sup>

### **Social Determinants of Health**

- Few data exist on social determinants of health for TAA.
- In a retrospective study of 60 784 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>111</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 92 028 patients between 2007 and 2014.<sup>112</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>113</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>114,115</sup> TAAs with familial and genetic causes may display faster rates of expansion ( $P < 0.0001$ ).<sup>116</sup> Expansion rate accelerates as the size increases.<sup>117</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>118</sup> In a nationwide Swedish program targeting males ≥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>119</sup>

- A meta-analysis of 15 475 individuals from 18 studies on small AAAs (3.0–5.4 cm) demonstrated a mean aneurysm growth rate of 0.22 cm/y, which did not vary significantly by age and sex.<sup>120</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>120</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>121–123</sup> Approximately 25% of patients with TAA have concomitant AAA.

#### *Genetics/Family History*

- Aortic dissection is heritable. In a study using 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>124</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-β pathway-related genes, including *TGFB1*, *TGFB2*, *SMAD3*, *TGFB2*, and *TGFB3*), vascular Ehlers-Danlos syndrome (*COL3A1*), arterial tortuosity syndrome (*SLC2A10*), and familial TAA syndrome (*ACTA2*, *TGBR2*, and variants in several other genes).
- 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>125,126</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>127</sup>
- A GWAS of individuals in the Million Veteran 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  $P<5\times10^{-8}$ ).<sup>128</sup>
- Genetic variants associated with intracranial aneurysms have been found in several genes, including *RBBP8*, *STRAD13/KL*, *SOX17*, and *CDKN2A/B* (all  $P<5\times10^{-8}$ ).<sup>129</sup> Rare variants in *ANGPTL6* are associated with familial cases of intracranial aneurysms ( $P<0.05$ ).<sup>130</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>128</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>131</sup> and functional analyses have demonstrated that this locus regulates endothelin-1 expression.<sup>132</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  $P<5\times10^{-8}$ ).<sup>133</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>134</sup>

#### *Awareness, Treatment, and Control*

- Aortic aneurysmal disease is typically asymptomatic until complications occur.
  - 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 Centers for Medicare & Medicaid data.<sup>135</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>136,137</sup>
    - In a sample of 12573 and 2732 Medicare patients from 1998 to 2007, for intact TAA, perioperative mortality was similar for 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>138</sup>

- Procedural volume affects outcomes for ruptured AAA repair. In a meta-analysis of 120 116 patients undergoing ruptured AAA repair, patients treated at low-volume centers had a greater overall mortality risk than those treated at high-volume centers (OR, 1.39 [95% CI, 1.22–1.59]). In multivariable-adjusted models, patients treated at low-volume centers had a greater mortality risk for open repair (OR, 1.68 [95% CI, 1.21–2.33]) but not endovascular repair (OR, 1.42 [95% CI, 0.84–2.41]).<sup>139</sup>
- In the United States, data from NIS showed that the risk of death after open thoracoabdominal aortic aneurysm repair in low-volume hospitals was significantly greater than at high-volume hospitals (OR, 1.921 [95% CI, 1.458–2.532];  $P<0.001$ ).<sup>140</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>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>141</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, 1.05–1.47]), AAA-related mortality (HR, 4.37 [95% CI, 2.51–7.66]), and complications at 1 year.<sup>142</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>143</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>144</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 ≤3 cases versus 3.8% in 14–62 cases;  $P<0.01$ ) and hospital (6.3% in ≤5 cases versus 3.8% in 14–62 cases;  $P<0.01$ ).<sup>145</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>146</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>147</sup>

### Mortality

2020, United States: Underlying cause mortality—9317. Any-mention mortality—17 816.

- 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>148</sup>
  - Mesenteric malperfusion with type A acute dissections was present in ≈3.7% of patients in IRAD and associated with greater mortality than among patients without malperfusion (63.2% versus 23.8%;  $P<0.001$ ).<sup>149</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>150</sup>
- AAA
  - Data from 23 838 patients with ruptured AAAs collected through the NIS 2005 to 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>151</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>152</sup>

- A meta-analysis with 619068 patients who underwent elective AAA repair observed a higher 30-day mortality rate in females compared with males (mortality rate, 0.04 [95% CI, 0.04–0.05] versus 0.02 [95% CI, 0.02–0.03]) despite a lower prevalence of comorbidities.<sup>153</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 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>154</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>155</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>156</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>157</sup>

#### AAA:

- The risk of AAA rupture is also proportionately related to diameter (Chart 25-8).<sup>158</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>159,160</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>120</sup>
- A Canadian registry observed that small AAAs ( $<5.5$  cm for males and  $<5.0$  cm for females) account for only 10% of all ruptured AAAs.<sup>161</sup>

### Health Care Use: Hospital Discharges and Ambulatory Care Visits

- In 2019, hospital discharges with aortic aneurysm as principal diagnoses totaled 71 000 (HCUP,<sup>10</sup> unpublished NHLBI tabulation).

### Cost

- A study comprising 1207 Medicare patients from the Vascular Quality Initiative showed that the median cost of index endovascular repair of AAA was \$25 745 (IQR, \$21 131–\$28 774), whereas the median cost of subsequent reintervention was \$22 165 (IQR, \$17 152–\$29 605).<sup>162</sup>

### Global Burden

#### (See Table 25-3 and Chart 25-9)

- Global mortality attributable to aortic aneurysm by sex according to the GBD Study 2020 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  $\approx 6.8\%$  in the North Carolina subcohort of the CHS between 1997 and 1998.<sup>163</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>164,165</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>166</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>166</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>167</sup>
- Atherosclerosis in another vascular bed is significantly associated with the presence of renal artery stenosis.<sup>165,166,168</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 ≥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>169</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 ≥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>170</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>171</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>172</sup>
  - In an analysis of Medicare recipients, patients with atherosclerotic renal artery stenosis were at higher risk of incident congestive HF, stroke, death, and need for renal replacement therapy (all  $P < 0.0001$ ).<sup>166</sup>

**Table 25-1.** PAD in the United States

Population group	Mortality, 2020, all ages*	Hospital discharges, 2019, all ages
Both sexes	12 086	78 000
Males	5778 (47.8%)†	...
Females	6308 (52.2%)†	...
NH White males	4431	...
NH White females	4833	...
NH Black males	786	...
NH Black females	853	...
Hispanic males	374	...
Hispanic females	391	...
NH Asian or Pacific Islander males	133‡	...
NH Asian or Pacific Islander females	181‡	...
NH American Indian/Alaska Native	78	...

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 (for underlying cause of PAD): Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics System.<sup>67</sup> Hospital discharges (with a principal discharge of PAD): Unpublished NHLBI tabulation using Hospital Cost and Utilization Project.<sup>10</sup>



**Table 25-2. Global Mortality and Prevalence of Lower-Extremity PAD by Sex, 2020**

	Both sexes combined		Males		Females	
	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)
Total number (millions), 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)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; PAD, peripheral artery disease; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>173</sup>

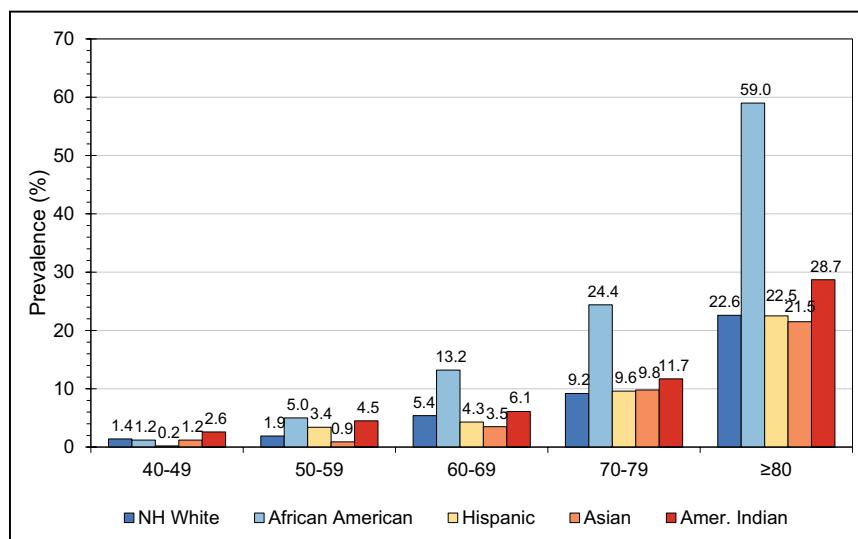
**Table 25-3. Global Mortality of Aortic Aneurysm by Sex, 2020**

	Both sexes (95% UI)	Males (95% UI)	Females (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)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

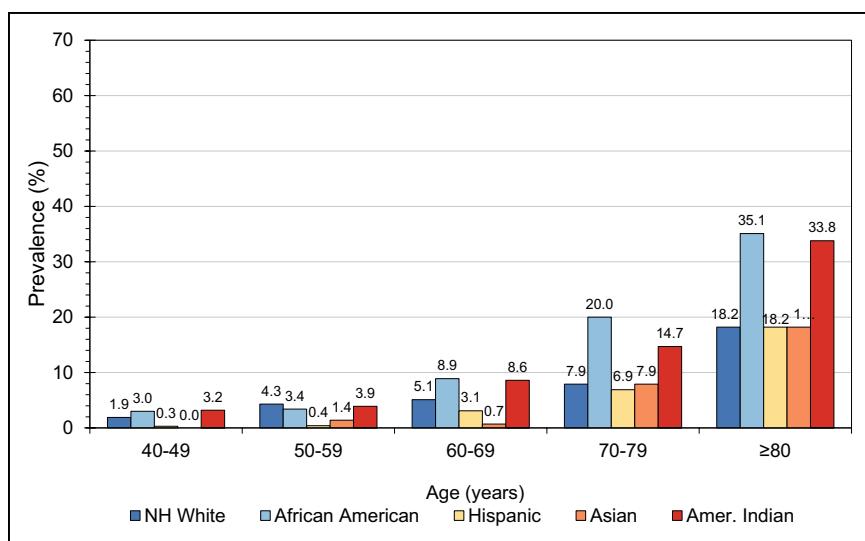
GBD indicates Global Burden of Disease; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>173</sup>

**Chart 25-1. Estimates of prevalence of PAD in males by age and ethnicity, United States, 2000.**

Amer. indicates American; NH, non-Hispanic; and PAD, peripheral artery disease.

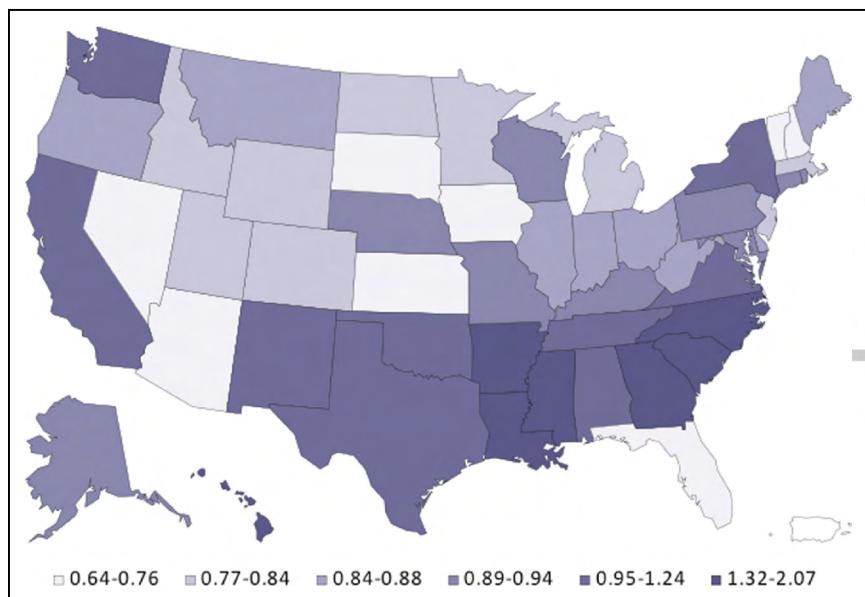
Source: Data derived from Allison et al.<sup>1</sup>



**Chart 25-2. Estimates of prevalence of PAD in females by age and ethnicity, United States, 2000.**

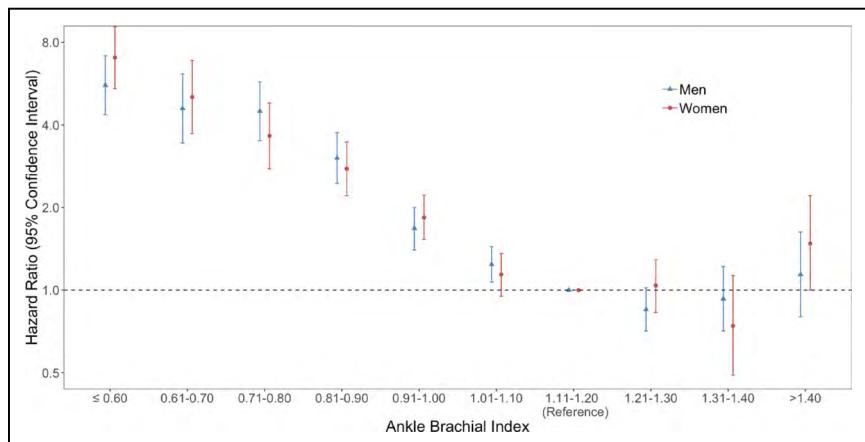
Amer. indicates American; NH, non-Hispanic; and PAD, peripheral artery disease.

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.**

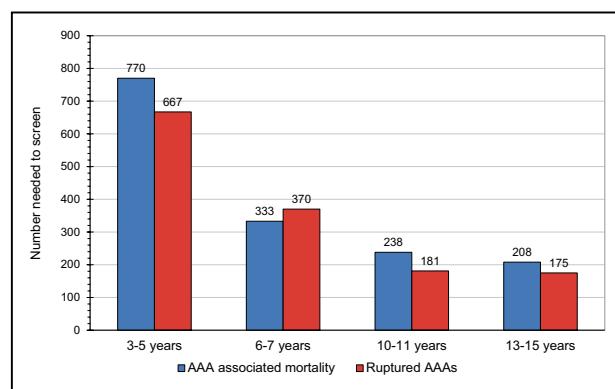
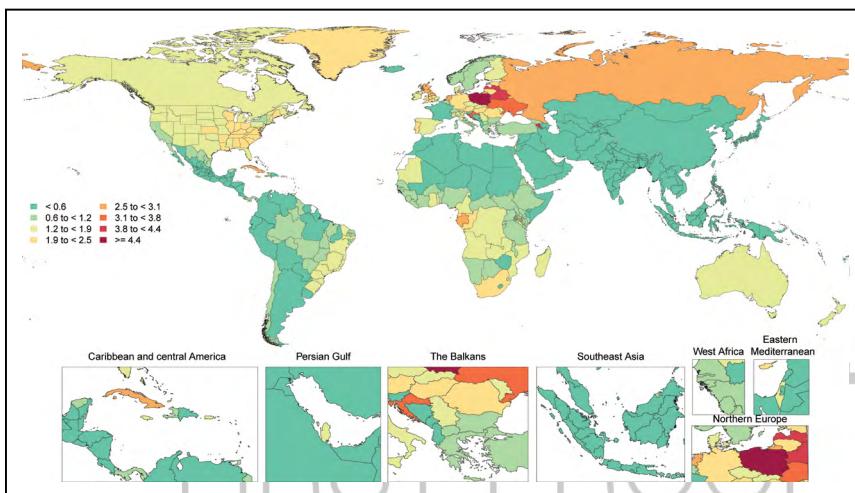
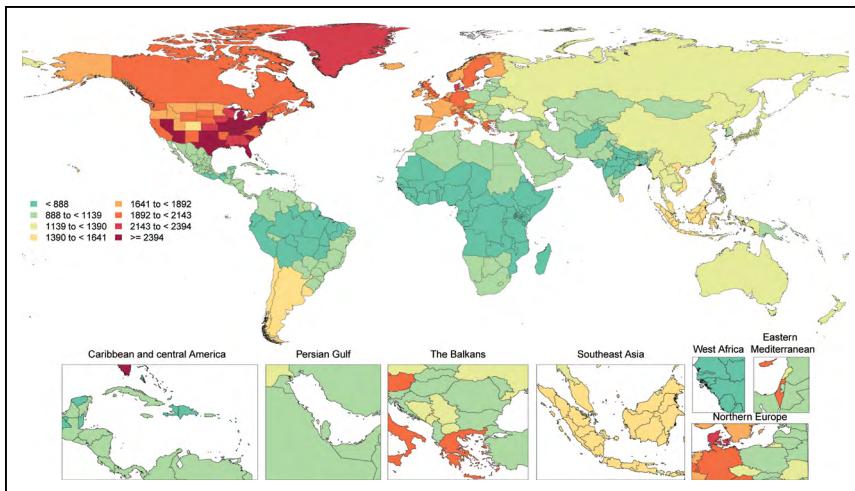
Source: Reprinted from Jones et al<sup>73</sup> with permission. Copyright © 2012 American College of Cardiology Foundation.



**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>

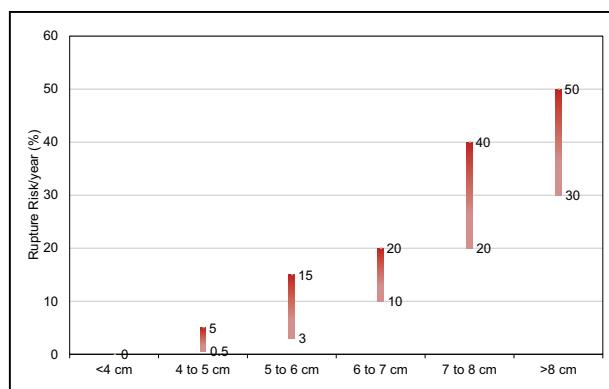


**Chart 25-7. Numbers needed to screen to avoid an AAA-associated death and a ruptured AAA, 1988 to 1999 (baseline years), with average follow-up of 4 to 15 years.**

Global data.

AAA indicates abdominal aortic aneurysm.

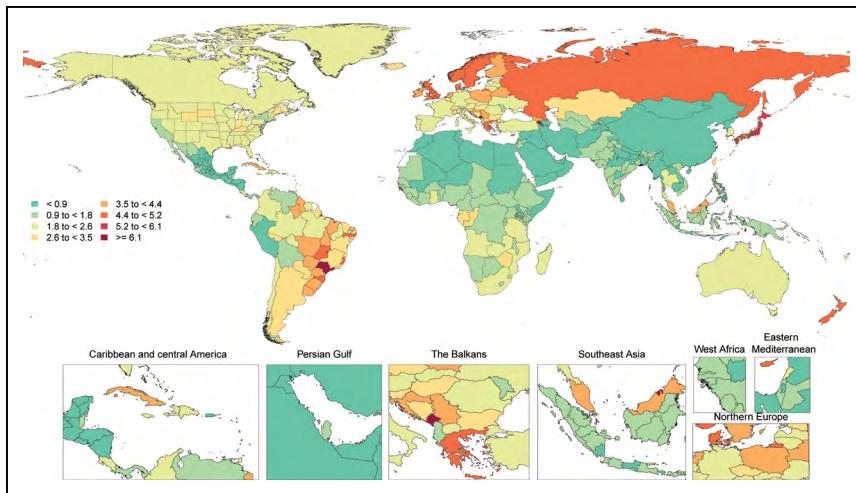
Source: Data derived from Eckstein et al.<sup>118</sup>



**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>158</sup>



**Chart 25-9. Age-standardized global mortality rates of aortic aneurysm per 100 000, both sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease.

Source: Data courtesy of the GBD Study 2020. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>173</sup>

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# Circulation

## 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 as 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 settings and clinicians and data transfer, analysis, and dissemination. Process measures focus on tasks that are directly under the control of the clinician (eg, did patients receive a prescription for a statin after an MI?), whereas outcomes measures focus on metrics that are meaningful to patients (eg, what proportion of individuals are alive at 30 days after a hospitalization for an MI?). Outcomes measures can also monitor for unintended consequences of quality assurance programs focused on a process measures.

Decades of clinical registries in the United States and worldwide have helped measure and improve quality of care delivered and, in so doing, improve CVH 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

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

of cardiovascular conditions. Outpatient postmarketing registries have increasingly been sponsored by pharmaceutical or device companies and managed by contract research organizations such as for anticoagulation in AF. Last, medical claims data from payers (Medicare, commercial claims) or integrated health care systems (Veterans Affairs) have also examined quality.

In the following sections, data on quality of care are presented across these 6 domains, grouped by disease or therapeutic area. When possible, data are reported from recently published literature or as standardized quality indicators drawn from quality-improvement registries with methods that are consistent with performance measures endorsed by the ACC and AHA.<sup>2,5,6</sup> Additional data on adherence to ACC/AHA clinical practice guidelines are included to supplement performance measures data. A few examples of how social determinants of health affect the cardiovascular care and outcomes are included; a more extensive discussion related to health equity is now included in individual condition-specific chapters. 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 MI



**(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 show the latest metrics of AMI quality of care at the time of presentation and at hospital discharge).

### Quality and Outcomes in Medicare and Medicaid Beneficiaries

- A 20-year evaluation from January 1, 1995, to December 31, 2014, assessed AMI outcomes in older adults.<sup>8</sup> The sample included 4367 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 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>9</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>10</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];  $P_{\text{interaction}}=0.48$ ).
- In a cohort analysis of 4070 US acute care hospitals, 2820 hospitals had >25 admissions for AMI, CHF, or pneumonia. There was modest correlation in the 30-day risk-standardized readmission rates for patients with traditional Medicare and Medicare Advantage (correlation coefficients, 0.31 for AMI, 0.40 for HF, and 0.41 for pneumonia).<sup>11</sup> The traditional Medicare risk-standardized readmission rate showed a systematic underestimation of risk for AMI and other conditions. Furthermore, the inclusion of Medicare Advantage data for at least 1 of these conditions changed the penalty status for 23% of hospitals.

### Quality and Outcomes Across Hospitals

- 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>
- 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>12</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>13</sup>
- 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>14</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.

### Effect of Health Policy on Quality of AMI Care

- 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>15</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 the 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 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%;  $P=0.76$ ).

### Social Determinants and Health Equity in AMI Care

- 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 ( $P_{\text{trend}}=0.002$ ). It is notable that 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 of Black race 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>17</sup>
- Among 237 549 AMI survivors in the US Nationwide Readmissions Database, sex differences in HF hospitalization risk were explored.<sup>18</sup> In a propensity-matched time-to-event analysis, females had a 13% higher risk of 6-month HF readmission compared with males (6.4% versus 5.8%; HR, 1.13 [95% CI, 1.05–1.21];  $P<0.001$ ).
- An analysis of patients seen in primary care at the Veterans Affairs health care system, including 147 600 veteran patients, identified sex-related disparities in secondary prevention.<sup>19</sup> Among patients with premature IHD, females received less antiplatelet (aOR, 0.47 [95% CI, 0.45–0.50]), any statin (aOR, 0.62 [95% CI, 0.59–0.66]), and high-intensity statin (aOR, 0.63 [95% CI, 0.59–0.66]) therapy and had lower adherence to statin therapy than males (mean $\pm$ SD proportion of days covered,  $0.68\pm0.34$  versus  $0.73\pm0.31$ ;  $\beta$  coefficient,  $-0.02$  [95% CI,  $-0.03$  to  $-0.01$ ]) compared with males.
- In a health care system cohort of 27 694 patients (52% males, 91% White individuals) examined from January 1, 2011, through December 31, 2018, area deprivation index as a measure of living in socioeconomically disadvantaged communities was associated with readmission after cardiac hospitalization.<sup>20</sup> Patients with myocardial ischemia living in the areas with the greatest deprivation index had a 2-fold greater hazard of 1-year readmission (HR, 2.04 [95% CI, 1.44–2.91]). In addition, higher area deprivation index was associated with greater 1-year mortality.
- Among 4667 patients in a study using a North Carolina statewide electronic database of all EMS patient care reports from 2011 to 2017, 62% of

EMS encounters met the 11-minute benchmark for response time and 49% met the 15-minute benchmark for scene time.<sup>21</sup> The response times were longer in patients from rural than in those from urban locations. In addition, older age and female sex were associated with lower adherence to the scene time benchmark.

- NCDR data in 390 692 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>22</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>23</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 patients at 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.

### COVID-19 and AMI Care

- A multicenter, prospective, international registry of COVID-19-positive patients with STEMI ( $n=144$ ) and non-ST-elevation ACS ( $n=121$ ) included data across 55 centers from March 1 to July 31, 2020.<sup>24</sup> Compared with national pre-COVID-19 databases, symptom-to-admission times were longer in patients with COVID-19 (patients with COVID-19 and STEMI versus control subjects: median, 339 minutes versus 173 minutes;  $P<0.001$ ; patients with COVID-19 and non-ST-elevation ACS versus control subjects: 417 minutes versus 295 minutes;  $P=0.012$ ). Higher mortality was also observed in patients with COVID-19 and STEMI versus control subjects (22.9% versus 5.7%;  $P<0.001$ ) and

patients with COVID-19 and non-ST-elevation ACS versus control subjects (6.6% versus 1.2%;  $P<0.001$ ), which persisted after propensity adjustment. Furthermore, patients with COVID-19 and STEMI were more likely to have cardiogenic shock (20.1% versus 8.7% in control subjects;  $P<0.001$ ).

- A prospective multicenter study in Israel examined 1466 consecutive patients with STEMI, of whom 774 (53%) were hospitalized during the COVID-19 pandemic in 2020, and compared these patients with prepandemic control patients from 2018.<sup>25</sup> Patients with COVID-19 and STEMI showed a prolonged median time from symptom onset to reperfusion (180 minutes [IQR, 122–292 minutes] versus 290 minutes [IQR, 161–1080 minutes];  $P<0.001$ ). In multivariable analysis, an increased risk in patients with COVID-19 was observed in the composite end point of malignant arrhythmia, congestive HF, or in-hospital mortality (OR, 1.65 [95% CI, 1.03–2.68];  $P=0.04$ ).

## Heart Failure

### (See Tables 26-4 and 26-5)

- Current US HF quality data are captured by the widespread but voluntary GWTG-HF program (Tables 26-4 and 26-5) and analyses of health care claims data.

### Hospitalizations for HF

- In a cohort study using data from 8272270 adult hospitalizations of 5 092 626 unique patients (mean age, 72.1 years; 48.9% females) in the Nationwide Readmission Database from 2010 through 2017, primary HF hospitalization rates per 1000 US adults declined from 4.4 in 2010 to 4.1 in 2013 and then increased to 4.9 in 2017.<sup>26</sup> Similar trends were noted in the rate per 1000 US adults of postdischarge HF readmissions (1.0 in 2010 to 0.9 in 2014 to 1.1 in 2017) and all-cause 30-day readmissions (0.8 in 2010 to 0.7 in 2014 to 0.9 in 2017). The observed increase in the rate of HF hospitalizations in recent years may represent an actual increase in HF hospitalizations, increased detection attributable to rising use of HF biomarkers, the use of more sensitive definitions of HFpEF, or changing coding practices.
- By 2023, a majority of Medicare beneficiaries are projected to be enrolled in Medicare Advantage Plans compared with fee-for-service Medicare.<sup>27</sup> Thus, examining outcomes among beneficiaries enrolled in Medicare Advantage plans will be increasingly important in the future. In 1 study of 262 626 patients hospitalized with HF included in GWTG-HF, patients enrolled 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];  $P=0.04$ ).<sup>28</sup> In addition, no difference was reported in in-hospital mortality.

- According to NIS data, HF hospitalization rates decreased 30.8% between 2002 and 2013.<sup>29</sup> Over this period, the age-standardized HF hospitalization rate (per 100 000) declined from 526.86 in 2002 to 364.66 in 2013, attributable to a decline in the age-standardized HF hospitalization rate of 25.8% in males and 36.0% in females. The age-standardized HF hospitalization rate (per 100 000) decreased 29.6% for NH White adults from 448.29 in 2002 to 315.69 in 2013; 29.4% for Black adults from 1048.31 in 2002 to 739.72 in 2013; 48.4% for Hispanic adults from 649.53 in 2002 to 335.41 in 2013; and 47.5% for Asian American/Pacific Islander adults from 342.85 in 2002 to 179.90 in 2013.

### Effect of Health Policy on HF Hospitalizations

A number of studies noted a decline in HF readmissions after the implementation of HRRP. However, there is evidence of a potential unintended effect of HRRP on mortality among patients with HF.

- 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>30</sup>
- Reductions in readmission rates were greater for target versus nontarget conditions for patients at the penalized hospitals but not at nonpenalized hospitals.<sup>31</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>31</sup>
- In an analysis of almost 3 million admissions for HF among Medicare fee-for-service beneficiaries, 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>32</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>33</sup>

- In an analysis from 2005 to 2015 including 3.2 million hospitalizations for HF among Medicare fee-for-service beneficiaries, the announcement and implementation of HRRP were associated with an increase in death within 30 days of hospitalization.<sup>15</sup> Compared with this baseline trend, postdischarge mortality increased by 0.49% after the announcement of HRRP ( $P=0.01$ ) and 0.52% after implementation of HRRP ( $P=0.001$ ). The increase in mortality among patients with HF was related to outcomes among patients who were not readmitted but died within 30 days of discharge.

Other studies have shown that 30-day readmissions may have limitations as a metric of health care outcomes in HF patients because it may be unrelated to or inversely related to mortality. Furthermore, readmission reduction efforts have been associated with an increased number of total hospital visits after discharge when urgent care or emergency room visits are also considered.

- 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>34</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>35</sup>
  - There were no differences between the low (HF excess readmission ratio  $\leq 1$ ) and high (HF excess readmission ratio  $> 1$ ) 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 excess readmission ratio 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%;  $P=0.07$ ).
- One study examined postdischarge outcomes after 3038740 hospitalizations for HRRP-targeted health conditions (including 1357620 HF hospitalizations) among Medicare fee-for-service beneficiaries  $\geq 65$  years of age between January 1, 2012,

and October 1, 2015.<sup>36</sup> When all revisits after discharge were counted, the total number of hospital revisits per 100 patient discharges for target conditions increased across the study period (monthly increase, 0.023 visits per 100 patient discharges [95% CI, 0.010–0.035]). This change was attributable to monthly increases in treat-and-discharge visits to an ED (0.023 [95% CI, 0.015–0.032]) and observation stays (0.022 [95% CI, 0.020–0.025]), which were only partly offset by declines in readmissions ( $-0.023$  [95% CI,  $-0.035$  to  $-0.012$ ]). Furthermore, because the Centers for Medicare & Medicaid Services uses point estimates of 30-day risk-standardized readmission rates to compare hospitals under HRRP without considering its margin of error, hospitals may have been misclassified with regard to their penalty status.

- A cross-sectional study used bayesian deconvolution to estimate the rate of penalty status misclassification for hospitals participating in the HRRP in fiscal year 2019, using data from the CMS Hospital Compare website collected between July 1, 2014, and June 30, 2017.<sup>37</sup> Among 6964 hospitals (including 2626 hospitals for HF) that participated in the HRRP in fiscal year 2019, 13.5% (95% CI, 9.8%–17.2%) of hospitals that should have been penalized for HF were not, and 10.9% (95% CI, 7.2%–14.6%) were incorrectly penalized for HF. The margin of error associated with the 30-day risk-standardized readmission rates resulted in the misclassification of condition-specific penalty status for up to 31% of hospitals.

### Alternative Metrics of Care Quality for HF

- One study examined variation in quality measures and short-term outcomes across 4 US Census Bureau regions in 423333 patients hospitalized with HF and enrolled in the GWTG-HF registry from 2010 to 2016.<sup>38</sup> Although the study did not note any substantial differences by region in quality of care in patients hospitalized for HF, risk-adjusted inpatient mortality was found to be lower in the Midwest compared with the Northeast (HR, 0.64 [95% CI, 0.51–0.80]), which the authors attributed to unmeasured differences in patient characteristics and to longer length of stay in the Northeast.
- 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>12</sup>
- Among 106304 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>39</sup>

- 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%;  $-0.12\%$  per year;  $P<0.001$ ), but mean mortality among all other HF hospitals increased during the study period (from 10.9% to 12.0%; 0.17% per year;  $P<0.001$ ,  $P_{\text{interaction}}<0.001$ ).<sup>6</sup>
- In 125 595 patients with HF at 342 hospitals in the GWTG-HF registry, 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 ( $P=0.025$ ).<sup>40</sup> 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 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. Early visits with subspecialists were associated with lower mortality, particularly for individuals with HF and diabetes (HR, 0.58 [95% CI, 0.34–0.99]). Last, 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>41</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>42</sup>
- Although participation in cardiac rehabilitation improves exercise capacity, quality of life, and clinical outcomes in patients with HFrEF, uptake among eligible Medicare beneficiaries with HFrEF has been low. Among 11 696 Medicare beneficiaries hospitalized for HFrEF from quarter 1 of 2014 to quarter 2 of 2016, the quarterly participation rate within 6 months of discharge was 4.3% with a modest increase over the study period (2.8% in quarter 1 of 2014; 5.0% in quarter 2 of

2016).<sup>43</sup> Factors associated with participation in cardiac rehabilitation among eligible patients with HFrEF included younger age, male sex, race and ethnicity other than Black, previous cardiovascular procedures, and hospitalization at hospitals with cardiac rehabilitation facilities.

- 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 (22.2%) in the registry.<sup>44</sup>
- 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>45</sup>

### Patient-Reported Outcomes for HF

The use of patient-reported outcomes may provide understanding about patient well-being and prognosis.

- In a secondary analysis of the TOPCAT and HF-ACTION trials focused on patient-reported outcomes, the most recent score 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 those with HFrEF.<sup>46</sup>

### 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>47</sup>
- 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.<sup>48</sup> 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%.

**Blood Pressure**

- Trends in BP control from 1999 to 2000 through 2017 to 2018 in US adults with hypertension were assessed in a serial cross-sectional analysis of NHANES participants.<sup>49</sup> The data were weighted to be representative of US adults and included participants with a mean age of  $48 \pm 19$  years, with 50.1% females, 43.2% NH White adults, 21.6% NH Black adults, 5.3% NH Asian adults, and 26.1% Hispanic adults. In the 18262 adults with hypertension, the age-adjusted estimated proportion with controlled BP, defined as BP  $<140/90$  mmHg, improved 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 ( $P_{\text{trend}} < 0.001$ ), was similar in 2013 to 2014 (53.8% [95% CI, 48.7%–59.0%];  $P_{\text{trend}} = 0.14$ ), and then worsened to 43.7% (95% CI, 40.2%–47.2%) in 2017 to 2018 ( $P_{\text{trend}} = 0.003$ ).

**Social Determinants and Health Equity in Hypertension**

- Disparities in BP control were observed by age, race and ethnicity, insurance status, and health care use. For instance, an analysis of 16531 nonpregnant US adults in NHANES examined disparities by self-reported race and ethnicity in the cascade of hypertension prevalence, awareness, treatment, and control using data from 2013 to 2018.<sup>50</sup>
  - Compared with White adults, Black adults had a higher prevalence (45.3% versus 31.4%; aOR, 2.24 [95% CI, 1.97–2.56];  $P < 0.001$ ) but similar awareness and treatment rates. Hispanic adults had a similar prevalence but lower awareness (71.1% versus 79.1%; aOR, 0.72 [95% CI, 0.58–0.89];  $P = 0.005$ ) and treatment (60.5% versus 67.3%; aOR, 0.78 [95% CI, 0.66–0.94];  $P = 0.010$ ) rates compared with White adults. Asian adults had similar prevalence, lower awareness (72.5% versus 79.1%; aOR, 0.75 [95% CI, 0.58–0.97];  $P = 0.038$ ) and similar treatment rates relative to White adults.
  - Compared with the age-adjusted BP control rate of 49.0% of White adults, BP control rates were lower in Black adults (39.2%; aOR, 0.71 [95% CI, 0.59–0.85];  $P < 0.001$ ), Hispanic adults (40.0%; aOR, 0.71 [95% CI, 0.58–0.88];  $P = 0.003$ ), and Asian adults (37.8%; aOR, 0.68 [95% CI, 0.55–0.84];  $P = 0.001$ ).

**Diabetes**

- In 6653 NHANES participants from 1999 to 2018 who were  $>20$  years of age and reported physician-diagnosed diabetes (other than during pregnancy), trends in glycemic control and control of other cardiovascular risk factors were examined.<sup>51</sup>
  - Glycemic control, defined as an HbA1c  $<7\%$ , improved from 1999 to the early 2010s and then

worsened. The percentage of adult NHANES participants with diabetes achieving glycemic control in the 2007 to 2010 period was 57.4% (95% CI, 52.9%–61.8%), worsening to 50.5% (95% CI, 45.8%–55.3%) by 2015 to 2018.

- Lipid control, defined as non-HDL-C  $<130$  mg/dL, improved in the early 2000s and stalled from 2007 to 2010 (52.3% [95% CI, 49.2%–55.3%]) to 2015 to 2018 (55.7% [95% CI, 50.8%–60.5%]).
- BP control, defined as BP  $<140/90$  mmHg, declined from 2011 to 2014 (74.2% [95% CI, 70.7%–77.4%]) to 2015 to 2018 (70.4% [95% CI, 66.7%–73.8%]).
- Control of all 3 targets plateaued after 2010 and was 22.2% (95% CI, 17.9%–27.3%) in 2015 to 2018. There was no improvement in the use of glucose-lowering or antihypertensive medications after 2010 and in the use of statins after 2014.

**Appropriate Use of Statin Therapy**

- In a PINNACLE Registry study of 1655 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>52</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 [95% CI, 1.01–1.04]).
- In an examination of electronic health record data for patients seen in primary care or cardiology at an urban academic medical center in New York City from October 2018 to January 2020, 7550 patients were eligible for statin therapy on the basis of their ASCVD risk, but only 3994 (52.9%) were prescribed a statin.<sup>53</sup> After multivariable adjustment, females remained less likely to receive a prescription for statin therapy (aOR, 0.79 [95% CI, 0.71–0.88]).
- Among 24651 adults  $>75$  years of age (48% females) receiving ASCVD care at a health system in Northern California between 2007 and 2018, prescriptions for moderate- or high-intensity statin therapy increased over time.<sup>54</sup> However, fewer than half of patients (45%) received moderate- or high-intensity statins in 2018. Lower use of statin therapy was observed in females (OR, 0.77 [95% CI, 0.74–0.80]), patients with HF (OR, 0.69 [95% CI, 0.65–0.74]), patients with dementia (OR, 0.88 [95% CI, 0.82–0.95]), and underweight patients (OR, 0.64 [95% CI, 0.57–0.73]).

- Disparities in statin prescription rates were identified in an analysis of the Vascular Quality Initiative registry of patients undergoing lower-extremity PAD revascularization from January 1, 2014, to December 31, 2019.<sup>55</sup> Among 125 791 patients (mean age, 67.7 years; 62.7% males, 78.7% White individuals) undergoing 172 025 revascularization procedures, the overall proportion of patients receiving a statin prescription after the procedure improved from 75% in 2014 to 87% in 2019. However, only 30% of patients who were not taking a statin at the time of revascularization were newly discharged with a statin prescription. Furthermore, the likelihood of new statin prescription was lower among certain subgroups, including females, patients of older age, those using antiplatelet therapy, and those who had prior peripheral revascularization.

## Atrial Fibrillation

### Prescription of Oral Anticoagulation

- 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 ≥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>56</sup>
- In a cross-sectional analysis spanning 2013 to 2019 and including 34 174 hospitalized patients ≥65 years of age with AF from the GWTG-AF registry, overall discharge prescription of anticoagulation was 85.6%.<sup>57</sup> However, higher morbidity burden was associated with lower odds of anticoagulation prescription (aOR, 0.72 for patients with ≥6 comorbidities versus 0–2 comorbidities [95% CI, 0.60–0.86]). In those with ≥6 comorbidities, frequent falls/frailty was the most common reason for nonprescription of anticoagulation (31.0%).
- An AHA GWTG-Stroke study compared outcomes with DOAC therapy (dabigatran, rivaroxaban, or apixaban) versus warfarin in 11 662 patients ≥65 years of age with AF who were anticoagulation naive and discharged from 1041 hospitals after AIS in October 2011 to December 2014. Patients discharged on DOAC therapy had more favorable outcomes compared with those discharged on warfarin, including more days at home during the first year after discharge (mean±SD, 287.2±114.7 days versus 263.0±127.3 days; adjusted difference, 15.6 [99% CI, 9.0–22.1]), fewer MACEs (aHR, 0.89

[99% CI, 0.83–0.96]), and fewer deaths (aHR, 0.88 [95% CI, 0.82–0.95];  $P<0.001$ ).<sup>58</sup>

- 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>59</sup>

### Adherence to Anticoagulation

- A systematic review and meta-analysis demonstrated suboptimal adherence and persistence to DOACs in patients with AF.<sup>60</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 ≥80% adherence and 69% (95% CI, 65%–72%) showing persistence. Poor adherence to DOAC therapy was associated with greater risk of stroke (HR, 1.39 [95% CI, 1.06–1.81]).
- Using administrative health data from 1996 to 2019 in British Columbia, Canada, a study examined oral anticoagulant adherence trajectories over 5 years in 19 749 patients with AF (mean age, 70.6 years; 56% male; mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score, 2.8).<sup>61</sup> Group-based trajectory modeling identified 74% of patients as having “consistent adherence,” 12% as having “rapid decline and discontinuation,” 10% as having “rapid decline and partial recovery,” and 4% as having “slow decline and discontinuation.”<sup>61</sup> Clinical and demographic characteristics were not able to provide strong performance in predicting these adherence trajectories.

### Inappropriate Prescriptions and Periprocedural Adverse Events

- In a NCDR PINNACLE registry study, 107 759 of 658 250 (16.4%) of patients with AF without CVD were inappropriately prescribed combination antiplatelet and anticoagulant therapy, and 5731 of 150 079 (3.8%) patients with AF with reduced LVEF received an inappropriate prescription for a nondihydropyridine calcium channel blocker.<sup>62</sup> The adjusted practice-level median OR for inappropriate prescriptions in AF patients was 1.70 (95% CI, 1.61–1.82), consistent with a 70% likelihood of 2 random practices treating identical patients with AF differently.
- In the NCDR LAOO Registry, 49 357 patients (mean age, 76.1 years; 41.3% females) with AF undergoing left atrial appendage occlusion with the Watchman device from January 1, 2016, to

June 30, 2019, were analyzed.<sup>63</sup> After multivariable adjustment, females had a higher risk of in-hospital adverse events after left atrial appendage occlusion than males (1284 [6.3%] versus 1144 [3.9%];  $P<0.001$ ; OR, 1.63 [95% CI, 1.49–1.77];  $P<0.001$ ).

### Social Determinants of Health and Health Equity in AF Care

- Health care insurance coverage may influence oral anticoagulant and novel oral anticoagulant use. An analysis of 363 309 patients with prevalent AF from the PINNACLE-AF outpatient registry found considerable variation in oral anticoagulant use across insurance plans.<sup>64</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%;  $P<0.001$ ).

## Stroke

### (See Tables 26-3 and 26-7)

#### Prehospital Care

- A retrospective, pre-post study examined the effect of a regional prehospital EMS transport policy to triage patients with suspected large- vessel stroke to CSCs.<sup>65</sup> The outcome was treatment rates before and after implementation of this triage policy in patients with AIS at 15 primary stroke centers and 8 CSCs in Chicago, IL. Among 7709 patients with stroke, the rate of endovascular therapy increased overall among all patients with AIS (from 4.9% [95% CI, 4.1%–5.8%] to 7.4% [95% CI, 7.5%–8.5%];  $P<0.001$ ) and among EMS-transported patients with AIS within 6 hours of onset (4.8% [95% CI, 3.0%–7.8%] to 13.6% [95% CI, 10.4%–17.6%];  $P<0.001$ ). This was noted to be a 1-time step change in rate of endovascular therapy at the time of implementation of the new triage policy. The authors concluded that “the implementation of a prehospital transport policy for CSC triage in Chicago was associated with a significant, rapid, and sustained increase in endovascular therapy rate for patients with AIS without deleterious associations with thrombolysis rates or times.”<sup>65</sup>

#### Acute Stroke Care

- 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 an analysis comparing individuals presenting with stroke at institutions participating in the GWTG-Stroke program and those at institutions not enrolled in the program, individuals 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>66</sup>
- 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>67</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.
- 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>68</sup>
- 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>69</sup>

#### Poststroke Care and Outcomes

- A study of 2083 patients with ischemic stroke from 82 hospitals with data in both the AVAIL registry and GWTG-Stroke found that one-third of patients with acute stroke were functionally dependent or dead at 3 months after stroke. Functional rates varied considerably across hospitals, which indicates the need to understand which process measures could be targeted to minimize hospital variation and to improve poststroke functional outcomes.<sup>70</sup>
- A retrospective, difference-in-differences analysis of GWTG-Stroke registry data compared 342 765 first-time ischemic stroke admissions from 2012

to 2018 for patients 19 to 64 years of age in 45 states (27 that expanded Medicaid and 18 that did not).<sup>71</sup> As expected, expansion of Medicaid resulted in an increase in the proportion of stroke admissions covered by Medicaid (from 12.2% to 18.1% in expansion states and from 10.0% to only 10.6% in nonexpansion states). Medicaid expansion was associated with increased odds of discharge to a skilled nursing facility (aOR, 1.33 [95% CI, 1.12–1.59]) and, among eligible patients, transfer to any rehabilitation facility (aOR, 1.24 [95% CI, 1.08–1.41]) and lower odds of discharge home (aOR, 0.89 [95% CI, 0.80–0.98]) but was not associated with other outcomes such as stroke severity, use of emergency services, time to acute care, in-hospital mortality, or level of disability.

- 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>72</sup>

## Implantable Defibrillators and Cardiac Resynchronization Therapy

- In observational analysis of patients hospitalized with HF and an EF ≤35% without an implantable cardioverter defibrillator in the GWTG-HF Program (2011–2014), females were less likely than males to receive predischarge implantable cardioverter defibrillator counseling (19.3% versus 24.6%; aOR, 0.84 [95% CI, 0.78–0.91]), and individuals from underrepresented racial and ethnic group populations were less likely to receive counseling than patients from White populations (Black, 22.6%; Hispanic, 18.6%; other racial and ethnic group, 14.4%; versus White, 24.3%; aOR versus White populations, 0.69 [95% CI, 0.63–0.76] for Black individuals; aOR, 0.62 [95% CI, 0.55–0.70] for Hispanic individuals; aOR, 0.53 [95% CI, 0.43–0.65] for other patients).<sup>73</sup> Among patients who were counseled, females and males were similarly likely to receive an implantable cardioverter defibrillator (aOR, 1.13 [95% CI, 0.99–1.29]), but compared with White individuals, Black individuals (aOR, 0.70 [95% CI, 0.56–0.88]) and Hispanic individuals

(aOR, 0.68 [95% CI, 0.46–1.01]) were less likely to receive an implantable cardioverter defibrillator.

- 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>74</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 a multicenter retrospective analysis of 106 patients ≤21 years of age without prior cardiac disease who received an implantable cardioverter defibrillator after SCA, 20 (19%) received appropriate shocks and 16 (15%) received inappropriate shocks over a median follow-up of 3 years.<sup>75</sup> The appropriate use of device therapy was high, regardless of underlying disease. Lack of a definitive cause of the SCA was not associated with lower risk of subsequent events.
- In an analysis from the GWTG-HF including >18 000 patients, the timeliness of cardiac resynchronization therapy was associated with improved 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>76</sup>

## Transcatheter Aortic Valve Replacement

Since its approval for commercial use in 2011, TAVR has rapidly become the primary modality for the management of aortic stenosis.

### Access

A multicenter, nationwide cross-sectional analysis of Medicare claims data (2012–2018) examined receipt of TAVR among beneficiaries of fee-for-service Medicare who were ≥66 years of age living in the 25 largest metropolitan core-based statistical areas.<sup>77</sup> When analyzed by zip code, receipt of TAVR was inversely related to median household income, proportion of beneficiaries also enrolled in Medicaid, and increased community-level social deprivation. For instance, for each \$1000 decrease in median household income, the number of

TAVR procedures performed per 100 000 Medicare beneficiaries declined by 0.2% (95% CI, 0.1%–0.4%). Zip codes with higher proportions of patients of Black race and Hispanic ethnicity had lower rates of TAVR, even after accounting for differences in socioeconomic markers, age, and clinical comorbidities.

### Clinical Outcomes

A retrospective cohort study using data from the STS/ACC Transcatheter Valve Therapies Registry was used to develop a novel ranked composite performance measure for TAVR quality that incorporated stroke; major, life-threatening, or disabling bleeding; stage III acute kidney injury; and moderate or severe perivalvular regurgitation.<sup>78</sup> When this new outcomes-based metric of TAVR quality was applied to 3-year rolling data, there was significant site-level variation in quality of care in TAVR in the United States, with 25 of 301 sites (8%) performing better than expected, 242 of 301 sites (80%) performing as expected, and 34 of 301 (11%) sites performing worse than expected on the basis of predicted outcomes. However, the reliability of this metric exceeded 0.7 only in sites that performed at least 100 procedures over a 3-year period.

## Resuscitation

### (See Table 26-8)

#### In-Hospital Cardiac Arrests

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>79</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>80</sup>
- Of 103 932 IHCAs between 2000 and 2014, 12.7% had delays to epinephrine administration, with marked variation across hospitals. The delay was inversely correlated to risk-standardized survival. Whether a reduction in this process measure could improve outcomes has not yet been demonstrated.<sup>81</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>82</sup>

- Data from the GWTG-Resuscitation including 268 031 patients demonstrated a longitudinal reduction in time to receiving each medication, including epinephrine, vasopressin, amiodarone, lidocaine, atropine, and other medications, from 2001 to 2016 in IHCAs.<sup>83</sup>
- Among 192 adult hospitals in the GWTG-Resuscitation program, risk-standardized survival after IHCA rates (total of 44 477 IHCAs) varied widely between hospitals (median, 24.7%; range, 9.2%–37.5%).<sup>84</sup> After adjustment for resuscitation practices, hospitals with a very active physician champion were more likely to be in a higher survival quintile compared with sites without a very active resuscitation champion (aOR, 3.90 [95% CI, 1.39–10.95]). There was no difference in survival between sites with very active nonphysician champions and those without very active champions (aOR, 1.28 [95% CI, 0.62–2.65]).
- 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>85</sup>

#### Out-of-Hospital Cardiac Arrests

- In a study including 84 089 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>86</sup>
- In an analysis of the impact of the 2010 and 2015 resuscitation guidelines,<sup>87,88</sup> a study including 231 739 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>89</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 CPR in 2020 (61% to 51%;  $P = 0.02$ ) and lower use of automated external defibrillators (5% to 1%;  $P = 0.02$ ) were seen.<sup>90</sup> The authors also reported longer EMS response time (6.6±2.0 to 7.6±3.0 minutes, respectively;  $P < 0.001$ ) and lower survival to hospital discharge (14.7% to 7.9%;  $P = 0.02$ ).

**Table 26-1.** Time Trends in the CAD Quality-of-Care Measures in the Chest Pain-MI Registry, United States, 2010 to 2021

Quality-of-care measure	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019*	2020	2021
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	97.7
Aspirin at discharge‡	98	98.3	98.4	98.4	98.7	98.7	98.7	98.7	98.9	98.3	98.6	98.7
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	97.2
Statin use at discharge	92	98.4	98.8	98.8	99.1	99.2	99.4	99.4	99.5	99.4	NA	NA
High-intensity statin at discharge	NA	88.1	92.4	94.3								
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	87.7
Adult smoking cessation advice/counseling	98	98.4	98.4	98.4	98.6	98.0	98.1	98.0	98.2	NA	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	85.0

Values are percentages.

ACC indicates American College of Cardiology; ACE, angiotensin-converting enzyme; AHA, American Heart Association; 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/ACC Clinical Performance and Quality Measures for Adults With ST-Elevation and Non-ST-Elevation Myocardial Infarction.”<sup>91</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>92</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 2021

Quality metrics	2018	2019	2020	2021
ECG within 10 min of arrival <sup>†</sup>	68.6	64.0	59.0	56.0
Aspirin within 24 h of arrival	98.7	97.6	97.4	97.7
Any anticoagulant use <sup>‡</sup>	96.1	NA	NA	NA
Dosing errors				
UFH dose	43.2	NA	NA	NA
Enoxaparin dose	9.8	NA	NA	NA
Glycoprotein IIb/IIIa inhibitor dose	4.3	NA	NA	NA
Discharge				
Aspirin at discharge	98.9	98.3	98.6	98.7
Prescribed statins on discharge	99.5	NA	NA	NA
High-intensity statin at discharge	NA	88.1	92.4	94.3
Adult smoking cessation advice/counseling	98.2	NA	NA	NA
Cardiac rehabilitation referral	83.3	82.7	83.7	85.0
In-hospital mortality <sup>§</sup> (95% CI)	4.12 (3.96–4.39)	NA	5.4 (5.24–5.69)	5.63 (5.34–6.03)

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.

\*Effective January 2019, this metric was updated in the American College of Cardiology’s (ACC’s) Chest Pain-MI Registry to include patient records in the denominator with incomplete data; consequently, the registry saw a decline in performance (includes all patients with ST-segment-elevation myocardial infarction before hospital admittance and patients with non-ST-segment-elevation myocardial infarction; exclusions are patients with a prehospital ECG, patients transferred in, or patients with a nonsystem reason for delay).

†Includes UFH, low-molecular-weight heparin, or direct thrombin inhibitor use.

‡Includes all patients. Risk-standardized mortality.

§Source: Data from the ACC’s Chest Pain-MI Registry.<sup>7</sup>

**Table 26-3. Timely Reperfusion for AMI and Stroke, United States**

Quality-of-care measure	GWTG-Stroke (for stroke): July 1, 2018–June 30, 2019	GWTG-Stroke: 2020	GWTG-Stroke, 2021	Chest Pain-MI Registry: STEMI, 2019	Chest Pain-MI Registry: STEMI, 2020	Chest Pain-MI Registry: STEMI, 2021
STEMI						
PCI within 90 min*	NA			94.0	93.0	93.0
Stroke						
IV tPA in patients who arrived <2 h after symptom onset, treated ≤3 h	88.2	90.0	86.7	NA	NA	NA
IV tPA in patients who arrived <3.5 h after symptom onset, treated ≤4.5 h	84.2†	91.3†	88.0†	NA	NA	NA
IV tPA door-to-needle time ≤60 min	84.2	87.7	87.5	NA	NA	NA

Values are percentages. GWTG data for 2019 to 2020 are not available.

AMI indicates acute myocardial infarction; GWTG, 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-type plasminogen activator.

\*Excludes transfers and is measuring hospital arrival; arrival by emergency medical service is 96%.

†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, GWTG-Stroke, 2020 and 2021.

**Table 26-4. HF Quality-of-Care Measures, United States, 2020 and 2021**

Quality-of-care measure	AHA GWTG-HF, 2020	AHA GWTG-HF, 2021
ACE inhibitors/ARBs or ARNI at discharge	90.2	91.7
Evidence-based specific β-blockers	92.0	93.4
Measure LV function	99.0	99.2
Postdischarge appointment for patients with HF	84.9	85.5

Values are percentages.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; GWTG, Get With The Guidelines; HF, heart failure; and LV, left ventricular.

Source: Unpublished American Heart Association tabulation, GWTG-HF, 2020 and 2021.

**Table 26-5. Quality of Care by Race and Ethnicity and Sex in the GWTG-HF Program, United States, 2021**

Quality-of-care measure	Race and ethnicity			Sex	
	White	Black	Hispanic	Males	Females
Postdischarge appointment for patients with HF*	86.2	83.9	85.0	85.5	85.6
Measurement of LV function*	99.3	99.3	99.3	99.3	99.2
ACE inhibitors/ARBs or ARNI at discharge*	90.8	93.1	93.5	89.4	91
Smoking cessation	82.3	78.4	71.4	80.6	81.6
Evidence-based specific β-blockers*	92.6	94.9	93.4	93.7	92.7
Hydralazine nitrate at discharge	29.2	28.1	23.2	29.9	25.1
HF composite (4 achievement measures)	93.1	92.8	92.9	93	92.9

Values are percentages.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; GWTG, Get With The Guidelines; HF, heart failure; and LV, left ventricular.

\*Indicates the 4 key achievement measures targeted in GWTG-HF.

Source: Unpublished American Heart Association tabulation, 2021.

**Table 26-6. National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set on CVD, Diabetes, Tobacco, Nutrition, and Lifestyle, United States, 2020**

	Commercial*		Medicare*		Medicaid*
	HMO	PPO	HMO	PPO	HMO
<b>CVD</b>					
β-Blocker persistence after MI†	85.9	86.6	88.8	91.3	80.4
BP control‡	51.8	46.2	63.0	61.8	55.9
Statin therapy for patients with CVD	81.8	81.3	83.6	82.6	78.3
<b>Diabetes</b>					
HbA1c testing	88.0	87.0	91.9	92.7	82.8
HbA1c >9.0%	37.5	43.9	27.4	23.4	45.4
Eye examination performed	49.0	46.9	68.3	68.5	50.6
Monitoring nephropathy	90.1§	88.7§	94.0	94.5	89.7§
BP <140/90 mm Hg	54.5	49.0	64.9	65.0	58.2
Statin therapy for patients with diabetes	65.1	63.8	77.9	75.2	64.3
<b>Tobacco, nutrition, and lifestyle</b>					
Advising smokers and tobacco users to quit	79.5	67.0§	86.5	83.2	74.8
BMI percentile assessment in children and adolescents (3–17 y of age)	65.9	58.5	NA	NA	74.5
Nutrition counseling (children and adolescents [3–17 y of age])	60.2	52.9	NA	NA	67.3
Counseling for PA (children and adolescents [3–17 y of age])	56.4	49.0	NA	NA	63.3
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)	85.9		86.6	American Heart Association. 88.3	91.3
PA advice in older adults (≥65 y of age; 2016 data)	51.8		46.2	63.0	61.8

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.

\*Data presented are from 2020 unless otherwise noted.

†β-Blocker persistence: received persistent β-blocker treatment for 6 months after hospital discharge for acute MI.

‡Adults 18 to 59 years of age with BP &lt;140/90 mm Hg, adults 60 to 85 years of age with a diagnosis of diabetes and BP &lt;140/90 mm Hg, and adults 60 to 85 years of age without a diagnosis of diabetes and BP &lt;150/90 mm Hg.

§2019 data.

||2018 data.

Source: Healthcare Effectiveness Data and Information Set.<sup>47</sup>**Table 26-7. Quality of Care by Race and Ethnicity and Sex in the GWTG-Stroke Program, United States, 2021**

Quality-of-care measure	Race and ethnicity			Sex	
	White	Black	Hispanic	Males	Females
IV tPA in patients who arrived <3.5 h after symptom onset, treated ≤4.5 h*	88.1	87.1	91.1	89.1	88.4
IV tPA door-to-needle time ≤60 min	86.1	86.3	86.9	87	85.7
Thrombolytic complications: IV tPA and life-threatening, serious systemic hemorrhage	7.6	6.0	7.3	6.3	8.2
Antithrombotic agents <48 h after admission	96	95.3	95.5	95.7	95.2
VTE prophylaxis by second hospital day	95.5	95.6	95.6	95.6	95.6
Antithrombotic agents at discharge	98.2	97.9	95.3	95.2	95
Anticoagulation for AF/atrial flutter at discharge	96.2	95.9	95.7	96.2	96.2
Counseling for smoking cessation	96.9	97.1	95.5	96.2	96.2
Lifestyle changes recommended for BMI >25 kg/m <sup>2</sup>	65.5	70.4	73	67	66.5
Composite quality-of-care measure	96.2	96.4	96.3	96.4	96.1

Values are percentages.

AF indicates atrial fibrillation; BMI, body mass index; GWTG, Get With The Guidelines; IV, intravenous; tPA, tissue-type plasminogen activator; and VTE, venous thromboembolism.

\*This measure was changed in 2016 to include in-hospital strokes in the denominator.

Source: Unpublished American Heart Association tabulation, GWTG-Stroke, 2021.

**Table 26-8. Quality of Care of Patients With IHCA Among GWTG-Resuscitation Hospitals, United States, 2021**

	Adults	Children
Event outside critical care setting	39.2	27.9
Hospital survival to discharge for IHCA outside the ICU	13.2	21.2
End-tidal CO <sub>2</sub> monitoring used during arrest (all IHCA events)	17.4	29.1
Induced hypothermia used when initial rhythm was shockable (all IHCA events)	1.1	0.3
For IHCA with survival, induced hypothermia initiated	6.1	8.3

Values are mean percentages.

GWTG indicates Get With The Guidelines; ICU, intensive care unit; and IHCA, in-hospital cardiac arrest.

Source: GWTG-Resuscitation Registry unpublished data, 2021.

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## 27. MEDICAL PROCEDURES

**See Table 27-1 and Charts 27-1 through 27-3**

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[Click here to return to the Abbreviations](#)

### Trends in Operations and Procedures

(See Table 27-1 and Chart 27-1)

Based on HCUP data from the Agency for Healthcare Research and Quality for the year 2018<sup>1</sup> (Table 27-1):

- There were 481 780 PCIs performed on an inpatient basis in the United States.
- A total of 114 715 inpatient procedures involving carotid endarterectomy or stenting were performed.
- A total of 10 905 left atrial appendage-related procedures were performed.
- A total of 60 335 inpatient peripheral arterial bypass procedures were performed.
- The trends in the numbers of 5 common cardiovascular procedures in the United States from 2016 to 2018 are presented in Chart 27-1. Of the 5 procedures, PCI was the most common procedure for all years presented (Chart 27-1).

### Cardiac Open Heart Surgery in Adults

- 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 161 816 procedures involved isolated CABG in 2019.<sup>2</sup> CABG made up a little more than half of all adult cardiac surgical procedures performed (N=301 077).
- Among other major procedures in 2019, there were 20 965 isolated aortic valve replacements and 10 748 isolated mitral valve replacements; 12 570 isolated mitral valve repairs, 14 246 procedures involving both aortic valve replacement and CABG, 3441 procedures involving both mitral valve replacement and CABG, 4153 procedures involving both mitral valve repair and CABG, and 2624 procedures involving both mitral valve replacement and aortic valve replacement.<sup>2</sup> A notable trend has

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As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

been a decrease in the number of procedures involving isolated aortic valve replacement and procedures involving combined aortic valve replacement and CABG.

- Operative mortality for various adult cardiac surgical procedures in 2019 was as follows: isolated CABG, 2.2%; isolated aortic valve replacement, 1.9%; aortic valve replacement plus CABG, 3.6%; mitral valve replacement, 4.6%; mitral valve replacement plus CABG, 8.8%; mitral valve repair, 1.1%; and mitral valve repair plus CABG, 5.0%.<sup>2</sup> Operative mortality for these analyses is defined as “(1) all deaths, regardless of cause, occurring during the hospitalization in which the operation was performed, even if after 30 days (including patients transferred to other acute care facilities); and (2) all deaths, regardless of cause, occurring after discharge from the hospital, but before the end of the 30th postoperative day.”<sup>2</sup>
- Median length of stay was 6 days for isolated CABG. It was longest for mitral valve replacement plus CABG (9 days).<sup>2</sup>

### Transcatheter Aortic Valve Replacement

- The STS-ACC TVT registry collects data on TAVR procedures performed in the United States.<sup>4</sup> Between 2011 and 2019, it collected data on 276 316 TAVR procedures in the United States. Some notable findings include the following:
- TAVR volumes continue to grow, with 13 723 TAVR procedures in 2011 to 2013 to 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 SAVR (n=57 626). The number of intermediate- and low-risk patients receiving TAVR has grown steadily. Similarly, elective or planned valve-in-valve TAVR cases have increased steadily from 305 cases between 2011 and 2013 to 4508 in 2019. The number of sites in the United States performing TAVR was 715 by the end of August 2020.<sup>5</sup> The median age of patients undergoing TAVR in 2019 was 80 years (IQR, 73–85 years) compared with 84 years in the initial years after FDA approval of TAVR.
- 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 ( $P<0.0001$ ). The 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 patients discharged home.

- The femoral artery remains the most frequent access site (used in 95.3% of 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 123 777 congenital heart surgeries performed from January 2015 to December 2018. The in-hospital mortality rate was 2.8% during that time period.
- The 5 most common diagnoses were type 2 VSD (6.2%), open sternum with open skin (6.1%), HLHS (5.8%), patent ductus arteriosus (4.0%), and secundum ASD (4.0%).
- The 5 most common primary procedures were delayed sternal closure (8.3%), patch VSD repair (6.4%), mediastinal exploration (3.5%), patch ASD repair (3.2%), and complete atrioventricular canal repair (2.8%).

## Heart Transplantations

(See Charts 27-2 and 27-3)

According to data from the Organ Procurement and Transplantation Network<sup>7</sup>:

- In 2021, 3817 heart transplantations were performed in the United States, the most ever (Chart 27-2). A total of 45 combined heart-lung transplantations were performed in 2021 (down from 58 in 2020).
- The highest numbers of heart transplantations were performed in California (529), Texas (359), New York (307), and Florida (263).
- Of the recipients in 2021, 71.8% were males, 58.1% were White people, 24.3% were Black people, 11.8% were Hispanic people, and 4.2% were Asian people. Heart transplantations by recipient age are shown in Chart 27-3. The largest proportion of these patients (42.4%) 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 3-year survival rate was 85.2% for both males and 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 79.8%, respectively. For Asian individuals, they were 91.4% and 80.1%, respectively.
- Between 2011 and 2014, the median waiting time for individuals in United Network for Organ Sharing heart status 1A was 87 days (95% CI, 80–94). As a comparison, the median waiting time was 67 days (95% CI, 61–73) for patients with heart status 1A between 2007 and 2010.

- As of February 21, 2022, 3436 individuals were on the transplantation waiting list for a heart transplantation, and 38 people were on the list for a heart/lung transplantation.

## 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. 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. A more recent study from the same data set showed that there was regional heterogeneity in the United States in terms of reduction in cardiovascular procedures with facilities in the Northeast region seeing the largest declines (76%), followed by the Midwest (74%), South (62%), and West (44%).<sup>8</sup> A greater proportion of US centers reported use of telehealth for direct patient care (90%) versus non-US centers (65%);  $P<0.001$  for the comparison. The use of telehealth for patient care did not differ across various US regions.
- A retrospective study using claims data compared US surgical procedural volumes during the initial shutdown period (March 15–May 2, 2020) and later COVID-19 surge (October 22, 2020–January 31, 2021) with corresponding prepandemic 2019 dates.<sup>9</sup> The investigators reported IRRs comparing procedural volumes across various time points. The total number of procedures during the initial shutdown period (458 469 procedures) was 48% lower compared with the corresponding period in 2019 (905 444 procedures; IRR, 0.52 [95% CI, 0.44–0.60];  $P<0.001$ ). Almost all surgical procedures decreased during the initial shutdown period except organ transplantations and cesarean deliveries compared with the 2019 baseline. During the surge period, surgical procedure volumes were comparable to 2019 levels (IRR, 0.97 [95% CI, 0.95–1.00];  $P=0.10$ ) except for ear-nose-throat procedures (IRR, 0.70 [95% CI, 0.65–0.75];  $P<0.001$ ). These results indicate that after the initial shutdown, health care systems have been able to adapt and function at prepandemic capacity.

- 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>10</sup> For example, the hospitalization rates for AMI were 4.1 per 100 000 person-weeks for the period of January 1 through 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 AMI (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 AMI. A similar study from the United Kingdom showed a 54% and 32% reduction in hospitalization for AMI and HF, respectively, with the first wave of COVID-19.<sup>11</sup> After recovering in June 2020, the hospitalization rates showed another decline with the second wave of COVID-19. The hospitalizations for AMI 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 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>12</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. Estimated Inpatient Cardiovascular Operations, Procedures, and Patient Data by Sex and Age (in Thousands), United States, 2018**

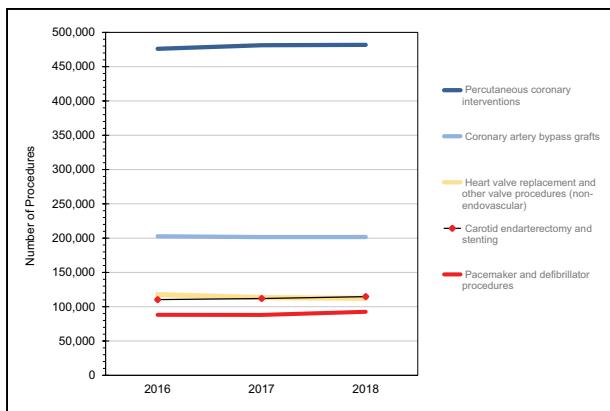
Operation/procedure	CCSR code	All	Sex		Age, y			
			Male	Female	18–44	45–64	65–84	≥85
Heart biopsy	CAR001	640	370	270	80	210	285	*
Heart conduction mechanism procedures	CAR002	68215	42810	25405	3785	21470	39020	3510
CABG	CAR003	201585	152635	48950	4615	76675	116750	3500
PCI	CAR004	481780	323140	158615	22645	200690	228190	30055
Other coronary artery procedures (excluding CABG and PCI)	CAR005	8260	5905	2355	660	2895	3495	190
Carotid endarterectomy and stenting	CAR006	114715	65710	49005	2530	28385	75705	7615
Embolectomy, endarterectomy, and related vessel procedures (nonendovascular; excluding carotid)	CAR007	77705	46440	31260	5005	27080	39510	5430
Angioplasty and related vessel procedures (endovascular; excluding carotid)	CAR008	201755	110600	91155	15610	69110	96525	17150
Left atrial appendage procedures	CAR009	10905	7590	3315	350	3295	6995	225
Ligation and embolization of vessels	CAR010	85290	45880	39395	16985	28610	26765	3565
Vessel repair and replacement	CAR012	103310	65205	38100	13290	32920	45335	3950
Heart and great vessel bypass procedures	CAR013	7140	4170	2970	390	385	315	*
Peripheral arterial bypass procedures	CAR014	60335	39340	20990	2950	23515	31030	2570
Peripheral arteriovenous fistula and shunt procedures	CAR015	23895	13740	10150	3440	9930	9675	765
Portal and other venous bypass procedures	CAR016	8360	5320	3040	1255	4460	2460	65
Pericardial procedures	CAR017	26085	15205	10880	3820	9515	10335	955
Heart transplantation	CAR018	3520	2385	1135	580	1745	705	0
Septal repair and other therapeutic heart procedures	CAR019	38700	20925	17775	4865	9625	11065	550
Saphenous vein harvest and other therapeutic vessel removal	CAR020	223895	165350	58535	10445	83940	122935	4445
Artery, vein, and great vessel procedures, NEC	CAR021	14525	6790	7730	1945	4780	6395	695
Heart valve replacement and other valve procedures (nonendovascular)	CAR022	112375	70480	41895	10100	36715	58380	1665
Heart valve replacement and other valve procedures (endovascular)	CAR023	74975	39955	35020	950	5020	45915	21920
Pacemaker and defibrillator procedures	CAR026	92610	61110	31495	6250	26880	47995	10185
Heart assist device procedures	CAR027	26575	19180	7390	2010	10230	12495	1560
Inferior vena cava filter procedures	CAR028	1075	525	550	225	390	355	*

These data do not reflect any procedures performed on an outpatient basis. Over time, many more procedures are being performed on an outpatient basis. Weighted national estimates are from HCUP NIS AHRQ and based on data collected by individual states and provided AHRQ by the states. Total number of weighted discharges in the United States is based on HCUP NIS=35 527 481. Statistics based on estimates with a relative SE (SE/weighted estimate) >0.30 or with SE=0 in the nationwide statistics (NIS, NEDS, and KID) are not reliable.

AHRQ indicates Agency for Healthcare Research and Quality; CABG, coronary artery bypass graft; CCSR, clinical classifications software refined; HCUP, Healthcare Cost and Utilization Project; KID, Kids' Inpatient Database; NEC, not elsewhere classified; NEDS, Nationwide Emergency Department Sample; NIS, National/Nationwide Inpatient Sample; and PCI, percutaneous coronary intervention.

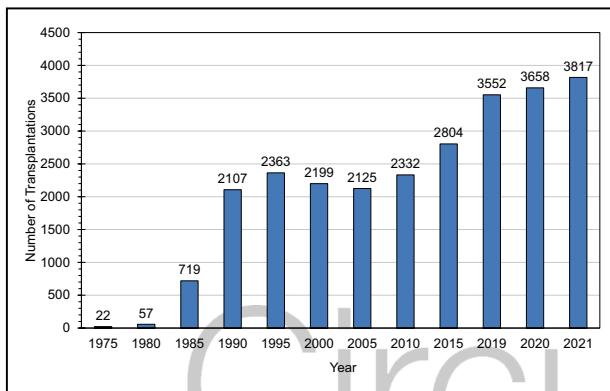
\*Unreliable and suppressed statistics.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using HCUP.<sup>1</sup>



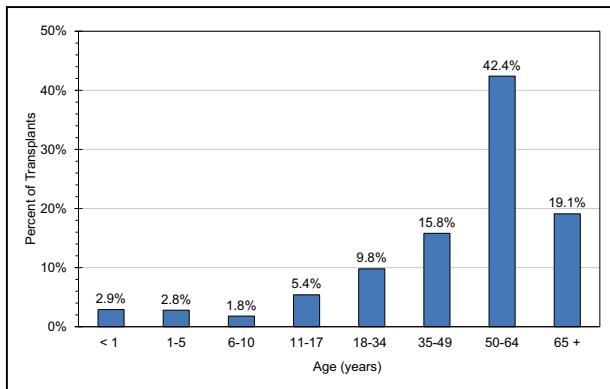
**Chart 27-1. Estimated inpatient cardiovascular operations and procedures, United States, 2016 to 2018.**

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.<sup>1</sup>



**Chart 27-2. Trends in heart transplants, United States, 1975 to 2021.**

Source: Data derived from the Organ Procurement and Transplantation Network.<sup>7</sup>



**Chart 27-3. Heart transplantations by recipient age, United States, 2021.**

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 (2018–2019),<sup>1</sup> the annual direct and indirect cost of CVD in the United States is an estimated \$407.3 billion (Table 28-1 and Chart 28-1). This figure includes \$251.4 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 \$155.9 billion in lost future productivity (indirect costs) attributed to premature CVD mortality in 2018 to 2019.

The direct costs for CVD for 2018 to 2019 (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 2018 to 2019 (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 2018 to 2019. 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 2019 to account for the 2014 to 2019

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 2018 to 2019 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 2018 to 2019, 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 2018 to 2019 Agency for Healthcare Research and Quality total direct expenditures for cancer, which was \$126.6 billion (44% for outpatient or office-based events, 28% for inpatient stays, and 22% 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 22 leading chronic diseases on the MEPS list. HD is the fifth 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 \$251.4 billion in 2018 to 2019 (Chart 28-3).

### Economic Value of CVD Risk Factor Control

One study analyzed individual-level Medicare and non-Medicare health care spending captured by Medicare Current Beneficiary Survey data from 1999 to 2012.<sup>6</sup> Overall, increased use of lipid-lowering, antihypertensive, and antidiabetic medications over time accounted for a combined 51% of the reduction in individual spending on CVD.

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As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

**Table 28-1. Estimated Direct and Indirect Costs (in Billions of Dollars) of CVD, United States, Average Annual, 2018 to 2019**

	HD*	Stroke	Hypertensive disease†	Other circulatory conditions‡	Total CVD
Direct costs§					
Hospital inpatient stays	56.9	20.0	7.0	27.5	111.4
Hospital ED visits	4.6	1.1	1.5	2.4	9.6
Hospital outpatient or office-based health care professional visits	29.7	6.5	15.6	15.1	66.9
Home health care	10.1	7.5	6.9	2.4	26.9
Prescribed medicines	15.7	1.4	15.4	4.1	36.6
Total expenditures	117.0	36.5	46.4	51.5	251.4
Indirect costs					
Lost productivity/mortality	122.9	20.0	5.8	7.2	155.9
Grand totals	239.9	56.5	52.2	58.7	407.3

Numbers do not add to total because of rounding.

CVD indicates cardiovascular disease; ED, emergency department; HD, heart disease; and HF, heart failure.

\*This category includes coronary HD, HF, 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.

§Medical Expenditure Panel Survey (MEPS) 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 2018 to 2019, discounted at 3%.

Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using the Household Component of the MEPS for direct costs (average annual 2018–2019).<sup>1</sup> Indirect mortality costs are based on 2018 to 2019 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 2019 from change in worker compensation reported by the US Bureau of Labor Statistics.<sup>5</sup>

# FIRST PROOF ONLY

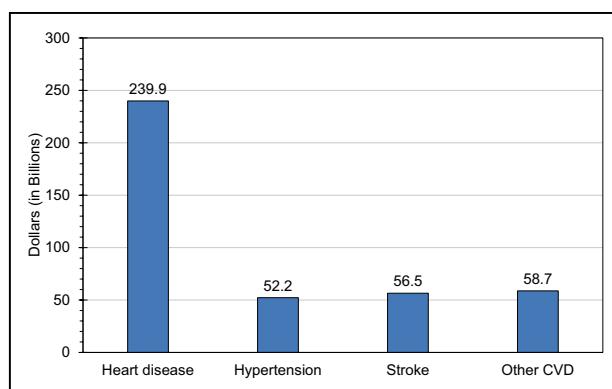
**Table 28-2. Costs of CVD in Billions of Dollars by Age and Sex, United States, Average Annual, 2018 to 2019**

	Total	Males	Females	<65 y of age	≥65 y of age
All direct	251.4	137.4	114.1	112.5	139.0
Indirect, mortality only	155.9	116.5	39.4	128.3	27.6
Total	407.3	253.9	153.5	240.8	166.6

Numbers may not add to total because of rounding.

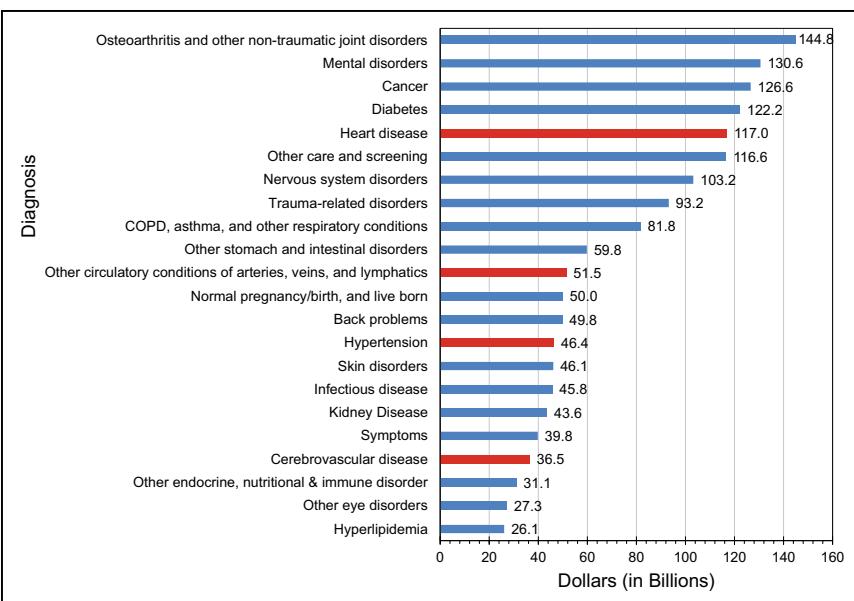
CVD indicates cardiovascular disease.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey, average annual 2018 to 2019 (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 2018 to 2019.**

CVD indicates cardiovascular disease.

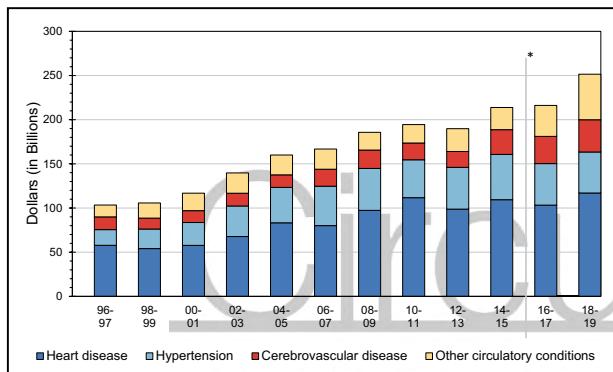
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey data and mortality data from the National Vital Statistics System.<sup>1,3</sup>



**Chart 28-2. The 22 leading diagnoses for direct health expenditures, United States, average annual 2018 to 2019 (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 2018–2019).**

\*International Classification of Diseases, Ninth Revision coding for 1996 to 2015; International Classification of Diseases, 10th Revision coding for 2016 to 2019.

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 2018–2019).<sup>1</sup>

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6. Cutler DM, Ghosh K, Messer KL, Raghunathan TE, Stewart ST, Rosen AB. Explaining the slowdown in medical spending growth among the elderly, 1999–2012. *Health Aff (Millwood)*. 2019;38:222–229. 10.1377/hlthaff.2018.05372

## 29. AT-A-GLANCE SUMMARY TABLES

See Tables 29-1 through 29-3

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[Click here to return to the Abbreviations](#)

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 17-2

- CHD in the United States—Table 21-1; AP in the United States—Table 21-2
- HF in the United States—Table 22-2

Note: In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.<sup>1</sup>

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

**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 <sup>†</sup>
<b>Overweight and obesity</b>							
Prevalence, 2017–2020							
Overweight and obesity, BMI $\geq 25.0 \text{ kg/m}^2$ <sup>‡</sup>	1.73 M (71.2%)	87.6 M (75.7%)	74.8%	69.9%	86.0%	61.8%	...
Obesity, BMI $\geq 30.0 \text{ kg/m}^2$ <sup>‡</sup>	98.4 M (41.4%)	47.4 M (41.2%)	42.7%	39.3%	44.6%	17.3%	...
<b>Blood cholesterol</b>							
Prevalence, 2017–2020							
TC $\geq 200 \text{ mg/dL}^{\ddagger}$	86.4 M (34.7%)	38.9 M (32.8%)	32.5%	27.5%	32.8%	40.7%	...
TC $\geq 240 \text{ mg/dL}^{\ddagger}$	24.7 M (10.0%)	11.0 M (9.5%)	9.6%	6.9%	9.3%	13.0%	...
LDL-C $\geq 130 \text{ mg/dL}^{\ddagger}$	63.1 M (25.5%)	30.3 M (25.6%)	25.0%	26.4%	23.7%	31.5%	...
HDL-C <40 mg/dL <sup>‡</sup>	41.3 M (16.9%)	29.9 M (24.9%)	25.0%	15.3%	29.5%	25.4%	...
<b>HBP</b>							
Prevalence, 2017–2020 <sup>†</sup>	122.4 M (46.7%)	62.8 M (50.4%)	48.9%	57.5%	50.3%	50.2%	...
Mortality, 2020 <sup>§,  </sup>	119 997	58 423 (48.7%) <sup>¶</sup>	38 801	12 033	4964	1854 <sup>#</sup>	873
<b>Diabetes</b>							
Prevalence, 2017–2020							
Diagnosed diabetes <sup>†</sup>	29.3 M (10.6%)	16.4 M (12.2%)	11.5%	11.8%	14.5%	14.4%	...
Undiagnosed diabetes <sup>†</sup>	9.7 M (3.5%)	4.6 M (3.5%)	2.6%	5.6%	5.3%	5.4%	...
Prediabetes <sup>†</sup>	115.9 M (46.4%)	63.5 M (52.9%)	57.2%	35.3%	50.7%	51.6%	...
Incidence, diagnosed diabetes, 2019 <sup>**</sup>	1.4 M	...	...	...	...	...	...
Mortality, 2020 <sup>§,  </sup>	102 188	57 532 (56.3%) <sup>¶</sup>	37 120	10 080	7136	2257 <sup>#</sup>	1356
<b>Total CVD</b>							
Prevalence, 2017–2020 <sup>†</sup>	127.9 M (48.6%)	65.4 M (52.4%)	51.2%	58.9%	51.9%	51.5%	...
Mortality, 2020 <sup>§,  </sup>	928 741	487 209 (52.5%) <sup>¶</sup>	364 143	66 675	36 966	14 796 <sup>#</sup>	5164
<b>Stroke</b>							
Prevalence, 2017–2020 <sup>†</sup>	9.4 M (3.3%)	4.0 M (2.9%)	2.7%	4.8%	2.5%	1.8%	...
New and recurrent strokes <sup>§</sup>	795.0 K	370.0 K (46.5%) <sup>¶</sup>	325.0 K <sup>††</sup>	45.0 K <sup>††</sup>	...	...	...

(Continued)

**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 <sup>*</sup>
Mortality, 2020 <sup>§</sup>	160 264	69 637 (43.5%) <sup>¶</sup>	49 490	10 276	6374	2981 <sup>#</sup>	848 <sup>#</sup>
<b>CHD</b>							
Prevalence, CHD, 2017–2020 <sup>†</sup>	20.5 M (7.1%)	11.7 M (8.7%)	9.4%	6.2%	6.8%	5.2%	...
Prevalence, MI, 2017–2020 <sup>†</sup>	9.3 M (3.2%)	6.1 M (4.5%)	4.8%	4.0%	3.1%	2.8%	...
Prevalence, AP, 2017–2020 <sup>†</sup>	10.8 M (3.9%)	5.6 M (4.3%)	4.7%	2.7%	3.6%	2.7%	...
New and recurrent MI and fatal CHD, 2005–2014 <sup>§§</sup>	1.05 M	610.0 K	520.0 K <sup>††</sup>	90.0K <sup>††</sup>	...	...	...
New and recurrent MI, 2005–2014 <sup>§§</sup>	805.0 K	470.0 K	...	...	...	...	...
Mortality, 2020, CHD <sup>§,  </sup>	382 820	227 887 (59.5%) <sup>¶</sup>	174 617	26 088	17 834	7077	2158
Mortality, 2020, MI <sup>§,  </sup>	109 199	65 137 (59.6%) <sup>¶</sup>	49 972	7282	5287	2021 <sup>#</sup>	674
<b>HF</b>							
Prevalence, 2017–2020 <sup>†</sup>	6.7M (2.3%)	3.7 M (2.7%)	2.9%	3.8%	1.8%	1.4%	...
Incidence, 2014 <sup>  </sup>	1.0 M	495.0 K	430.0 K <sup>††</sup>	65.0 K <sup>††</sup>	...	...	...
Mortality, 2020 <sup>§,  </sup>	85 855	40 897 (47.6%) <sup>¶</sup>	32 438	5173	2196	824 <sup>#</sup>	346

AP indicates angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes MI, AP, or both); CVD, cardiovascular disease; ellipses (...), data not available; HBP, high blood pressure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; K, thousands; LDL-C, low-density lipoprotein cholesterol; M, millions; MI, myocardial infarction (heart attack); NH, non-Hispanic; and TC, total cholesterol.

<sup>\*</sup>Both sexes.

<sup>†</sup>Age ≥20 years.

<sup>‡</sup>Total data for TC 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.

<sup>§</sup>All ages.

<sup>||</sup>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.

<sup>¶</sup>These percentages represent the portion of total incidence or mortality that is for males vs females.

<sup>||</sup>Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander.

<sup>††</sup>Age ≥18 years.

<sup>§§</sup>Estimates include Hispanic and NH males. Estimates for White males include other non-Black races.

<sup>#</sup>Estimate is considered unreliable or does not meet standards of reliability or precision.

<sup>§,||</sup>Age ≥35 years.

<sup>§,||</sup>Age ≥55 years.



# Circulation

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**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 <sup>*</sup>
<b>Overweight and obesity</b>							
Prevalence, 2017–2020							
Overweight and obesity, BMI ≥25.0 kg/m <sup>2</sup> <sup>‡</sup>	1.73 M (71.2%)	85.1 M (68.8%)	66.7%	79.2%	75.4%	45.9%	...
Obesity, BMI ≥30.0 kg/m <sup>2</sup> <sup>‡</sup>	98.4 M (41.4%)	51.0 M (41.4%)	39.4%	56.8%	44.1%	14.4%	...
<b>Blood cholesterol</b>							
Prevalence, 2017–2020							
TC ≥200 mg/dL <sup>‡</sup>	86.4 M (34.7%)	47.5 M (36.2%)	37.2%	29.6%	33.6%	37.7%	...
TC ≥240 mg/dL <sup>‡</sup>	24.7 M (10.0%)	13.7 M (10.4%)	10.7%	9.3%	10.0%	8.7%	...
LDL-C ≥130 mg/dL <sup>‡</sup>	63.1 M (25.5%)	32.8 M (25.4%)	24.0%	22.5%	27.5%	25.3%	...
HDL-C <40 mg/dL <sup>‡</sup>	41.3 M (16.9%)	11.4 M (9.3%)	8.8%	7.9%	11.8%	6.9%	...
<b>HBP</b>							
Prevalence, 2017–2020 <sup>†</sup>	122.4 M (46.7%)	59.6 M (43.0%)	42.6%	58.4%	35.3%	37.6%	...
Mortality, 2020 <sup>§,  </sup>	119 997	61 574 (51.3%) <sup>¶</sup>	43 308	11 216	4498	2026 <sup>#</sup>	873

(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*
Diabetes							
Prevalence, 2017–2020							
Diagnosed diabetes <sup>†</sup>	29.3 M (10.6%)	12.9 M (9.1%)	7.7%	13.3%	12.3%	9.9%	...
Undiagnosed diabetes <sup>†</sup>	9.7 M (3.5%)	5.1 M (3.5%)	2.8%	3.2%	4.5%	5.2%	...
Prediabetes <sup>†</sup>	115.9 M (46.4%)	52.4 M (40.0%)	38.8%	35.7%	41.3%	40.2%	...
Incidence, diagnosed diabetes, 2019 <sup>**</sup>	1.4 M	...	...	...	...	...	...
Mortality, 2020 <sup>§,  </sup>	102 188	44 656 (44.7%) <sup>¶</sup>	26 978	9415	5696	1866*	1356
Total CVD							
Prevalence, 2017–2020 <sup>†</sup>	127.9 M (48.6%)	62.5 M (44.8%)	44.6%	59.0%	37.3%	38.5%	...
Mortality, 2020 <sup>§,  </sup>	928 741	441 532 (47.5%) <sup>¶</sup>	333 102	61 464	30 386	13 524*	5164
Stroke							
Prevalence, 2017–2020 <sup>†</sup>	9.4 M (3.3%)	5.4 M (3.6%)	3.6%	5.4%	2.5%	1.5%	...
New and recurrent strokes <sup>§</sup>	795.0 K	425.0 K (53.5%) <sup>¶</sup>	365.0 K <sup>††</sup>	60.0 K <sup>††</sup>	...	...	...
Mortality, 2020 <sup>§</sup>	160 264	90 627 (56.5%) <sup>¶</sup>	67 262	12 128	6996	3674*	848 <sup>##</sup>
CHD							
Prevalence, CHD, 2017–2020 <sup>†</sup>	20.5 M (7.1%)	8.8 M (5.8%)	5.9%	6.3%	6.1%	3.9%	...
Prevalence, MI, 2017–2020 <sup>†</sup>	9.3 M (3.2%)	3.2 M (2.1%)	2.2%	2.3%	1.9%	0.5% American Heart Association. ...	...
Prevalence, AP, 2017–2020 <sup>†</sup>	10.8 M (3.9%)	5.2 M (3.6%)	3.5%	4.1%	4.3%	2.7% ...	...
New and recurrent MI and fatal CHD, 2005–2014 <sup>§§</sup>	1.05 M	445.0 K	370.0 K <sup>††</sup>	75.0 K <sup>††</sup>	...	...	...
New and recurrent MI, 2005–2014 <sup>§§</sup>	805.0 K	335.0 K	...	...	...	...	...
Mortality, 2020, CHD <sup>§,  </sup>	382 820	154 933 (40.5%) <sup>¶</sup>	116 492	20 595	11 789	4816	2158
Mortality, 2020, MI <sup>§,  </sup>	109 199	44 062 (40.4%) <sup>¶</sup>	32 831	6 029	3 495	1 384*	674
HF							
Prevalence, 2017–2020 <sup>†</sup>	6.7 M (2.3%)	3.0 M (1.9%)	1.6%	3.3%	1.6%	0.5%	...
Incidence, 2014 <sup>  </sup>	1.0 M	505.0 K	425.0 K <sup>††</sup>	80.0 K <sup>††</sup>	...	...	...
Mortality, 2020 <sup>§,  </sup>	85 855	44 958 (52.4%) <sup>¶</sup>	36 179	5 409	2 294	893*	346

AP indicates angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes MI, AP, or both); CVD, cardiovascular disease; ellipses (...), data not available; HBP, high blood pressure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; K, thousands; LDL-C, low-density lipoprotein cholesterol; M, millions; MI, myocardial infarction (heart attack); NH, non-Hispanic; and TC, total cholesterol.

\*Both sexes.

<sup>†</sup>Age ≥20 years.

<sup>\*\*</sup>Total data for TC 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.

<sup>§</sup>All ages.

<sup>¶</sup>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.

<sup>††</sup>These percentages represent the portion of total incidence or mortality that is for males vs females.

<sup>||</sup>Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander.

<sup>##</sup>Age ≥18 years.

<sup>§§</sup>Estimates include Hispanic and NH females. Estimates for White females include other non-Black races.

<sup>\*</sup>Estimate considered unreliable or does not meet standards of reliability or precision.

<sup>¶¶</sup>Age ≥35 years.

<sup>|||</sup>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, 2017–2020														
Overweight and obesity, 2–19 y of age*	26.9 M (36.8%)	13.8 M (37.3%)	13.1 M (36.2%)	35.3%	32.9%	31.7%	49.3%	46.7%	43.5%	26.0%	16.5%			
Obesity, 2–19 y of age*	14.5 M (19.8%)	7.8 M (21.1%)	6.7 M (18.6%)	17.7%	15.3%	18.3%	30.5%	30.1%	23.3%	13.7%	5.2%			
Blood cholesterol, 2017–2020														
Mean TC, mg/dL														
6–11 y of age	157.4	157.5	157.2	156.3	159.5	159.3	155.3	156.5	153.1	169.6	166.0			
12–19 y of age	154.8	150.1	159.7	148.8	162.4	153.1	156.8	149.8	154.9	156.3	161.0			
Mean HDL-C, mg/dL														
6–11 y of age	55.5	56.6	54.3	56.8	54.8	58.5	55.9	55.6	51.3	59.3	58.1			
12–19 y of age	51.7	49.0	54.6	48.2	55.2	53.8	55.9	48.2	52.2	51.1	55.3			
Mean LDL-C, mg/dL														
12–19 y of age	88.1	85.1	91.3	83.2	92.0	84.8	97.6	89.0	88.1	83.0	83.2			
CCDs (all age groups: children and adults)														
Mortality, 2020†‡§	2817	1534 (54.5%)§	1283 (45.5%)§	933	789	267	206	243	214	68	60			

CCD indicates congenital cardiovascular defect; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; M, millions; NH, non-Hispanic; and TC, total cholesterol.

\*In children, overweight and obesity are based on body mass index (BMI)—for-age values at or above the 85th percentile of the 2000 Centers for Disease Control and Prevention (CDC) growth charts. Obesity is based on BMI-for-age values at or above the 95th percentile of the CDC growth charts.

†All ages.

‡Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

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

||NH American Indian/Alaska Native, mortality: 29.



## REFERENCE

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2017–March 2020 prepanemic data files: development of files and prevalence estimates for selected health outcomes. 2021. Accessed March 17, 2022. <https://stacks.cdc.gov/view/cdc/106273>

## 30. GLOSSARY

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- *Age-adjusted rates*—Used mainly to compare the rates of ≥2 communities or population groups or the nation as a whole over time. The American Heart Association (AHA) uses a standard population (2000), so these rates are not affected by changes or differences in the age composition of the population. Unless otherwise noted, all death rates in this publication are age adjusted per 100 000 population and are based on underlying cause of death.
- *Agency for Healthcare Research and Quality (AHRQ)*—A part of the US Department of Health and Human Services, this is the lead agency charged with supporting research designed to improve the quality of health care, to reduce the cost of health care, to improve patient safety, to decrease the number of medical errors, and to broaden access to essential services. The AHRQ sponsors and conducts research that provides evidence-based information on health care outcomes, quality, cost, use, and access. The information helps health care decision makers (patients, clinicians, health system leaders, and 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 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):

The 2023 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2023. 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 Updates.

- 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 (AMI; I21–I22); certain current complications after AMI (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

- “cardiovascular disease” (“Total cardiovascular disease” in this Glossary).
- *Diseases of the heart (ICD-10 codes I00–I09, I11, I13, I20–I51)*—Classification the NCHS uses in compiling the leading causes of death. Includes acute rheumatic fever/chronic rheumatic heart diseases (I00–I09); hypertensive heart disease (I11); hypertensive heart and renal disease (I13); CHD (I20–I25); pulmonary heart disease and diseases of pulmonary circulation (I26–I28); heart failure (I50); and other forms of heart disease (I30–I49, I51). “Diseases of the heart” are not equivalent to “total cardiovascular disease,” which the AHA prefers to use to describe the leading causes of death.
  - *Hispanic origin*—In US government statistics, “Hispanic” includes people who trace their ancestry to Mexico, Puerto Rico, Cuba, Spain, the Spanish-speaking countries of Central or South America, the Dominican Republic, or other Spanish cultures, regardless of race. It does not include people from Brazil, Guyana, Suriname, Trinidad, Belize, or Portugal because Spanish is not the first language in those countries. Most of the data in this update are for all Hispanic people, as reported by government agencies or specific studies. In certain time-trend charts and tables, data for Mexican American people are shown because data are not available for all Hispanic people.
  - *Hospital discharges*—The number of inpatients (including newborn infants) discharged from short-stay hospitals for whom some type of disease was the principal diagnosis. Discharges include those discharged alive, dead, or “status unknown.”
  - *International Classification of Diseases (ICD) codes*—A classification system in standard use in the United States. The *ICD* is published by the World Health Organization. This system is reviewed and revised approximately every 10 to 20 years to ensure its continued flexibility and feasibility. The 10th revision (*ICD-10*) began with the release of 1999 final mortality data. The *ICD* revisions can cause considerable change in the number of deaths reported for a given disease. The NCHS provides “comparability ratios” to compensate for the “shifting” of deaths from one *ICD* code to another. To compare the number or rate of deaths with that of an earlier year, the “comparability-modified” number or rate is used.
  - *Incidence*—An estimate of the number of new cases of a disease that develop in a population, usually in a 1-year period. For some statistics, new and recurrent attacks, or cases, are combined. The incidence of a specific disease is estimated by multiplying the incidence rates reported in community- or hospital-based studies by the US population. The rates in this report change only when new data are available; they are not computed annually.

- *Infective endocarditis*—An infection of the inner lining (endocardium) of the heart or of the heart valves. The bacteria that most often cause endocarditis are streptococci, staphylococci, and enterococci.
- *Major cardiovascular diseases*—Disease classification commonly reported by the NCHS; represents *ICD-10* codes I00 to I78. The AHA does not use “major cardiovascular disease” 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.